UNIVERSITE SIDI MOHAMMED BEN ABDELLAH
FACULTE DE MEDECINE ET DE PHARMACIE
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LE DIABETE DE TYPE 1 CHEZ L'ENFANT : EPIDEMIOLOGIE ET FACTEURS ASSOCIES A L'ACIDOCETOSE ET A SA SEVERITE (A propos de 183 cas)

THESE

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LISTE DES ABREVIATIONS

AAE : Anticorps Anti-Endomysium

AAG : Anticorps Anti-Gliadine

AAN : Anticorps anti-noyaux

AAT : Anticorps anti-thyroïdien

AATG : Ac anti-thyroglobuline

Ac anti LC1 : Anticorps anti anti-cytosol

Ac anti-LKM1 : Anti-microsomes de type 1

ACD + : Acidocétose

ACD++ : Acidocétose sévère

ADA : American Diabetes Association

ADD : Age de découverte du diabète

AI : Auto-immune

AMG : Amaigrissement

AML : Anti-muscles lisses

ATG : Anticorps anti-transglutaminase

ATCD : Anrécédents

ATPO/AATPO : Ac anti-thyro-peroxydase

AVP : Atrophie villositaire partielle

AVST : Atrophie villositaire subtotale

AVT : Atrophie villositaire totale

BJ : Biopsie jéjunale

BNSE : Bas niveau socio-économique

DCCT : Diabetes Control and Complications Trial

Dg : Diagnostic

DHA : Déshydratation

DS : Déviation standard

DT1 : Diabète de type 1

DT2 : Diabète de type 2

ECG : Electrocardiogramme

ECBU : Examen cytobactériologique des urines

FC : Fréquence cardiaque

FR : Fréquence respiratoire

F : Fille

G : Garçon

GAD : Glutamate acide décarboxylase

H : Heure

HAI : Hépatite auto-immune

HAS : Haute autorité de santé

HGPO : Hyperglycémie provoquée par voie orale

HPIV : Hyperglycémie provoquée par voie intraveineuse

HTA : Hypertension artérielle

HTP : Hypertension portale

IA2A : Anticorps anti-tyrosine phosphatase

IAA : Anticorps anti-insuline

IAIHG : International Autoimmune Hepatitis Group

ICA : Anticorps anti-ilots de Langerhans

IL : Interleukine

INF : Inférieur

IP : Insuffisance pondérale

IPEX : Immunodysregulation polyendocrinopathy x linked

ISPAD : International society for pediatric and adolescent diabetes

L B : Lymphocyte B

L T : Lymphocyte T

LED : Lupus érythémateux disséminé

LT3	: Trïodothyronine libre
LT4	: Tétraïodothyronine libre
MAI	: Maladie auto-immune
MC	: Maladie cœliaque
MTAI	: Maladie thyroïdienne auto-immune
N	: Nombre
NFS	: Numération formule sanguine
NS	: Non significatif
Nv	: Nouveaux
OMS	: Organisation mondiale de santé
PEA	: Poly-endocrinopathie auto-immune
RAS	: Rien à signaler
RD	: Retard diagnostique
SN Resp	: Signes Respiratoires
SAP	: Seringue auto-pulsée
Sd	: Syndrome
SN	: Signes
SP	: Symptome
SPP	: Syndrome polyuro-polydépsique .
SUP	: Supérieur
TG	: Transglutaminase
Th1	: T helper 1
THAI	: Thyroïdite auto-immune.
THO	: Thyroïdite de Hashimoto
TR Consc	: Troubles de conscience
TSH us	: Thyréostimuline ultra-sensible
VMS	: Vomissement

INTRODUCTION

Le diabète de type 1 est l'une des maladies endocrines et métaboliques les plus fréquentes chez l'enfant. Il s'agit d'une affection auto-immune responsable d'un déficit majeur de la sécrétion pancréatique d'insuline dont les difficultés de prise en charge et les complications à moyen et à long terme sont souvent responsables de répercussions néfastes sur la qualité de vie de l'enfant et de son entourage et peuvent même engager le pronostic vital.

En effet, c'est une maladie exigeante et contraignante qui impose à l'enfant un nouveau mode de vie auquel même les adultes ne peuvent s'adapter parfaitement.

Le diabète de l'enfant est, dans la très grande majorité des cas, insulinodépendant (plus de 90 %) et de mécanisme auto-immun, avec présence d'un certain nombre d'auto-anticorps dirigés contre le pancréas.

Depuis ces vingt dernières années, on note une incidence croissante du diabète de type 1 à travers le monde [1-3].Cette tendance n'épargne pas les pays sous développés en en voie de développement. Certains auteurs rapportent que l'augmentation du taux d'incidence touche surtout les enfants des pays en développement ou ceux en transition économique au cours des dernières décennies [3,5].Dans cette perspective, nous devons nous interroger sur les moyens à mettre en œuvre ou à améliorer pour assurer une prise en charge optimale, et ce dès le diagnostic.

D'autre part, selon les données européennes du groupe collaboratif EURODIAB, le taux d'acidocétose diabétique inaugurale est estimé à 40% en Europe, avec de grandes variations géographiques soulignant l'importance de l'expérience dans la maladie diabétique pour aboutir à un diagnostic plus précoce sans atteindre le stade d'acidocétose.

Dans notre contexte, Malgré l'absence des données fiables, il est constaté que l'acidocétose reste le mode de révélation le plus fréquent de la maladie diabétique chez l'enfant.

Elle est la plus grande cause de mortalité et de morbidité dans le diabète de type 1 de l'enfant, avec un taux de mortalité entre 0,15 et 0,31%, principalement lié à la survenue d'un œdème cérébral responsable d'environ 50 à 80% des décès par l'acidocétose [57].

Elle constitue le mode de révélation le plus redouté dans le diabète de type 1.

Des facteurs de risque prédisposant à sa survenue ont été montrés (ISPAD 2014) [57].

- L'âge inférieur à 2 ans.
- Le retard diagnostique.
- Le bas niveau socioéconomique.
- Les pays ayant une prévalence basse de DT1.

Afin de mieux connaître la population d'enfants diabétiques dont nous avons la charge, nous avons réalisé une étude rétrospective visant à décrire le profil épidémiologique du DT1 dans notre population et de présenter les circonstances diagnostiques en centrant notre intérêt sur l'acidocétose inaugurale, afin d'en identifier des facteurs associés à sa révélation inaugurale et sa sévérité, sur lesquels nous pourrions intervenir pour un diagnostic plus précoce.

MATERIELS ET METHODES

I - Matériels de l'étude

1 - Type et lieu de l'étude :

- Il s'agit d'une étude rétrospective à propos de 183 cas.
- L'objet est l'analyse des caractéristiques des enfants diabétiques de type 1 pris en charge au service de pédiatrie médicale (au Centre Hospitalier Universitaire (CHU) de Fès), référés du service des urgences, ou de la réanimation pédiatrique, hospitalisés soit, pour la première fois pour diabète inaugural, ou bien pour rechute, entre le 1er Janvier 2009 et le 31 décembre 2013.

2 - Nos principaux objectifs sont :

- Décrire, dans un premier temps, le profil épidémiologique de diabète de type 1 dans notre population, les changements subits dans le temps, et le comparer aux autres populations et données de revue de la littérature.
- Identifier, dans un deuxième temps, les facteurs associés, médicaux, sociologiques ou économiques, à la révélation de diabète par l'acidocétose et à sa sévérité afin de cibler les populations à sur-risque.

3 - Population étudiée :

3.1. Critères d'inclusion

Ont été inclus les enfants, âgés de moins de 18 ans, hospitalisés au service de pédiatrie médicale (CHU de Fès) pour un diabète de type 1.

3.2. Critères d'exclusion

Ont été exclus :

- Les enfants présentant un autre type que le diabète de type 1.
- Les enfants suivis en consultation ambulatoire et jamais, hospitalisés au CHU de Fès.
- Les enfants dont le recueil de données était impossible ou insuffisant.

Pour analyser les facteurs associés à la révélation du diabète par l'acidocétose, nous avons admis tous les nouveaux cas avec l'exclusion des cas de rechute. Cela a abouti à une sélection finale de 149 nouveaux cas diagnostiqués diabétiques entre le 01/01/2009 et le 31/12/2013.

II- Méthode de l'étude

C'est une étude rétrospective pour laquelle un dossier de diabète a été préalablement établi afin de faciliter le recueil des données (anamnestiques ; cliniques ; biologiques et thérapeutiques …) puis collecté sur une fiche d'exploitation et saisi sur un fichier Excel et analysé par SPSS 20.00

Nous avons considéré chaque enfant diagnostiqué pour un diabète de type 1, insulinotraité. La définition du diabète sucré repose sur les critères clinico-biologiques de l'ISPAD 2014*[82]*.

Les critères diagnostiques du diabète sont basés sur la mesure des concentrations plasmatiques de glucose (glycémie) et la présence ou l'absence de symptômes.

- Les symptômes classiques du diabète avec une glycémie ≥11.1mmol / L
- (200 mg / dL) ou.
- Glycémie à jeun ≥7.0mmol / L (≥126mg / dl) (Le jeûne est défini comme une absence d'apport calorique pendant au moins 8 heures) ou.
- Un test HGPO à H_2 ≥11.1mmol / L (≥200mg / dl) (le test doit être effectué en utilisant une charge de glucose contenant l'équivalent de 75 g de glucose dissous dans l'eau ou 1,75 g / kg de poids corporel au maximum de 75 g ou.
- HbA1c >6.5%.

1 - Variables recueillis :

La collecte des données a regroupé les données épidémiologiques, les éléments liés au diagnostic, et les données familiales et socio-économiques et les données de la prise en charge thérapeutique.

1.1. Données anamnestiques

- Volet enfant : l'âge, le sexe, scolarité, antécédents personnels…
- Volet parents : le niveau socio-économique, la scolarité des parents, les antécédents familiaux…
- Volet diabète : les symptômes annonciateurs, les facteurs déclenchant, l'évolution des prodromes, l'âge et la saison de diagnostique…

1.2. Au cours de l'hospitalisation

- **Clinique :**
  - ✓ L'état général.
  - ✓ L'état d'hydratation.
  - ✓ L'état neurologique.
  - ✓ Les singes d'acidose.
  - ✓ L'existence de foyer infectieux.
- **Bilan para clinique initial :**
  - ✓ Glycémie capillaire et sanguine.
  - ✓ Glycosurie et acétonurie.
  - ✓ Ionogramme sanguin complet.
  - ✓ ECG.
  - ✓ Bilan infectieux :(radio thorax, ECBU).
  - ✓ Le reste du bilan en fonction du contexte clinique.
- **Prise en charge thérapeutique :**
  - ✓ Volet pharmacologique : (réhydratation, insulinothérapie, antibiothérapie, traitement adjuvant).
  - ✓ Volet éducatif

2- Groupe de comparaison (ACD− ; ACD+ ; ACD++).

Les situations de décompensation métabolique sont appréciées par la glycémie capillaire (en g/l) par la glycosurie et la cétonurie (dosage de l'acétoacétate) sur bandelettes urinaires (type Keto-Diastix®).

Les mesures urinaires rapportent des valeurs semi-quantitatives et sont exprimées en « croix » (+), la mesure de la glycosurie s'étend de 0 à 20 g/l et la cétonurie de 0 à 8-16 mmol/l.

Une cétonurie massive permet de nous orienter vers une acidocétose pour des valeurs supérieures ou égales à 2 croix.

Consensuellement, le diagnostic d'acidocétose (ACD+) est rendu par la mesure du pH et du taux de bicarbonates qui sont réalisée dans le cadre du bilan diagnostique du diabète de type 1 ainsi la présence de singes cliniques de l'acidocétose diabétique (ISPAD 2014)**[57].**

Selon ce consensus :

Les critères biochimiques au diagnostic :

- Hyperglycémie supérieure à 11 mmol/l (soit 2 g/l).
- pH veineux strictement inférieur à 7,30 et/ou taux de bicarbonates sanguins (HCO3-) strictement inférieur à 15 mmol/l.
- Présence associée de glycosurie, cétonurie, cétonémie.

Les signes cliniques de l'acidocétose diabétique comprennent :

- Déshydratation.
- Tachycardie.
- Tachypnée.
- Polypnée.
- Dyspnée de (Kussmaul).
- Nausée, vomissement.

- Douleurs abdominales.
- Confusion, somnolence, altération de la conscience.

Le degré de sévérité de l'acidocétose dépend de l'importance de l'acidose, avec trois catégories distinctes :

- Acidocétose peu sévère (ou modérée) pour un pH <7,30 et/ou HCO3- <15 mmol/l .
- Acidocétose moyennement sévère pour un pH <7,15 et/ou HCO3- <10 mmol/l.
- Acidocétose sévère pour un pH <7,10 et/ou HCO3- <5 mmol/l.

La valeur du pH et du taux de bicarbonates mesurés au diagnostic, associée à l'hyperglycémie (> 2g/l) à une glycosurie et cétonurie massive (> ou =2(+)) et la présence de signes cliniques de gravité permettent de scinder notre population en deux groupes :

- Un groupe sans acidocétose diabétique inaugurale(ACD−).
- Un groupe avec acidocétose diabétique inaugurale (ACD+).

Le sous-groupe des acidocétoses sévères (ACD++) est constitué par les enfants ayant un pH < 7,10 et/ou HCO3- < 5 mmol/l avec la présence de signes de gravité.

Tableau 1 : Les critères clinico-biologiques au diagnostic

	ACD-	*ACD+*	*ACD++*
pH	> ou =7,30	<7,30	<7,10
Bicarbonates	> ou =15	<15	<5
glycosurie	<2(+)	> ou = 2(+)	>3(+)
cétonurie	<2(+)	> ou = 2(+)	>3(+)
Haleine cétonique	+ /-	+	++
Troubles de conscience	absents	présents	Présents : obnubilation, coma
Signes respiratoires	absents	polypnée	dyspnée de Kussmaul
FR	normale	>20cpm	>30cpm
Etat hémodynamique	stable	instable	instable
FC	normale	tachycardie	tachycardie
Déshydratation(DHA)	absente ou légère	présente	importante intra et extracellulaire
Signes digestifs	absentes	présents	présents

Le dosage de l'hémoglobine glyquée (HbA1c) est aussi recueilli et s'exprime en pourcentage. L'HbA1c est un reflet de l'équilibre glycémique des trois mois précédents, pouvant alors nous renseigner approximativement sur la durée d'installation et d'évolution du diabète.

3- Analyse Statistique

La saisie des données a été effectuée sur fichier Excel.

L'analyse statistique a été réalisée à l'aide du logiciel SPSS, version 20.

Elle a comporté une description des caractéristiques socio-démographiques, du parcours de soins et de la présentation clinico-biologique initiale des enfants pris en charge pour la découverte d'un diabète de type 1.

Pour cette partie descriptive, les variables quantitatives ont été exprimées par leur moyenne et leur écart-type, ainsi que par leurs valeurs minimale et maximale. Les variables qualitatives ont été exprimées par leur effectif et leur fréquence.

Tous les items ont ensuite été comparés entre le groupe ayant présenté une acidocétose inaugurale (ACD +) et le groupe sans acidocétose révélatrice (ACD -).

Cette analyse bivariée a été réalisée au moyen d'un test t pour les variables quantitatives et d'un test du Chi-2 pour les variables qualitatives.

Le seuil de signification (p) retenu était de 5 %.

RESULTATS

I – Etude descriptive

1 – Analyse des paramètres épidémiologiques :

1.1. Age de découverte de diabète :

La moyenne d'âge de découverte de diabète de nos patients était de 6,64+/-3,81(ans) avec une médiane de 6 ans (19 mois-14 ans 7 mois).

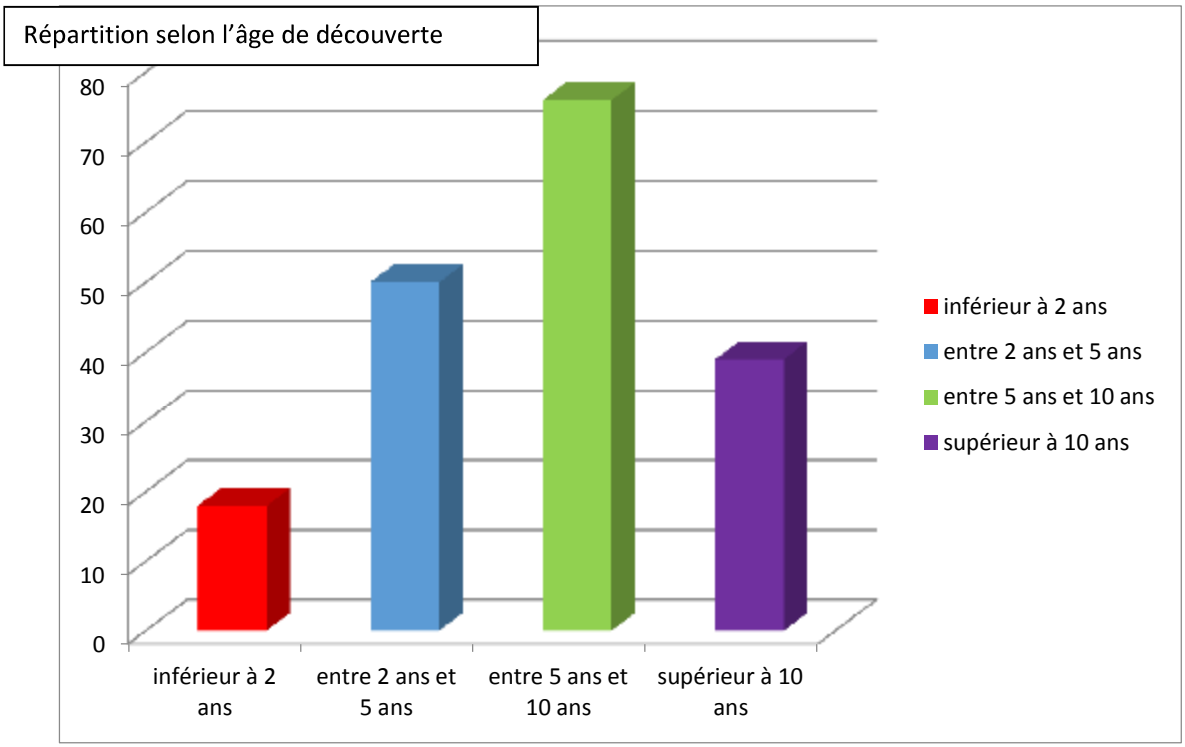


Figure 1 : l'âge de diagnostic des enfants diabétiques.

La tranche d'âge de 0 à 4 ans (<5ans) représente 37% avec 10% des formes de révélation avant l'âge de deux ans tandis que celle de 5 à 10 ans représente 42%.les enfants dont l'âge est supérieur à 10 ans représentent seulement 21%.

1.2. Sexe :

Le sexe ratio=0,87(53% des filles / 47% des garçons).

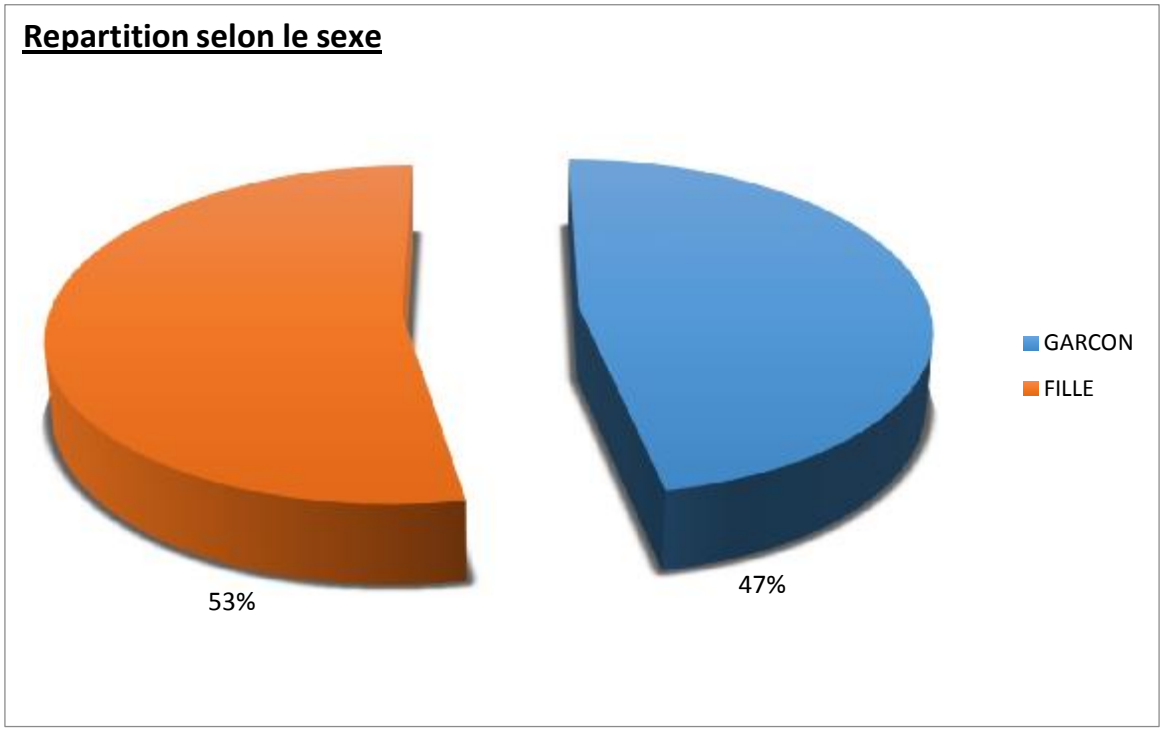


Figure 2 : Répartition des enfants diabétiques selon le sexe

1.3. Scolarité :

Cinquante-sept pour cent des enfants diabétiques étaient scolarisés dont 70% présentaient une concordance entre l'âge et le niveau scolaire.9% non scolarisé ; 3% cas d'abandon scolaire (5cas) par manque de moyens et difficulté d'accès à l'école ; 32% étaient non encore scolarisés.

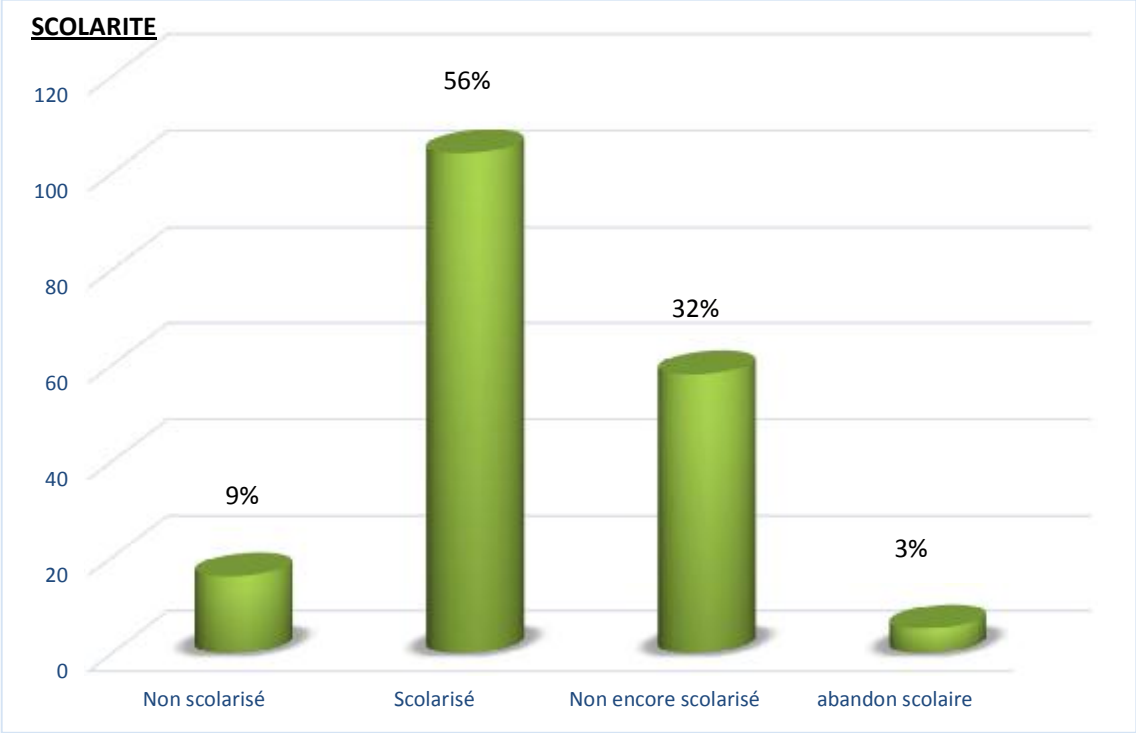


Figure 3 : La scolarité chez les enfants diabétiques

1.4. Lieu de résidence :

Environ 70 % de nos patients résident au milieu urbain.

1.5. Niveau socioéconomique :

Le niveau socioéconomique de nos patients était bas dans 57% des cas.

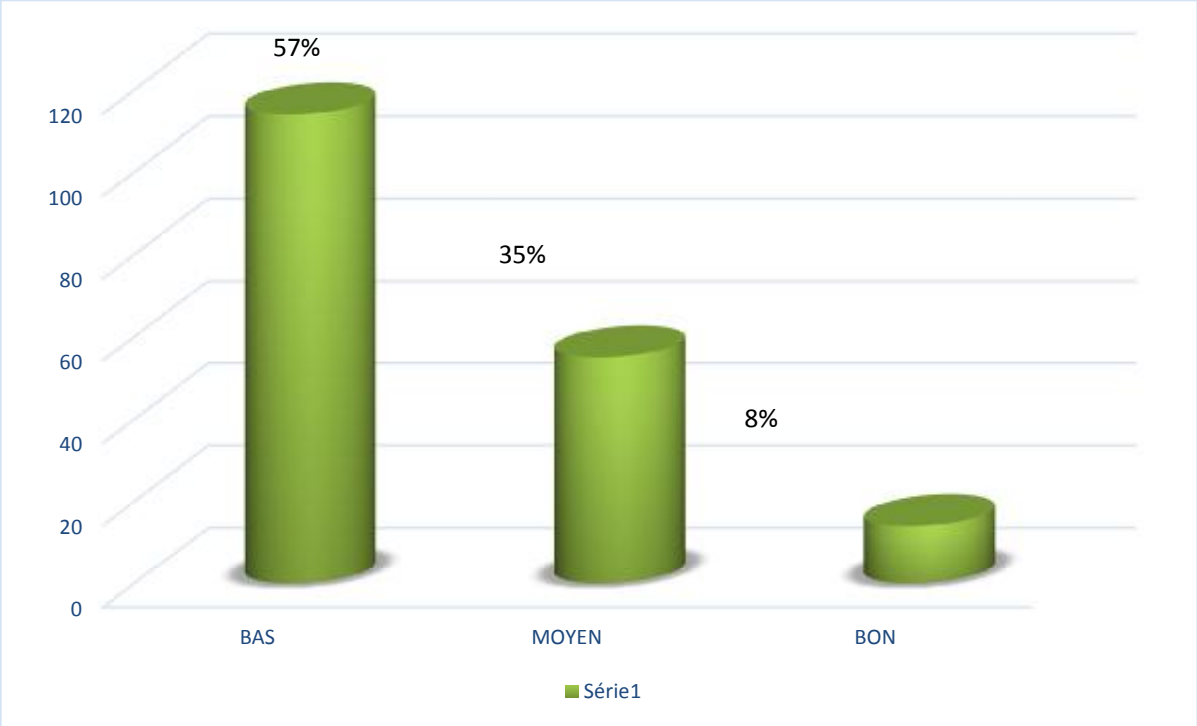


Figure 4 : niveau socio-économique.

44% des pères sont des fonctionnaires ; 38 % sont des journaliers ; 19% sont sans profession.

14% de nos patients n'ont pas de couverture sociale.

86 % de nos patients ont une couverture médicale, dont 48% entre eux ont le RAMED ,21% la CNOPS ,10% la CNSS, 9% FAR et 12% autre assurances.

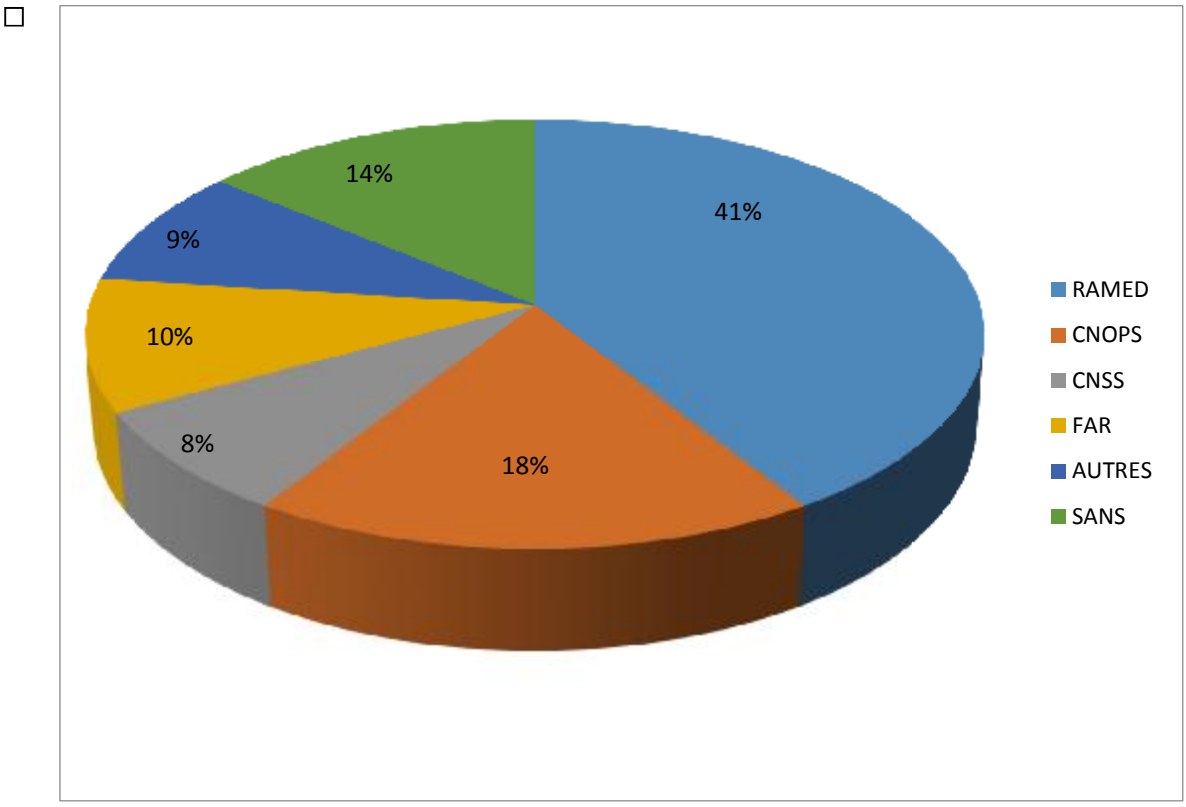


Figure 5 : Répartition des enfants diabétiques selon leurs assurances maladie

1.6. Saison :

Le diagnostic du diabète a été fait dans environ 33% en hiver ,27% automne et 24% au printemps, avec deux pics en décembre et janvier. Seulement 16 % ont été enregistrés en Eté

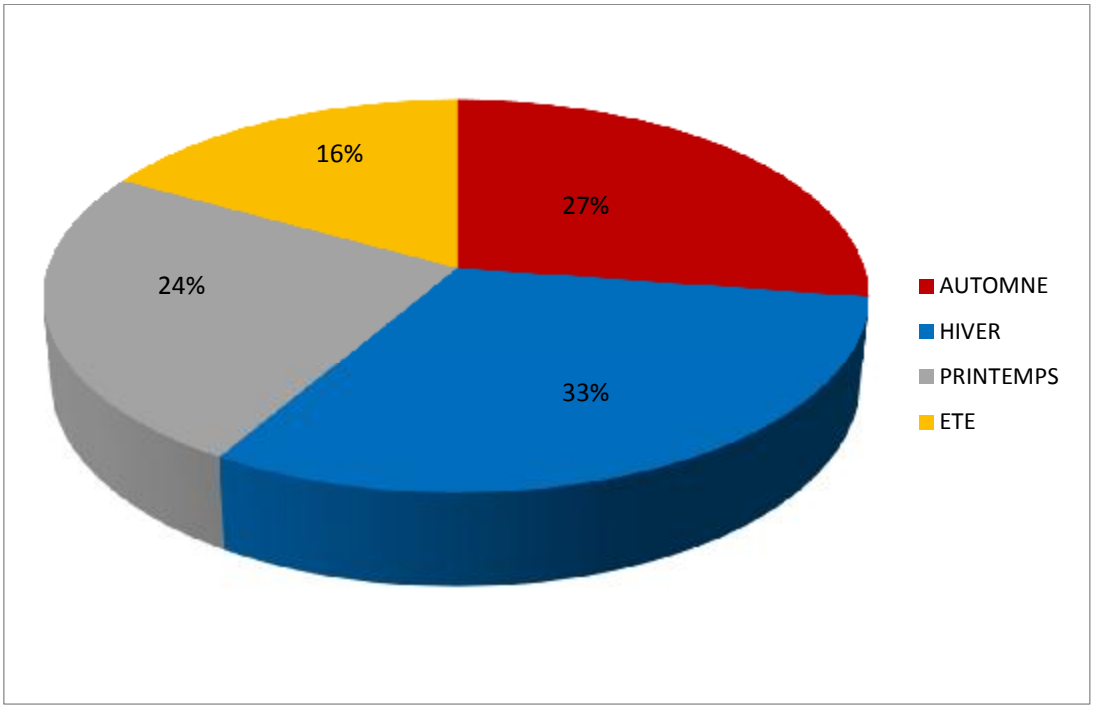


Figure 6 : Répartition des enfants diabétiques en fonction de la saison diagnostic

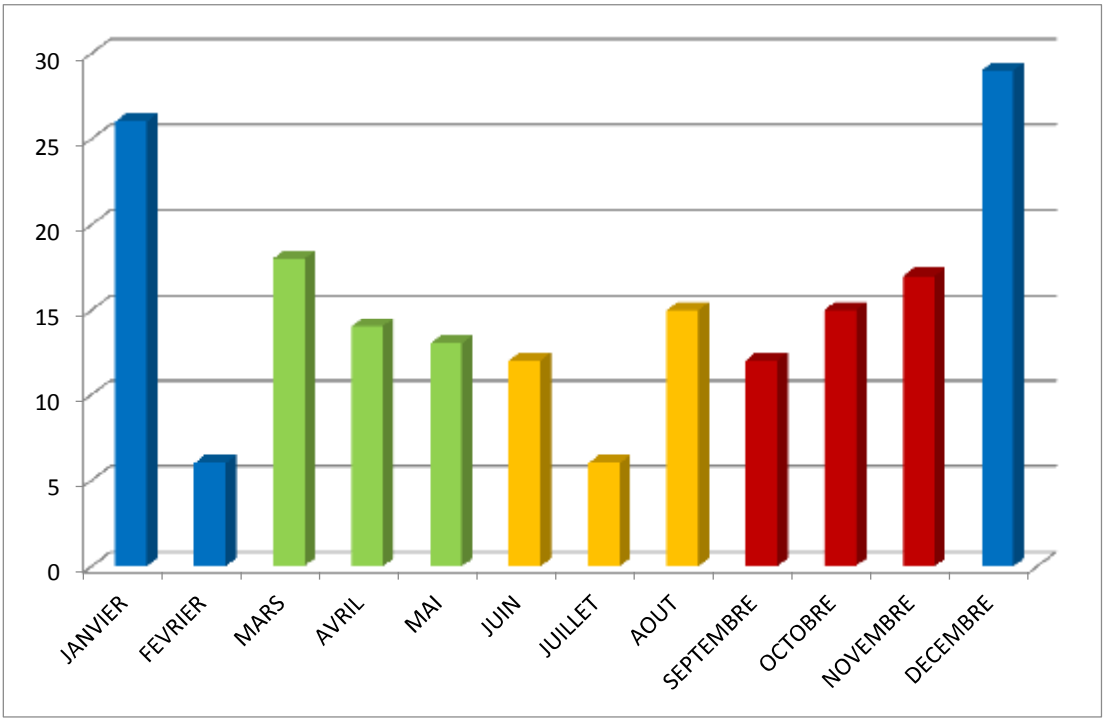


Figure 7 : Répartition des enfants diabétiques selon les mois d'installation du diabète

Les figures 8, 9, 10 et 11 : l'évolution en fonction des années et mois de découverte du diabète :

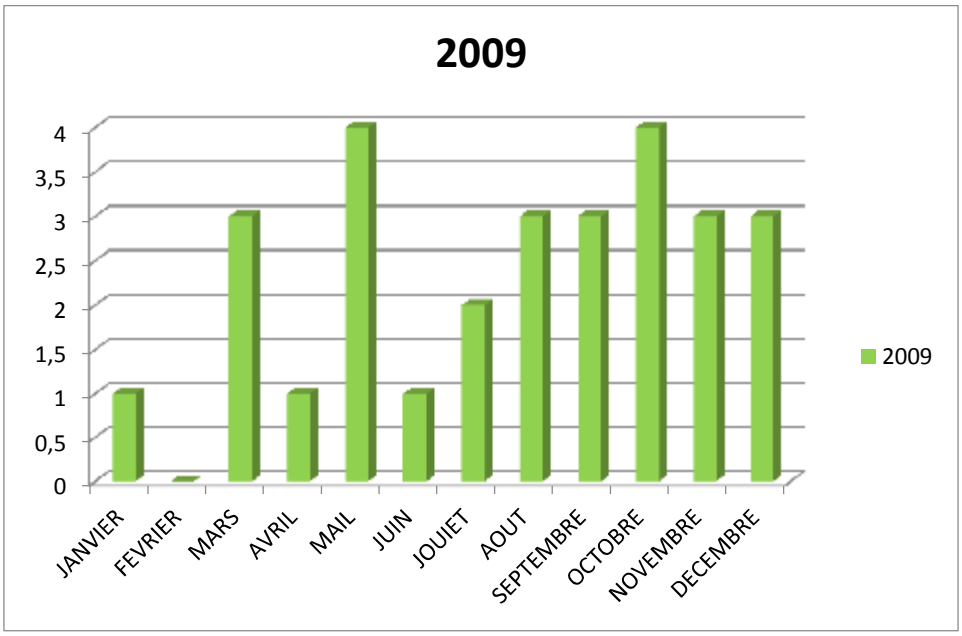


Figure 8 : Répartition des enfants diabétiques selon les mois d'installation du diabète en 2009

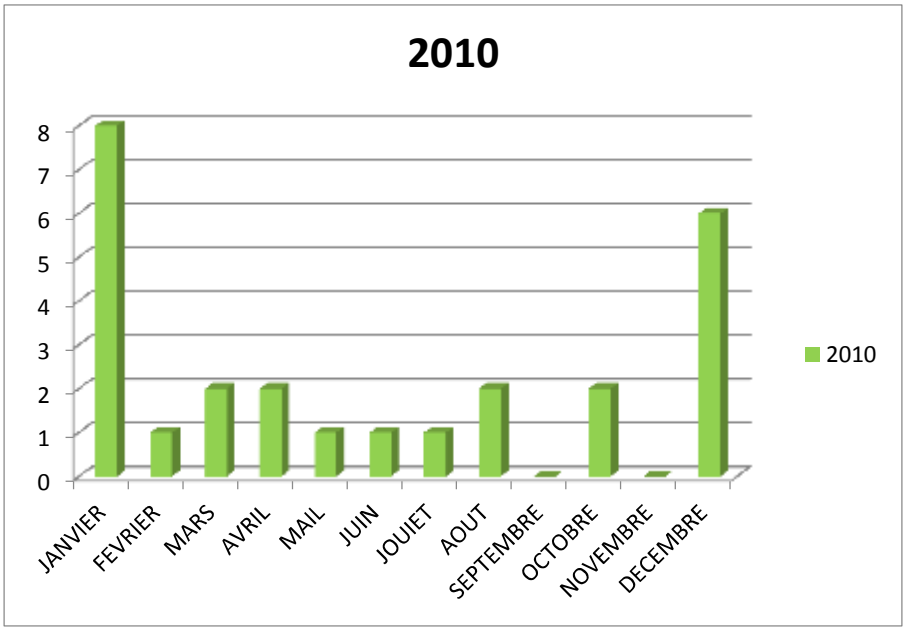


Figure 9 : Répartition des enfants diabétiques selon les mois d'installation du diabète en 2010

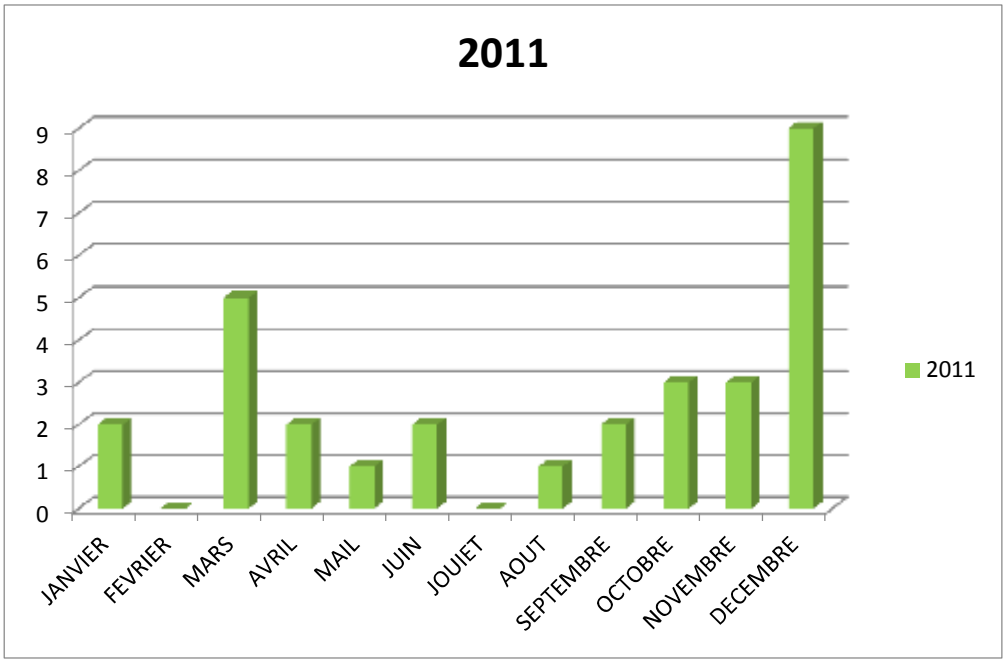


Figure 10 :Répartition des enfants diabétiques selon les mois d'installation du diabète en 2011

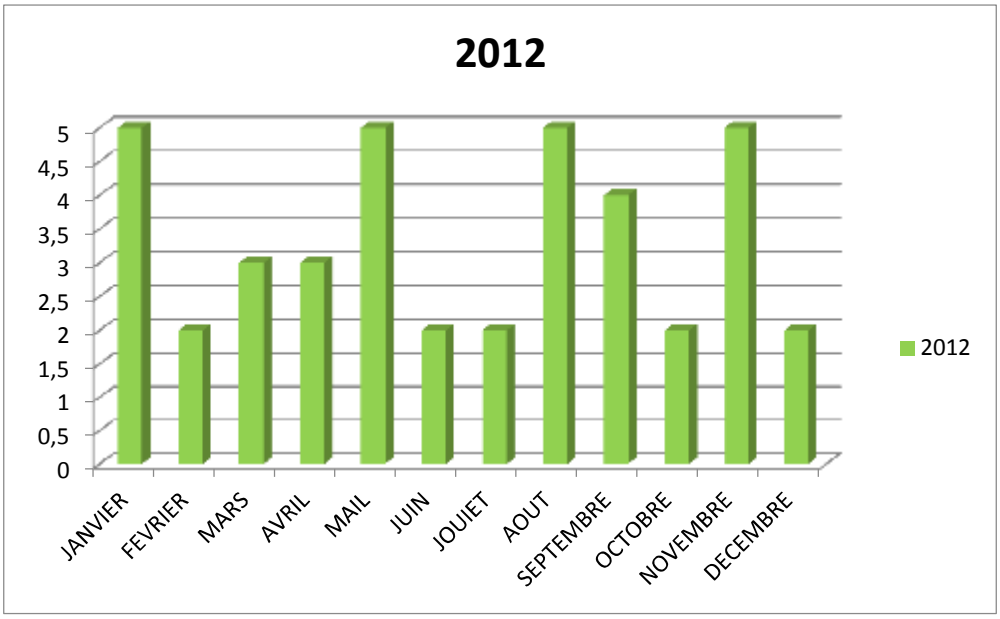


Figure 11 :Répartition des enfants diabétiques selon les mois d'installation du diabète en 2012

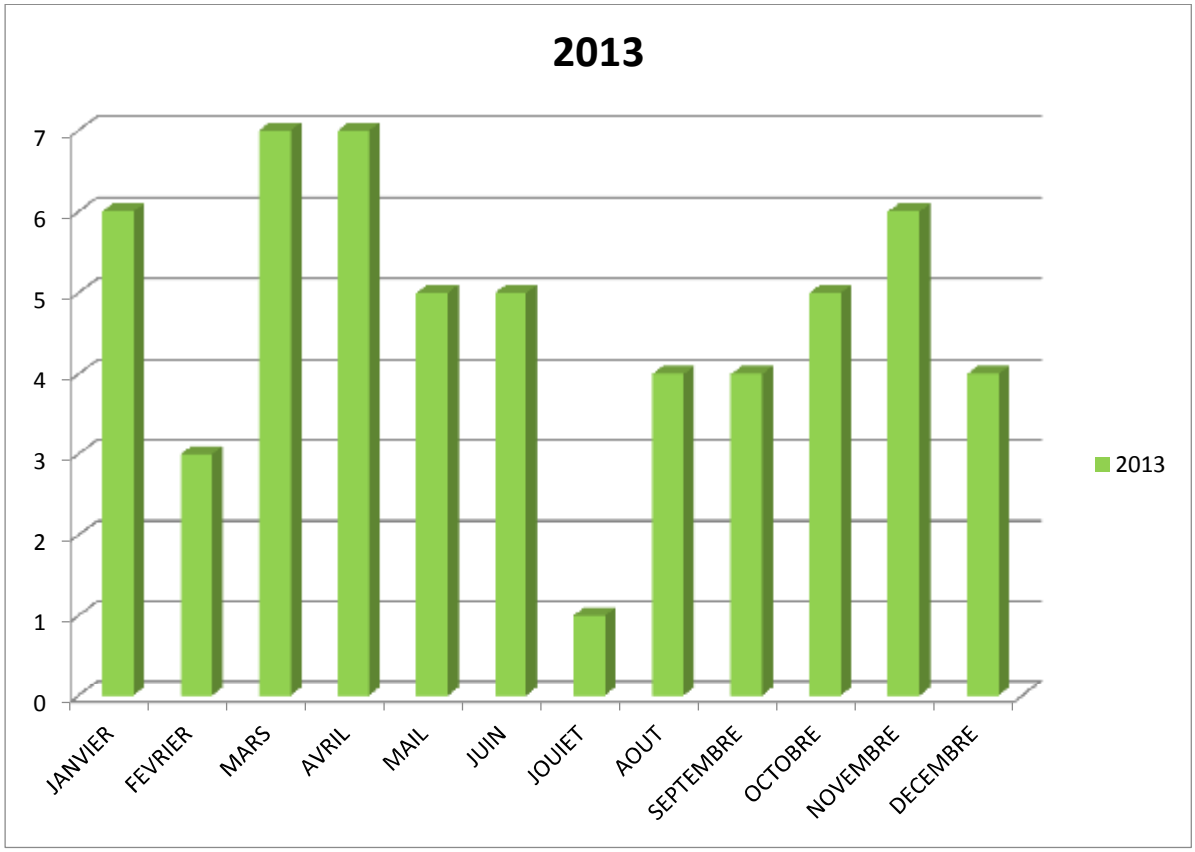


Figure 12 :Répartition des enfants diabétiques selon les mois d'installation du diabète en 2013

2 - Antécédents :

2.1 - Personnels

- On a révélé sept antécédents de grossesse pathologique (Deux cas de menace d'accouchement prématuré, deux cas allo immunisation fœto-maternelle ,une HTA gestationnelle, un diabète gestationnel et une anémie maternelle) avec 16 césariennes et un cas de souffrance néonatale.

Tableau 2 : Enfants diabétiques nés par césarienne

Nombre de cas	Indication de la césarienne
3	Défaut d'engagement à dilatation complète
2	Bassin rétréci
2	HTA gestationnelle
2	Macrosomie+diabète gestationnel
2	Utérus doublement cicatriciel
1	Hydrocéphalie prénatale
1	Siège
1	d'accouchement prématuré
1	un cas de présentation transverse
1	chorioamniotite

- L'allaitement maternel :
  - Exclusif chez 45% jusqu'à l'âge de 6 mois.
  - La durée moyenne d'allaitement maternel était de 10 +/-6,46 mois (2 mois à 30 mois).

Tableau 3 : la durée d'allaitement maternel par rapport d'âge de découverte de DT1.

	Age de découverte de DT1 (ans)			
	< 2	2 et 5	5 et 10	> 10
Durée moyenne d'allaitement maternel (mois)	8,64	10,7	9,5	11,5

- **L'âge d'introduction du gluten** a été dans 26% entre 4 et 6 mois, dans 67 % entre 7 et 8 mois, et dans 7% supérieur à 8 mois.

Tableau 4 : la durée d'allaitement maternel fonction de l'âge de découverte de DT1

	Age de découverte de DT1 (ans)			
	< 2	**2 et 5**	**5 et 10**	**> 10**
Age moyen d'introduction du gluten (mois)	5,14	6,50	5,64	6,40

- **Diabète** :

34 enfants ont été connus diabétique admis au service pour prise en charge d'une rechute sur un mode DAC avec une durée moyenne d'évolution du diabète de 48mois.

❖ **Maladies auto-immunes :**

Du point de vue des antécédents personnels de maladies auto-immunes, deux malades étaient connus cœliaques et une autre ayant un ATCD d'hépatite et de thyroïdite auto-immunes.

❖ **Les autres ATCD personnels** sont dominé par les infections à répétition et l'énurésie primaire.

Les antécédents	*Nombre de cas*
Infections à répétition	8
Enurésie primaire	5
Opérés pour Hydrocéphalie	2
Ictère cutanéo-muqueux	3
Ictère néonatal	4
Hypocalcémie	2
Asthme + RGO	1
Allergie aux protéines de lait de vaches	1
Retard psychomoteur	1
Tuberculose pulmonaire	1
Obésité	2
Détresse respiratoire néonatal	1

2.2 – Familiaux

❖ **Consanguinité**

On a trouvé la notion de consanguinité de premier degré dans 10% ; de deuxième degré dans 8% des cas.

❖ **Gémellité**

Deux cas de gémellité ont été notés (faux jumeaux), les deux jumeaux ne sont pas diabétique.

❖ **Diabète familial**

Le diabète type 2 a été retrouvé chez presque 45% des familles des enfants diabétique essentiellement la grande famille (grands parents oncles et tantes). Le diabète de type 1 a été retrouvé chez 6%.

Trois cas de diabète chez les parents : un cas chez la mère(DT2), et deux cas chez le père (1 cas de DT1 ; 1 cas de DT2).

❖ **Antécédent familiaux de pathologie auto-immune :**

Ce type d'antécédent a été noté chez trois malades, il s'agit de 3 enfants dont le premier a une mère cœliaque le deuxième présente un ATCD de maladie de Crohn et d'hypophysite lymphocytaire et dans le troisième cas, il s'agit d'un vitiligo.

❖ **Pathologie thyroïdienne**

Cinq enfants avaient des antécédents de pathologie thyroïdienne dans la famille. Trois enfants avaient des antécédents de goitre dans la famille avec supplémentation hormonale, deux avaient une notion de nodule thyroïdien.

❖ **Autres antécédents familiaux :**

La maladie asthmatique et la notion d'atopie familiale est présente chez quatre familles, l'hypertension artérielle familiale dans deux cas et la notion de contage tuberculeux chez un cas.

3- Révélation du diabète :

3.1 - les prodromes :

Dans la quasi-totalité des cas, le diabète est révélé par un syndrome cardinal, les signes digestifs représentent plus de 40% et les signes respiratoires 26% des cas.les signes neurologiques étaient présents dans 24% des cas, avec deux cas de coma (tableau 1).

Tableau 5 : symptomatologie révélatrice du diabète.

	FREQUENCE EN %
Sd polyurie polydipsie	86
Amaigrissement	60
Polyphagie	32
Anorexie	15
Fièvre	27
Enurésie secondaire	16
Vomissement	52
Douleurs abdominales	45
Signes respiratoires	26
Signes neurologiques	24
Coma	1

La durée moyenne d'évolution des prodromes avant l'admission à l'hôpital était de 21 + /- 15,7 jours (de 2 à 90 jours).Elle était dans 47% supérieure à 15 jours et dans 13% supérieure à 30 jours.

3.2 - Facteurs déclenchant :

Une infection associée était retrouvée chez 30% de nos patients (infections pulmonaires ; ORL ; urinaires ; génitales ; mycosiques et du tractus digestif).

Tableau 6 : les types d'infections chez l'enfant diabétique dans notre série.

TYPE D'INFECTION	PULMONAIRE	ORL	IU	GASTRO-ENTERITE	MYCOSIQUE	GENITALE
FREQUENCE (CAS)	14	9	27	2	2	1

Chez les patients déjà connus diabétiques, c'est l'alimentation non équilibrée qui était le principal facteur de rechute (100%), suivi par la mauvaise observance thérapeutique dans 70% des cas.

4- En hospitalier :

4.1 - secteur d'hospitalisation :

* 12% sont les enfants hospitalisés initialement au service de la réanimation avant d'être référés chez nous.
* 30% ont été hospitalisés au service des urgences.
* 58% les enfants admis directement au service de pédiatrie médical.

4.2 - A l'admission :

* 33% étaient admis dans un tableau d'acidocétose diabétique (ACD+).
* 46% étaient admis pour cétose sans acidose.
* 21% des malades étaient admis pour diabète inaugural (hyperglycémie isolée).

Tableau 7: répartition des enfants diabétique en fonction de l'ancienneté de leur diabète et la présentation clinique.

	NV CAS	RECHUTES
N	149	34
ACD+	44	15
ACD-	105	19
cétose sans acidose	71	14
hyperglycémie isolée	34	5

Parmi les malades déjà connus diabétiques admis en DAC (n=29), 4 patients seulement étaient suivie dans le passé dans notre formation. Deux entre eux ayant rechuté après, une perte de vue de plus de 12 mois à cause de la difficulté d'accès à notre consultation.

Les deux autres patients ayant rechutés suite à la mauvaise diététique, à la mal observance thérapeutique et l'arrêt de l'insulinothérapie.

4.3 - L'examen à l'admission :

4.3.1. L'état hémodynamique :

7 cas étaient admis en instabilité hémodynamique, hospitalisés initialement en secteur de réanimation.

4.3.2. L'état d'hydratation :

L'examen clinique à l'admission a révélé une déshydratation modérée à sévère dans environ 24% des cas.

Les enfants âgés de moins de 2 ont été admis dans 50% en DHA modérée à sévère, 2-5 ans (28%),> 5 ans (11%).

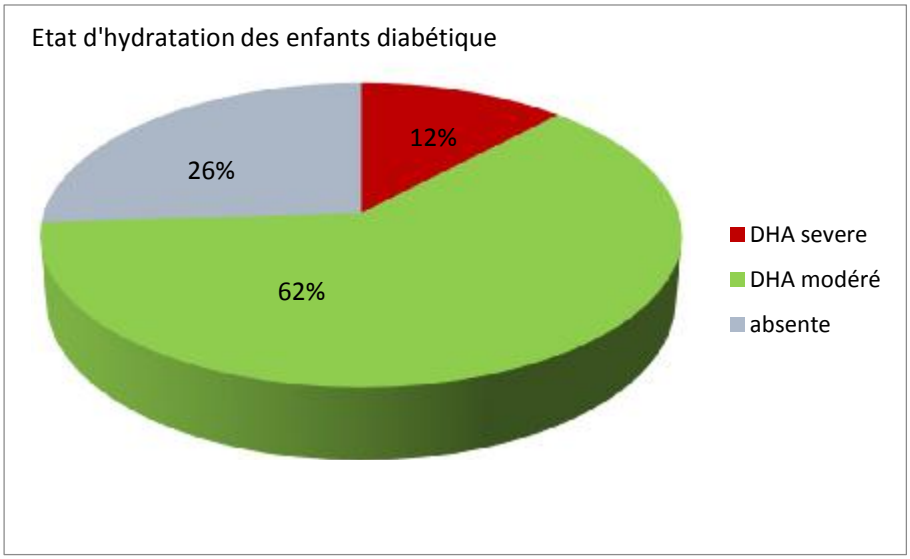


Figure 13 : état de déshydratation chez les enfants diabétiques dans notre série

4.3.3. L'état de conscience :

A l'admission les troubles de conscience étaient présents chez 15,30% des cas. Deux enfants ont été admis en coma

Tableau 8 : état de conscience des enfants diabétiques admis en DAC dans notre série.

GCS	Nombre de cas	Fréquence en(%)
14-15	157	85
8-13	24	13
<8	2	1

4.3.4. Les signes d'acidose :

Les signes d'acidose (haleine acétonémique, dyspnée de Kussmaul, polypnée, déshydratation, tachycardie, polypnée, nausée, vomissement, douleurs abdominales, Confusion, somnolence et altération de la conscience) étaient présents à l'admission chez 30% des patients.

4.3.5. La température :

46 enfants soit 25% avaient une température > 38,4°C à l'admission avec une fièvre notée sans foyer infectieux dans 12% des cas.

4.3.6. Foyer infectieux :

L'examen clinique a objectivé la présence de foyer infectieux chez 35 cas soit 20% (pulmonaire chez 11 enfants, angines chez 9 enfants, urinaire chez 8 enfants, gastro-entérite chez 2 enfants, mycosique chez 2 enfants et 2 cas d'otite moyenne).

4.4 - Para-clinique :

Tous les patients ont bénéficié à l'admission d'une glycémie capillaire et sanguine et d'un examen par kétodiastix à la recherche de glycosurie et de l'acétonurie.

4. 4.1) l'analyse des urines :

Tableau 9 : analyse des urines aux bandelettes chez les enfants diabétiques dans notre série.

	glycosurie		acétonurie	
	Nombre de cas	Fréquence en %	Nombre de cas	Fréquence en %
++	49	27	31	17
+++	66	36	61	33
++++	40	21	47	26

4.4. 2) Glycémie capillaire :

La moyenne des glycémies capillaire de nos patients était de 4+/ - 1,5 g /l .elle était supérieure à 6 g /l dans 20% des cas (38 cas).

4.4.3) Ionogramme :

- **L'équilibre acido-basique :**

Bicarbonates : réalisé chez 30%(55 cas) étaient en moyenne de 11,73 +/ - 6,7 mmol /l avec des valeurs extrêmes allant de 2 à 26 mmol/l.

Le pH est retrouvé sur les dossiers chez deux malades était pour le premier à 7,28 et pour le deuxième à 7,23.

- **La natrémie corrigée :**

La natrémie a été réalisée chez 88% a objectivé une hyper-natrémie dans 5% des cas et une hyponatrémie dans 17%.

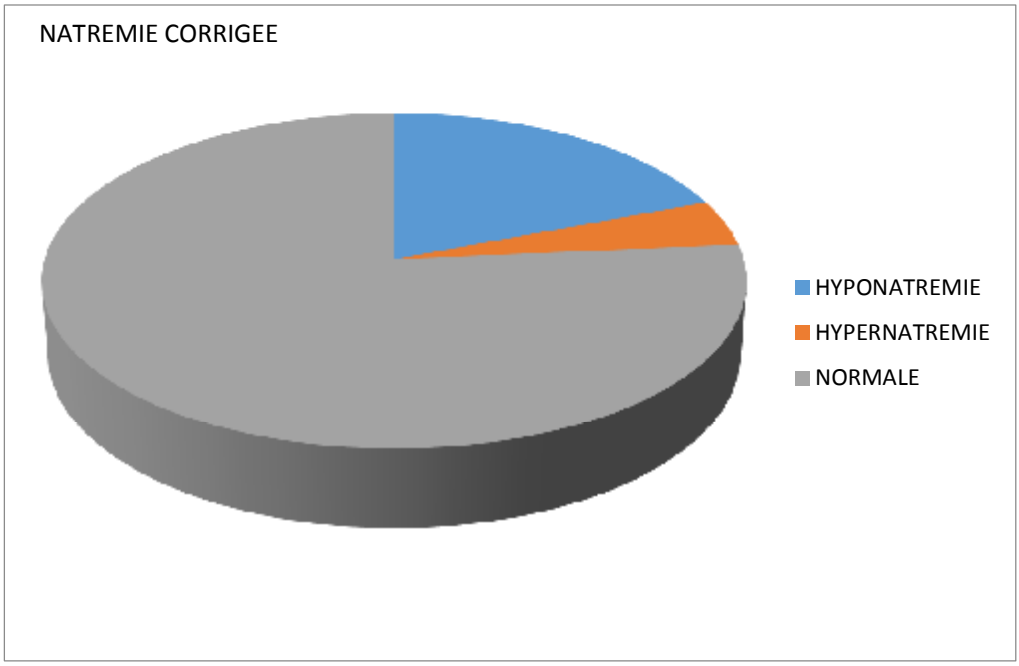


Figure 14 : la natrémie corrigée chez les enfants admis en DAC.

- **La kaliémie mesurée :**

La kaliémie, réalisée chez 84% et dont la moyenne=4,10mEq /L, a révélé 4 cas (2,6%) d'hyperkaliémie et 15 cas (10%) d'hypokaliémie.

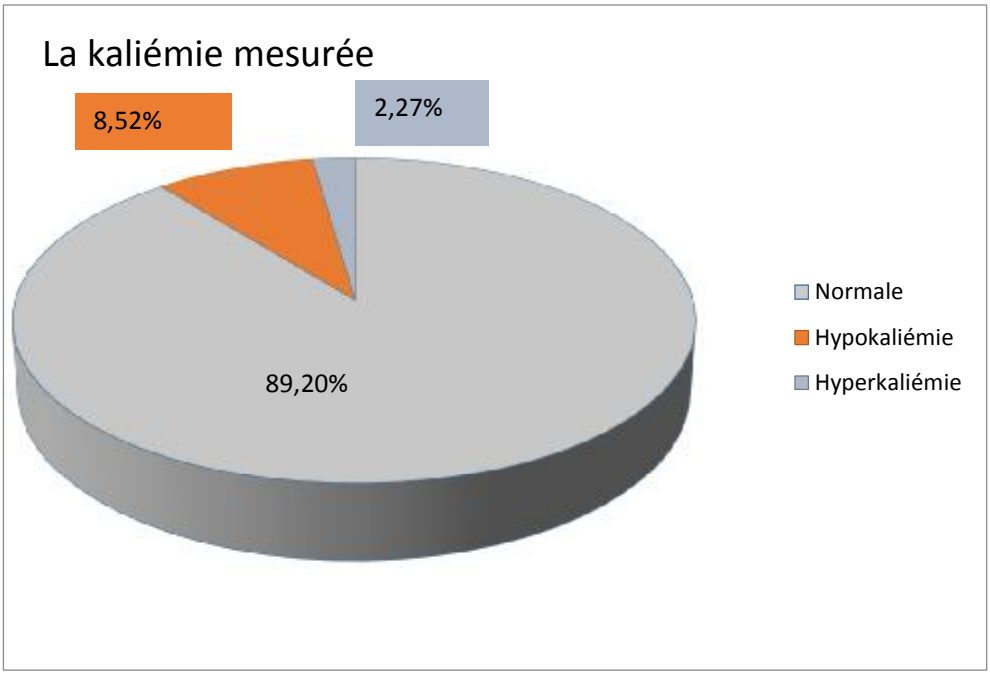


Figure 15 : la kaliémie mesurée chez les enfants admis en DAC.

- **Urée sanguine :**

Réalisée dans 89% avec une moyenne de 0,40g/L.

L'hyper-urémie a été présente chez 12% des enfants diabétique.

- **La créatinine sanguine :**

La créatininémie initiale, réalisée dans 90%des cas, était en moyenne 8,87mg /l avec des valeurs extrêmes allant de 1,8mg/l à 39mg/l.On a noté 12% de cas d'altération de la fonction rénale.

4.4.4) Bilan infectieux :

- **NFS :**

Réalisée chez la quasi-totalité de nos patients (92%).Elle a révélé une hyperleucocytose chez 94 cas (55,62%) avec une moyenne à 18490+ /-7915éléments /mm3.

- **CRP :**

Réalisée chez 82,51% de nos patients, elle était> 6 chez 43% avec une moyenne de 22 ,90+/-32,50 mg /l.

- **ECBU :**

Réalisé chez 153 enfants soit (83%).

15% sont des hyperleucocyturie sans bactériurie significative(cytologies positives avec cultures négatives).

11% sont des cultures positives(7 cas de culture positive à E-Coli ; 4 cas aux entérocoques et seul un cas à Klebsiella).

- **Radiographie thoracique :**

Réalisés chez 125 cas soit (68%) dont 14 étaient pathologiques objectivant un foyer de pneumonie.

- **PL :**

Retrouvée sur les dossiers de 6 malades revenues pour tous les patients en faveur d'une hyperglycorachie avec cytologie négative.

4.4.5) ECG et monitoring ECG :

Effectué chez 82 cas a mis en évidence de signes d'hyperkaliémie dans un seul cas.

4.4.6) Le reste du bilan en fonction du contexte clinique :

TDM cérébrale a été réalisée chez 3 patients pour troubles de conscience sévères revenue normale.

Echographie abdominale chez 8 cas.

4.4.7) Bilan immunologique :

La recherche des Ac des MAI fréquemment associées au DT1 a été effectuée chez malades (45%), ce bilan est revenu positif chez 8 malades.

D'autre part, le dosage des auto-anticorps du DT1 n'a été réalisé que chez 7 patients (revenu positif) :

Tableau 10 : Résultats de recherche des Ac de MAI associées dans notre série.

	Nombre	Auto anticorps positifs
MC isolée	1	AAG+ATG
	2	AAG
	1	AAE
MC+THAI	1	ATG+ATPO
THAI isolée	1	AATG+ATPO
	1	ATPO
THAI+HAI	1	ATPO

(Ac : Anticorps. MC : Maladie cœliaque. THAI : thyroïdite auto-immune. HAI: hépatite auto immune. AAG: Ac anti-gliadine. ATG: Ac anti-transglutaminase. AAE: Ac anti-endomysium. ATPO: Ac anti-thyro-peroxydase. AATG: Ac anti-thyroglobuline).

* le bilan thyroïdien réalisé dans 40% des cas a objectivé 3 cas de THAI.
* La recherche de la maladie cœliaque a été faite chez 52% des cas dont seulement5 cas, revenu positive.
* Le dosage de la vitamine D est réalisé dans 54% mettant en évidence 3 cas de carence en vit D et 9 cas d'insuffisance en vit D.

4-5-thérapeutique :

4.5.1) Traitement pharmacologique :

- 78% de nos patients ont reçus le schéma de l'insulinothérapie IV + remplissage avec réhydratation par voie IV dont 70% ont bénéficié d'un remplissage par sérum salé, et 14% d'une perfusion de sérum bicarbonaté.
- 12% ont suivi le protocole d'insulinothérapie à la SAP.
- Le délai moyenne du passage à l'insulinothérapie par voie sous cutanée était de 34,41 +/-21,30 heures.
- Le relais par l'insulinothérapie par voie sous cutanée a été fait selon le schéma de deux injections par jour associant l'insuline rapide et intermédiaire chez 88% de nos patients avec une dose moyenne d'insuline de 0,81UI/Kg/J.

- 32 patients (22,5%) ont bénéficiés de schéma des analogues ultra rapides avec plusieurs injections quotidiennes fonction dextro.
- L'administration des analogues de l'insuline à longue durée d'action avec des boulus des analogues ultra-rapides a été réalisée chez 21 cas (15%).

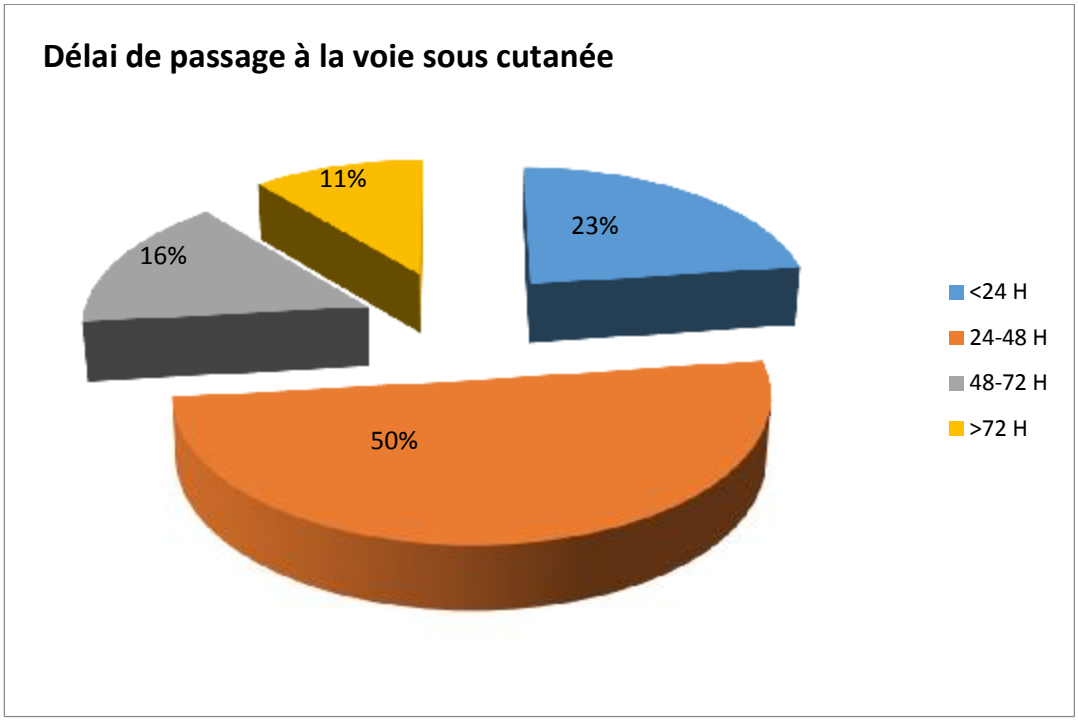


Figure 16 : délai de passage à la voie sous cutanée.

4.5.2) Le traitement adjuvant :

39% de nos malades ont bénéficié d'un traitement antibiotique.

Les antifongiques locaux ont été instaurés chez 3 malades (1,6%).

4.5.3) Evolution :

L'évolution immédiate était généralement bonne chez tous nos patients sans décès.

Au secteur de réanimation : on a noté 2 cas d'hypoglycémie sévère jugulés rapidement, 12 cas d'hypoglycémie modérée, huit cas d'hypokaliémie.

Au service de pédiatrie médicale, il a été enregistré 2 cas d'hypoglycémie modérée et un seul cas d'hypokaliémie.

Le délai moyen d'amélioration était de 42+/- 22 heures.

4.5.4) Education thérapeutique :

Tous nos patients ont bénéficié de séances d'éducation dès l'instauration du diagnostic.

4.5.5) Hospitalisation :

La durée moyenne d'hospitalisation au service de pédiatrie était de 8,5 jours.

Les enfants diabétiques étaient accompagnés par leurs mères au cours de l'hospitalisation dans 90% des cas.

On a noté 22 cas (12%) de séjour au service de la réanimation avec une durée moyenne d'hospitalisation de 5,8 jours.

II-ETUDE ANALYTIQUE

1 - Population étudiée

L'ensemble du recueil, soumis aux critères d'inclusion et d'exclusion, a abouti à une sélection finale de 149 enfants nouvellement diagnostiqués diabétiques entre le 01/01/2009 et le 31/12/2013.

Le tableau 11 renseigne sur la répartition des enfants en fonction de leur année de prise en charge diagnostique et le mode de révélation en effectif (n) et en pourcentage (%).

Tableau 11 : la répartition des enfants en fonction de leur année de prise en charge diagnostique et le mode de révélation

		2009	2010	2011	2012	2013
Nouveaux cas (total)	N	18	20	26	36	49
ACD-	n	11	12	19	27	36
	%	61	60	73	75	78
Cétose sans acidose	n	9	8	8	18	23
	%	50	40	31	50	47
hyperglycémie isolée	n	2	4	11	9	13
	%	16	20	42	25	33
ACD+	n	7	8	7	9	13
	%	**39**	**40**	**26**	**25**	**22**
ACD++	n	2	2	4	2	4
	%	**11**	**10**	**7,7**	**9**	**8**

Globalement, le nombre de prise en charge diagnostique annuelle a augmenté depuis 2009, avec un accroissement de 60% jusque 2013.

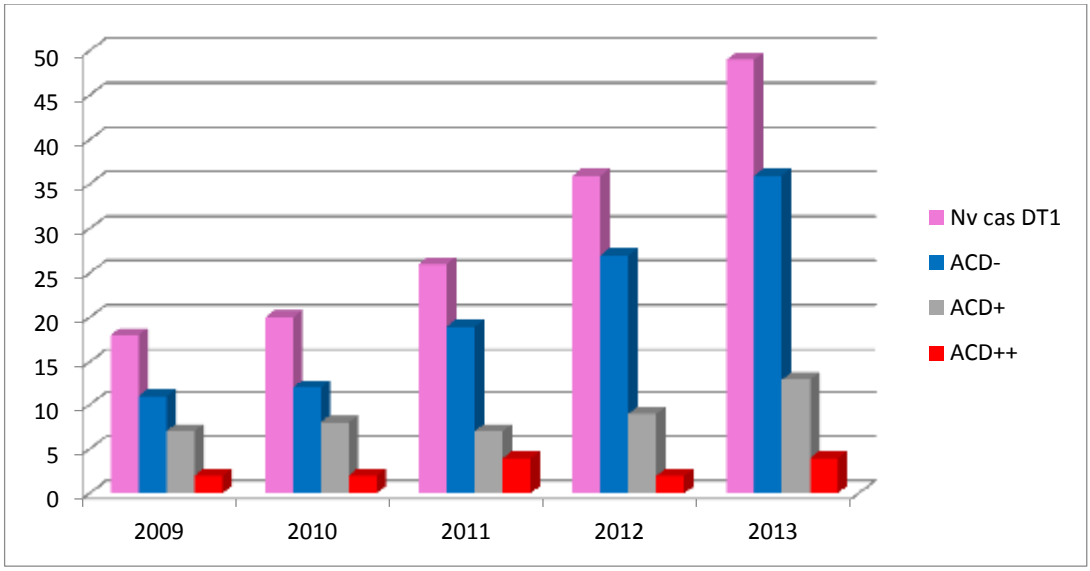


Figure 17 : Répartition des enfants en fonction de leur année de prise en charge diagnostique et mode de révélation de diabète

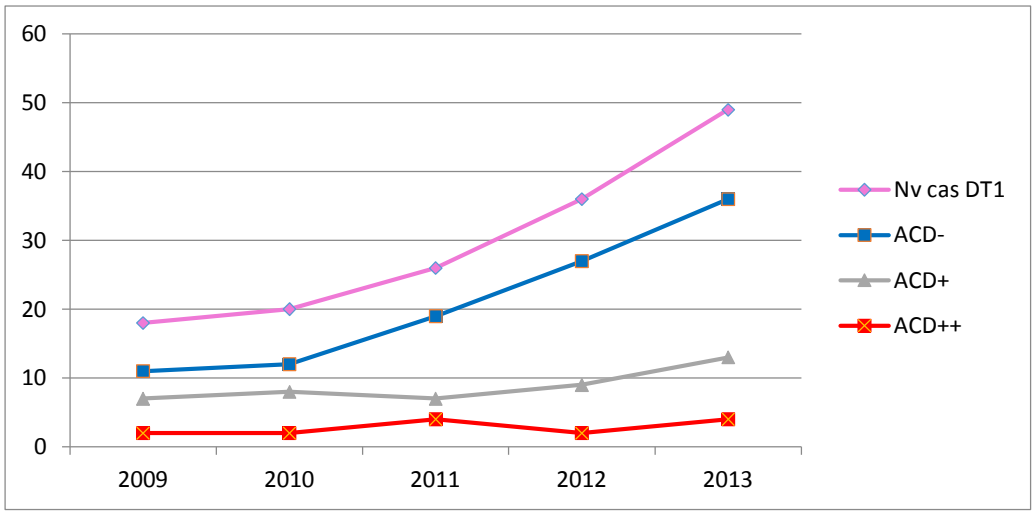


Figure 18 : Evolution annuelle du nombre d'enfants diabétiques pris en charge au diagnostic. Courbe de tendance en pointillés.

L'acidocétose a révélé le diabète de type 1 chez 44 enfants dont 14 formes sévères, soit un taux d'acidocétose inaugurale de 29,5%. L'acidocétose sévère a représenté 32% des cas d'acidocétose et 9% des formes de révélation du diabète de type 1 (tableau 2 et figure 2).

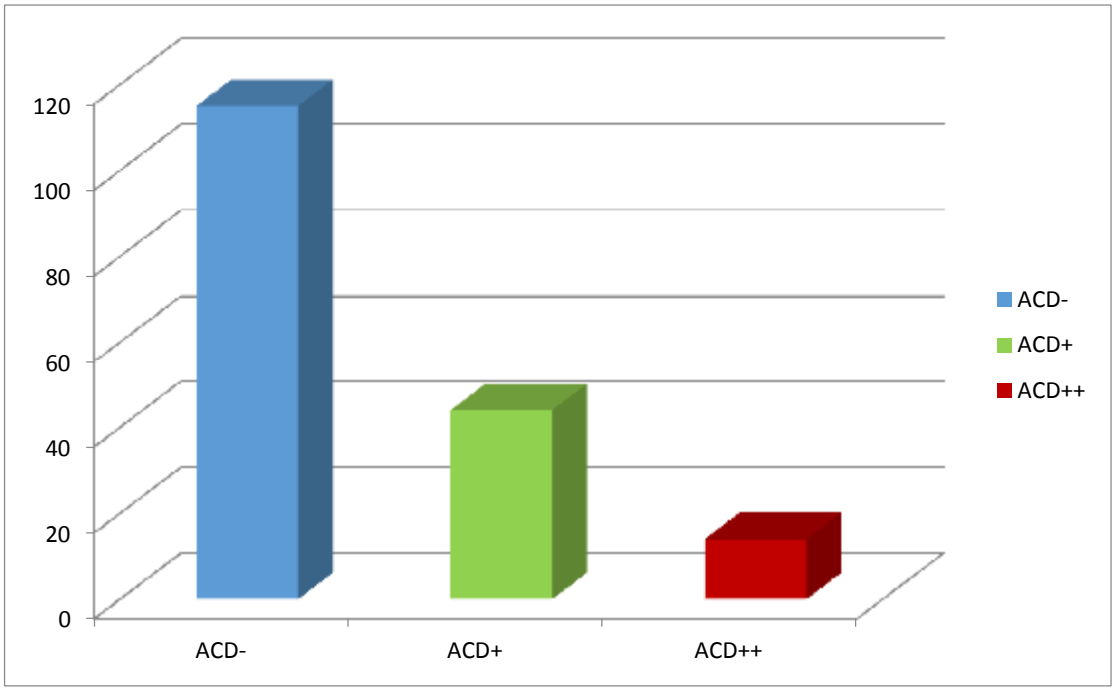


Figure 19 : formes de révélation du diabète de type 1.

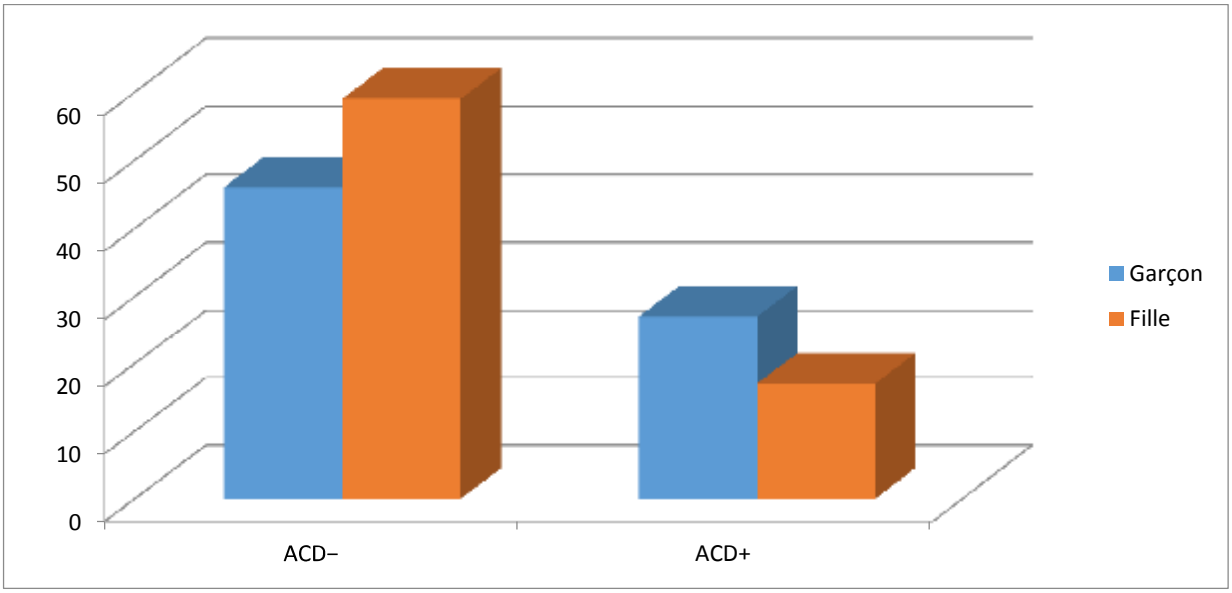
2 - Analyse des paramètres épidémiologiques

2.1) Le sexe

Tableau 12 : corrélation entre le sexe et ACD+

		ACD+	*ACD-*	*p*
SEXE	**F**	39%	57%	**NS**
	G	61%	43%	

Sex Ratio (SR) était de 0,95/1, La répartition garçons/filles n'est pas restée équivalente dans chaque groupe [43% de garçons (ACD -), 61% (ACD +), Non Significatif (NS)].



La figure 20 : la répartition des nouveaux cas de diabète de type 1 en fonction du sexe, et du mode de présentation initiale

2.2) L'âge :

Tableau 13 : corrélation entre l'âge et ACD+

	ACD+	*ACD−*	*p*
AGE	5,27	6,73	0,037

L'âge moyen au diagnostic a été de 5,27 ± 4,11 ans pour le groupe de ACD+ et 6,73 ± 3,76 ans pour le groupe de ACD – avec différence significative (p=0,037).

La répartition par groupes d'âge est détaillée sur la figure 21.

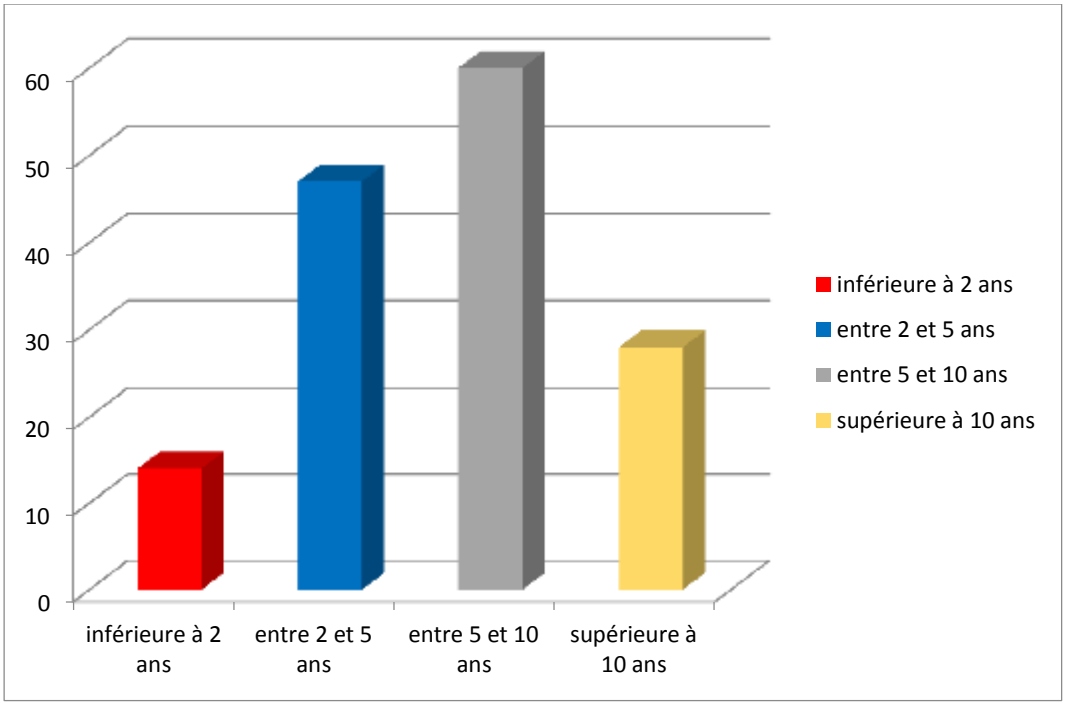


Figure 21. Répartition de la population diabétique par groupe d'âge.

L'évolution annuelle du nombre d'enfants révélés diabétiques est variable selon l'âge au diagnostic, comme montrée sur la figure 4.

La proportion d'enfants de moins de cinq ans pris en charge pour un diabète de type 1 a fortement crû au fil des années. Elle a représenté le troisième groupe en 2009 alors qu'en 2013 elle se situe en première position.

L'évolution annuelle de La tranche d'âge des enfants < de 2 ans s'est multiplié par 5 du 2009 au 2013.

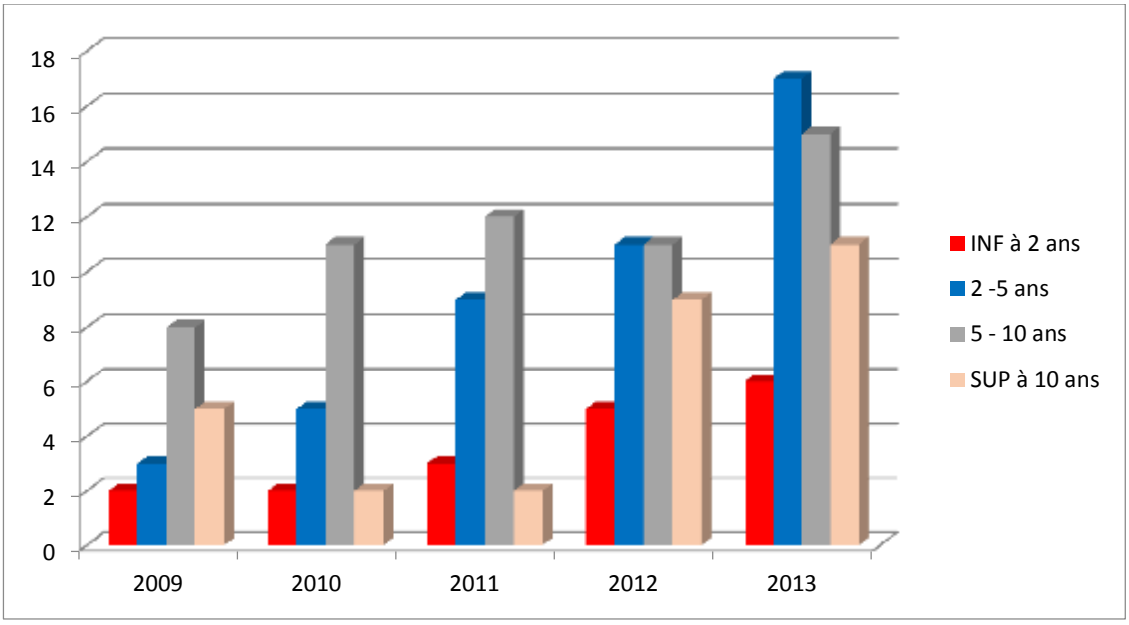


Figure 22. Evolution du nombre de nouveaux diagnostics par groupe d'âge, et par année.

Dans le groupe ACD -, la classe d'âge la plus représentée était celle des 5 -10 ans, alors que dans le groupe ACD +, 0- 5 ans prédominait .

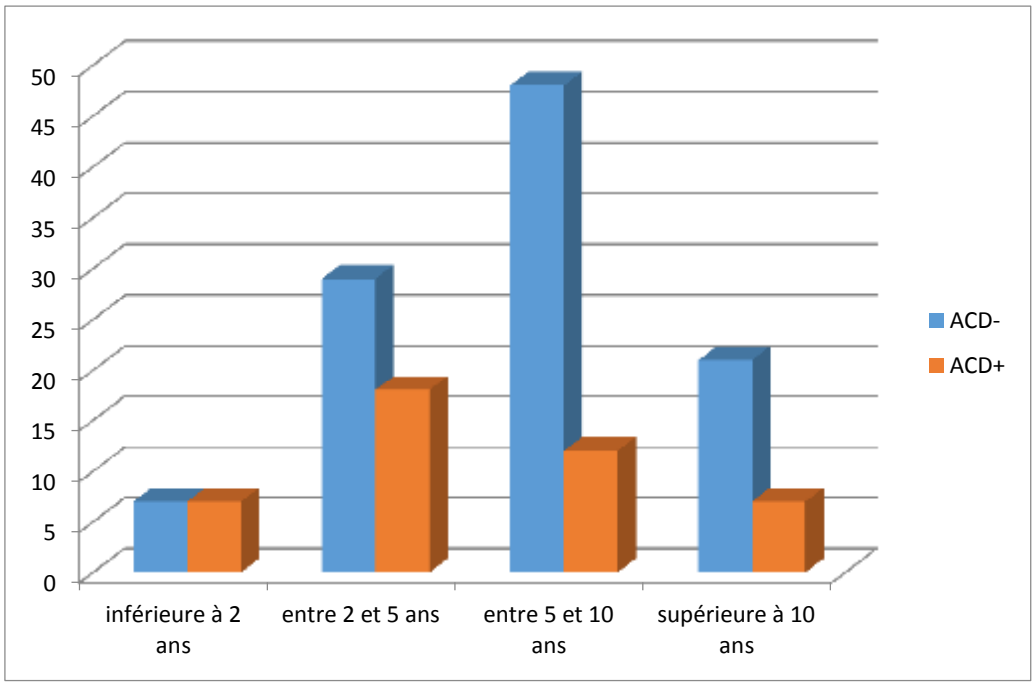


Figure 23. Répartition, par groupe d'âge, des nouveaux cas de diabète de type 1 selon le mode de présentation initiale.

Tableau 14 : corrélation entre l'âge < 5 ans et ACD+.

	ACD+	*ACD-*	*p*
< 5 ans	56%	34%	0,011

Il y a eu plus de révélations de diabète de type 1 sous forme d'acidocétose chez les enfants de moins de 5 ans plus précisément, les moins de 5 ans représentaient 34% du groupe ACD -, et 56% du groupe ACD + **(différence significative avec p=0,011).**

2.3) Saison :

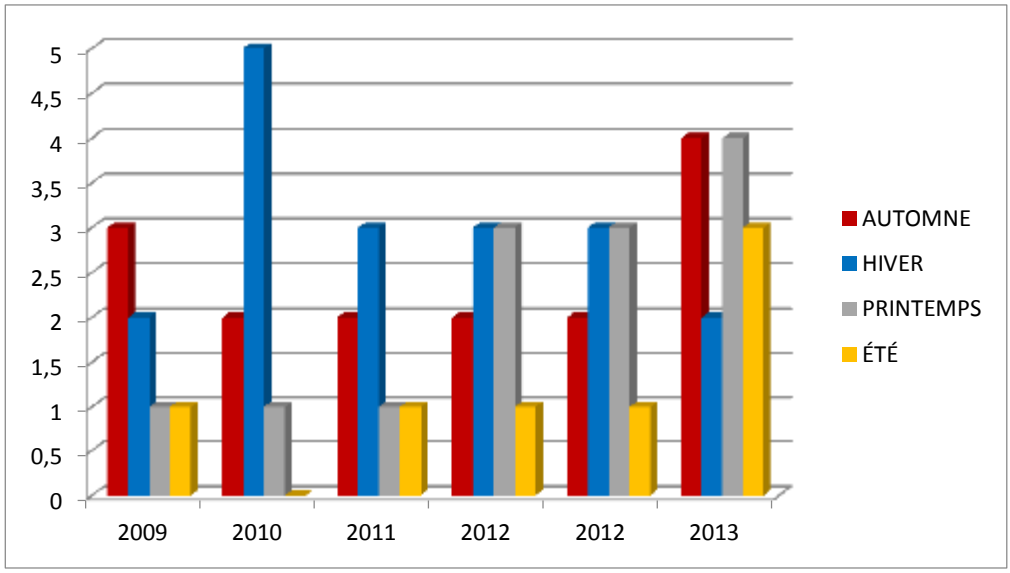


Figure 24 : répartition des nouveau cas en fonction des années et des saisons

2.4) L'origine et lieu de résidence :

Tableau 15 : corrélation entre l'origine rurale et ACD+.

	ACD+	*ACD-*	*p*
Origine rurale	48%	22%	0,02

La majorité de nos enfants étaient d'origine urbaine alors que **l'origine rurale**ne représentait que 30%.(**48% du groupe ACD+/ 22% du groupe ACD avec une différence significative ; p=0,02.**)

2.5) Niveau socioéconomique :

Tableau 16 : corrélation entre le BNSE et ACD+.

	ACD+	*ACD-*	*p*
BNSE	68%	49%	0,037

Il y a eu plus de révélations de diabète de type 1 sous forme acidocétosique chez les enfants de **bas niveau socioéconomique(68% des familles du groupe ACD + se considéraient plutôt de bas niveau socioéconomique contre 49% des familles de groupe ACD− ;avec une différence significative ; p=0,037)**

3 - Antécédents familiaux de diabète :

Tableau 17 : corrélation entre les ATCD familiaux de diabète et ACD+

	ACD+	*ACD-*	*p*
ATCD familiaux de diabète	28%	52%	0,007

Des antécédents familiaux de diabète étaient retrouvés chez 44,3% des patients diagnostiqués diabétiques.

La répartition des antécédents de diabète est différente d'une façon significative.

Il y avait plus d'enfants **sans antécédents familiaux** de diabète dans le groupe ACD + (72%) que dans le groupe ACD - (48%), avec différence significative p=0,007.

Il semble que d'avoir des antécédents familiaux de diabète est un facteur protecteur de révélation de DT1 par ACD+.

4 - Circonstances de découverte du diabète :

4.1. Prodromes et symptômes présentés

Tableau 18. Description clinique des symptômes présentés avant le diagnostic - en effectif (n) et en pourcentage(%) -

	ACD+		*ACD −*		*p*
	n	%	n	%	
SPP	40	90	103	98	NS
AMG	27	61	79	75	NS
POLYPHAGIE	13	29	44	42	NS
ANOREXIE	8	18	14	13	NS
FIEVRE	15	34	25	24	NS
ENURESIE II	6	13	21	20	NS
VOMISSEMENT	34	77	32	30	<0,001
DL ABD	33	75	26	25	=0,02
SN RESP	25	56	8	8	<0,001
TR CONSC	23	52	7	6,50	<0,001

Le syndrome polyuro-polydispsique était au premier plan. Les symptômes digestifs faisaient essentiellement partie du tableau clinique des acidocétoses inaugurales, **de manière significative (p<0,001).**

4.2. La confirmation diagnostique :

Les enfants se sont rendus à l'hôpital, adressés par des médecins généralistes [39% (ACD -), 34% (ACD +), NS]. Les familles ont pris elles-mêmes l'initiative de consulter à l'hôpital dans 26% des cas du groupe ACD – et dans 20% des cas du groupe ACD +.

Les pédiatres étaient sollicités dans [24% (ACD –), 15,5% (ACD +), NS]. L'admission en hospitalisation était aussi assurée dans le cadre de transferts inter-hospitaliers secondaires [20% (ACD –), 31% (ACD +), NS].

Dans le groupe ACD –, le diagnostic était posé le plus souvent en ambulatoire par le médecin traitant de l'enfant, alors que dans le groupe ACD +, le diagnostic était fait lors de l'admission dans la structure hospitalière d'accueil (service des urgences , service spécialisé).

Les familles ont également été à l'origine de quelques diagnostics.

Le diagnostic était porté avant l'hospitalisation chez 61% des enfants du groupe ACD –, et 37% des diagnostics du groupe ACD + ,alors que 63% des diagnostics positifs au sein du groupe ACD+ étaient posés en hospitalisation (**avec différence significative p=0,006**) .

4.3 Durée d'évolution des prodromes :

Tableau 19 : corrélation entre la durée d'évolution des prodromes et ACD+

	ACD+	*ACD–*	*p*
Durée moyenne d'évolution des SP	29,76	21,13	0,02

La durée moyenne d'évolution des symptômes était de 21,13 ± 15,08 jours chez le groupe ACD– ; 29,76 ± 15,39 jours chez le groupe ACD+ (avec **différence significative entre les deux groupes ; p=0,02).**

La durée d'évolution des symptômes était supérieure **un mois** chez 30% des cas d'ACD+ ; 10% dans le groupe ACD–(avec différence significative p=0,01).

4.4. Le délai entre la première consultation et l'hospitalisation (retard diagnostic) :

Tableau 20 : corrélation entre le retard diagnostique et ACD+

	ACD+	*ACD-*	*p*
Le délai entre la première consultation et l'hospitalisation (jours)	2,26	1,48	0,001

Le délai entre la première consultation et l'hospitalisation était plus marqué dans le groupe ACD +, avec une moyenne de 2,26 ± 1,4 jours, et avec 56% enfants adressés dans un délai dépassant les 24 heures.

Pour le groupe ACD− la moyenne de délai entre la première consultation médicale et l'hospitalisation était de 1,48 ± 1,17 jour.

Il existe une différence significative entre les groupes (p=0,001).

Deux explications ont été apportées pour justifier ce délai :

- Soit le diagnostic était fait avant l'hospitalisation, mais des examens complémentaires biologiques étaient réalisés en ambulatoire.
- Soit le diabète n'était pas reconnu et d'autres diagnostics erronés étaient évoqués.

Dans le groupe ACD -, le délai de prise en charge hospitalière était lié aux examens complémentaires dans 70% des cas. Dans le groupe ACD +, ce sont les erreurs diagnostiques (62%) qui ont retardé l'hospitalisation.

5 - En hospitalier :

5.1 Tableau clinique et biologique à l'admission.

Les enfants diabétiques révélés par une acidocétose présentaient un tableau clinique plus bruyant. Au premier plan, étaient des troubles digestifs (vomissements), associés à une déshydratation et une perte de poids dépassant le plus souvent les 10% du poids du corps.

La polypnée et les troubles neurologique accompagnaient le tableau.

Dans le groupe ACD -, 51% des enfants étaient dans une situation de cétose sans acidose. Le diagnostic de cétose était le plus souvent fait par l'analyse urinaire. La mesure de la cétonémie capillaire n'est pas était utilisée dans les deux groupes .

Le dosage de l'HbA1c ne montrait pas de différence significative entre les deux groupes (9,80%ACD+ ; 9,20%ACD-).

Le traitement basé sur l'insulinothérapie variait significativement dans les deux groupes par sa voie d'administration. La voie d'administration de l'insuline était sous-cutanée dans le groupe ACD - dans 40%), alors qu'était privilégiéela voie intraveineuse dans le groupe ACD + (100%, $p<0,0001$).

5.2 Durée d'hospitalisation

Tableau 21 : corrélation entre la durée d'hospitalisation et ACD+.

	ACD+	*ACD-*	*p*
Durée d'hospitalisation	11	8	NS

La durée d'hospitalisation (en jours), indépendamment du secteur, n'est pas significativement différente entre les deux groupes[8 ± 4 (ACD -), 11 ± 12 (ACD +) , NS].

Le séjour en réanimation concernait seulement le groupe ACD +, avec une durée moyenne de 1,65 ± 3,7 jours (p<0,0001).

5 .3 durée totale de perfusion :

Tableau 22 : corrélation entre la durée totale de perfusion et ACD+.

	ACD+	*ACD−*	*p*
Durée totale de perfusion (heures)	42	31	0,01

Elle était en moyen 31 ± 20 heures pour le groupe ACD− ; 42 ± 20 heure (ACD+) ; p=0,01.

5.4 Délai d'amélioration :

Tableau 23 : corrélation entre le délai d'amélioration et ACD+.

	ACD+	*ACD−*	*p*
Délai d'amélioration (heure)	52	36	<0,001

La moyenne du délai d'amélioration était 36 ± 16,5 heures(ACD−) 52 ,6 ± 23,5 heures (ACD+) ; p<0,001.

5.5 Délai de passage à la voie sous cutanée :

Tableau 24 : corrélation entre le Délai de passage à la voie sous cutanée et ACD+.

	ACD+	*ACD-*	*p*
Délai de passage à la voie SC (heures)	39	27	=0,04

Il était en moyen de 27,5 ± 20 heures (ACD−), 39 ± 21heures (ACD+) ; p=0,04.

5.6. Complications :

Les complications thérapeutiques ou iatrogènes avaient concerné 18% des cas du groupe ACD+ ; 6% groupe ACD− ; p=0,018.Au total 12 cas (3 cas d'hypokaliémie

et 9 cas d'hypoglycémie sans aucun cas de décès) dont 9 étaient hospitalisés à la réanimation.

Le tableau 25 résume les caractéristiques de la population présentant une ACD+ comparées au celles du groupe ACD-.

Tableau 25 : les caractéristiques de la population présentant une ACD+ comparées au celles du groupe ACD-

		ACD+	ACD-	p
Paramètres épidémiologiques				
	SEX F	39%	57%	NS
	G	61%	43%	
	AGE moyen	5,27	6,73	0,037
	< 5 ans	56%	34%	0,011
	Origine rurale	48%	22%	0,02
	BNSE	68%	49%	0,037
	ATCD familiaux de diabète	28%	52%	0,007
paramètres cliniques				
	SPP	90%	98%	NS
	AMG	61%	75%	NS
	POLYPHAGIE	29%	42%	NS
	ANOREXIE	18%	13%	NS
	FIEVRE	34%	24%	NS
	ENURESIE II	13%	20%	NS
	VOMISSEMENT	77%	30%	<0,001
	DL ABD	75%	25%	0,02
	SN RESP	56%	8%	<0,001
	TR CONSC	52%	6,50%	<0,001
	Durée moyenne d'évolution des SN	29,76	21,13	0,02
	Le délai entre la première consultation et l'hospitalisation (jours) : retard diagnostic	2,26	1,48	0,001
paramètres thérapeutiques	Durée d'hospitalisation	11	8	NS
	Durée totale de perfusion (heures)	42	31	0,01
	Délai d'amélioration (heure)	52	36	<0,001
	Délai de passage à la voie SC (heure)	39	27	0,04

6 – Sévérité de l'acidocétose inaugurale

6.1. Caractéristiques générales

Le tableau 26 reprend les caractéristiques de la population d'enfants ayant présenté une acidocétose inaugurale sévère (ACD ++), comparativement à ceux ayant fait une acidocétose (ACD +).

Tableau 26 : les caractéristiques de la population présentant une ACD++ comparées au celles du groupe ACD+

		ACD++	ACD+	p	
Paramètres épidémiologiques	AGE moyen	2 ,64	5,27	0,037	
	< 5 ans	83%	43%	0,008	
	<2 ans	50%	2%	<0,001	
	Origine rurale	50%	45%	NS	
	BNSE	68%	56%	NS	
	ATCD familiaux de diabète	21%	28%	NS	
paramètres cliniques					
	SPP	78	96	NS	
	AMG	78	53	NS	
	POLYPHAGIE	28	30	NS	
	ANOREXIE	21	16	NS	
	FIEVRE	50	26	NS	
	ENURESIE II	0	73	NS	
	VOMISSEMENT	78	70	NS	
	DL ABD	78	70	NS	
	SN RESP	78	46	0,045	
	TR CONSC	71	20	<0,001	
	Durée moyenne d'évolution des SN	32	29	NS	
	Le délai entre la première consultation et l'hospitalisation (jours) :retard diagnostic	2,42	2,26	NS	
paramètres thérapeutiques					
	Durée d'hospitalisation	9	10,72	NS	
	Durée totale de perfusion (heures)	44	41	NS	
	Délai d'amélioration (heure)	60	49	NS	
	Délai de passage à la voie SC (heure)	39,5	38,5	NS	

6.2. Age :

L'âge moyen des enfants avec ACD ++ était plus bas que dans l'autre groupe 2,64±2 (ACD++) 6,5±4,1 (ACD+) avec une différence significative ; p=0,003.

La proportion de jeunes enfants (<5 ans) supérieure [43% (ACD +), 83% (ACD ++), p=0,008].

Les enfants diabétiques < 2 ans représentaient 50% des ACD++, sans aucun cas noté dans le groupe ACD+.

Il n'y a pas eu de forme sévère d'acidocétose chez les 10 ans et plus.

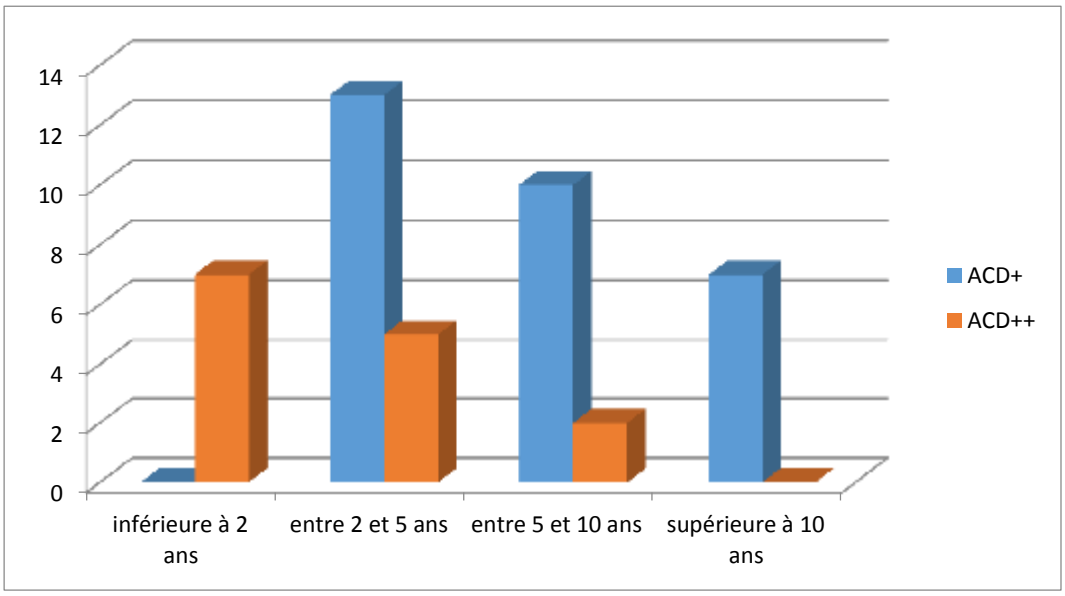


Figure 25. Répartition par groupes d'âge des acidocétoses modérées (ACD +) et sévères (ACD++)

L'Acidocétose diabétique sévère ACD++ se démarque significativement par la sévérité du tableau clinique avec la présence de critères de gravité (déshydratation, polypnée et troubles de conscience) et une symptomatologie digestive plus marquée .

6.3. Facteurs prédisposant à la sévérité de l'acidocétose :

L'analyse paramètres épidémiologiques les antécédents personnels et familiaux et de la présentation clinico-biologique pour permettre d'identifier des facteurs qui peuvent êtres prédictifs de la sévérité de l'acidocétose diabétique inaugurale.

En sont ressorties une seule différence significative portant sur l'âge de découverte plus jeune (<5 ans ; p=0,008/<2 ans ; p<<0,0001).

DISCUSSION

I - Epidémiologie (données de la littérature):

Le diabète sucré est l'une des pathologies chroniques les plus fréquentes chez l'enfant, essentiellement sous sa forme auto-immune, insulinodépendante, communément appelée « type 1 ».

Depuis ces vingt dernières années, on note une incidence croissante du diabète de type 1 à travers le monde [1]. Plus particulièrement en Europe, le taux d'accroissement annuel a été estimé à 3,4% sur la période 1989-1998 et à 3,3% sur celle étalant du 1999 à 2008, en soulignant de grandes disparités géographiques [2-4].

Certains auteurs rapportent que l'augmentation du taux d'incidence touche surtout les enfants des pays en développement ou ceux en transition économique au cours des dernières décennies [3,5]. Mais Il existe des preuves pour un plateau d'incidence dans certains pays au cours des dernières années [6-10].

Au delà de l'augmentation globale de l'incidence du diabète de type 1, ces études mettent l'accent sur la tranche d'âge 0-4 ans qui connaît un taux d'accroissement annuel très important (0-4 =7,59% ; 5-9=4,09% ; 10-14=1,28% [12]. Au regard de ces résultats, certains auteurs suggèrent que les chiffres ne traduisent pas une augmentation globale de l'incidence mais un décalage vers un plus jeune âge du début de la maladie[2-4 ,12].

Ce glissement vers un diabète infantile risque d'avoir de lourdes

conséquences en termes de prise en charge qui sera très spécifique et fortement consommatrice vu les caractéristiques de la maladie chez l'enfant en bas âge (variabilité glycémique, risque accru d'hypoglycémies sévères, immaturité de l'enfant, fréquence des infections…etc.[12,61 ,62].

Il reste cependant que l'incidence globale s'accroît faisant du DT1 une épidémie internationale.

1 - Dans le monde :

Dans la plupart des pays occidentaux, le diabète de type 1 représente plus de 90% de diabète de l'enfant et l'adolescent.

Il représente 5-10 % de la totalité des personnes atteintes de diabète dans le monde.

Globalement, environ 80 000 enfants de moins de 15 ans sont estimés à développer le DT1 chaque année à travers le monde [14].

L'incidence du DT1 varie considérablement entre les différents pays, différentes populations ethniques (figure 35) avec le plus hauts taux d'incidence observés en Finlande 43,9 cas pour 100 000 habitants [15].

La Sardaigne (37,8 cas pour 100 000 habitants), [24,25].Europe du Nord [16,17].et Canada [18].

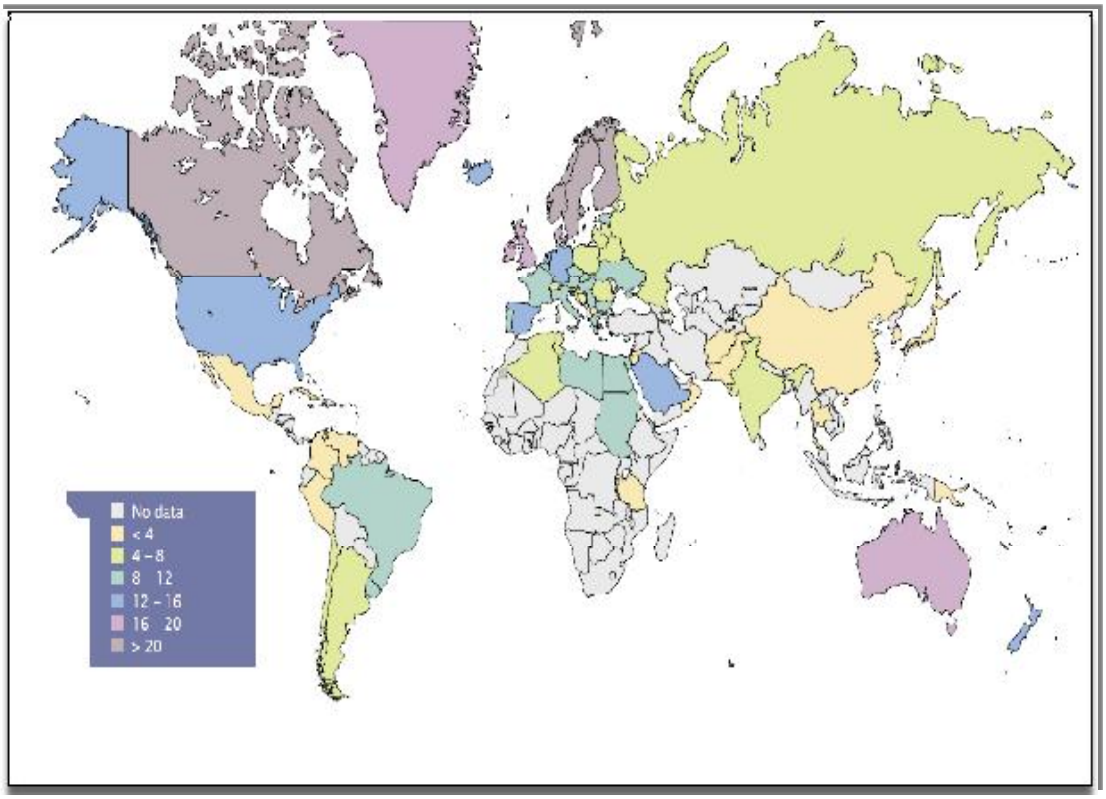


Figure 26: Taux d'incidence du DT1 chez les enfants de 0 à14 ans.

(en 2003) (Cas pour 100.000 habitants par an) [3]

Sur les quelque 500 000 enfants environ vivent avec le DT1, environ

26 % sont de l'Europe, et 22 % d'Amérique du Nord et de la région des Caraïbes [14].

En Asie, le DT1 représente environ le tiers des cas [19,20], dont le taux d'incidence est très faible.

Au Japon environ 2 cas pour 100 000 habitants [21]. Chine (Shanghai) 3,1 pour 100 000 habitants [22]. Taiwan environ 5 pour 100 000 habitants [23].

Les taux d'incidence annuelle moyenne pour le DT1 chez les enfants (< 15 ans d'âge) comparant différents pays dans le monde sont présentés dans la figure. 36

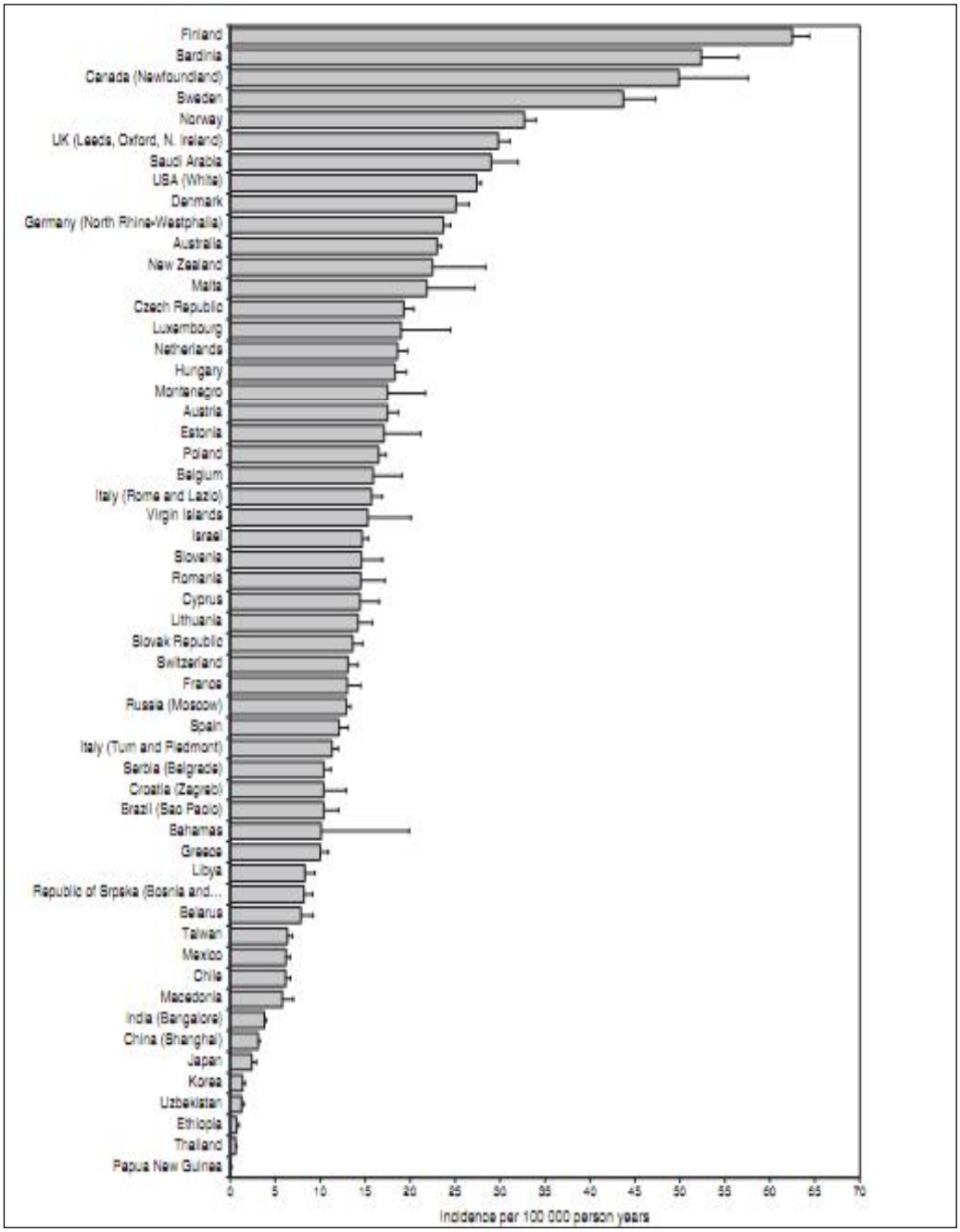


Figure 27: Incidence du DT1, standardisée sur l'âge, survenant avant l'âge de 14 ans entre 1990 et 1999, DIAMOND [1]

Une variation saisonnière rapportée dans la présentation de nouveaux cas est bien décrite, le pic étant en hiver, alors que d'autres rapports montrent des taux plus importants dans les saisons plus chaudes [22], ou une variation saisonnière différente d'une année à l'autre [26,27].

2 - En Europe :

Selon les résultats du réseau Eurodiab [2,3] le taux d'accroissement annuel a été estimé à 3,4% sur la période 1989-2008 , l'incidence du DT1 varie dans des proportions significatives en Europe et, plus qu'un gradient Nord-Sud, c'est une distribution plus complexe, avec également une opposition Est-Ouest qui est constatée Figure 37 .

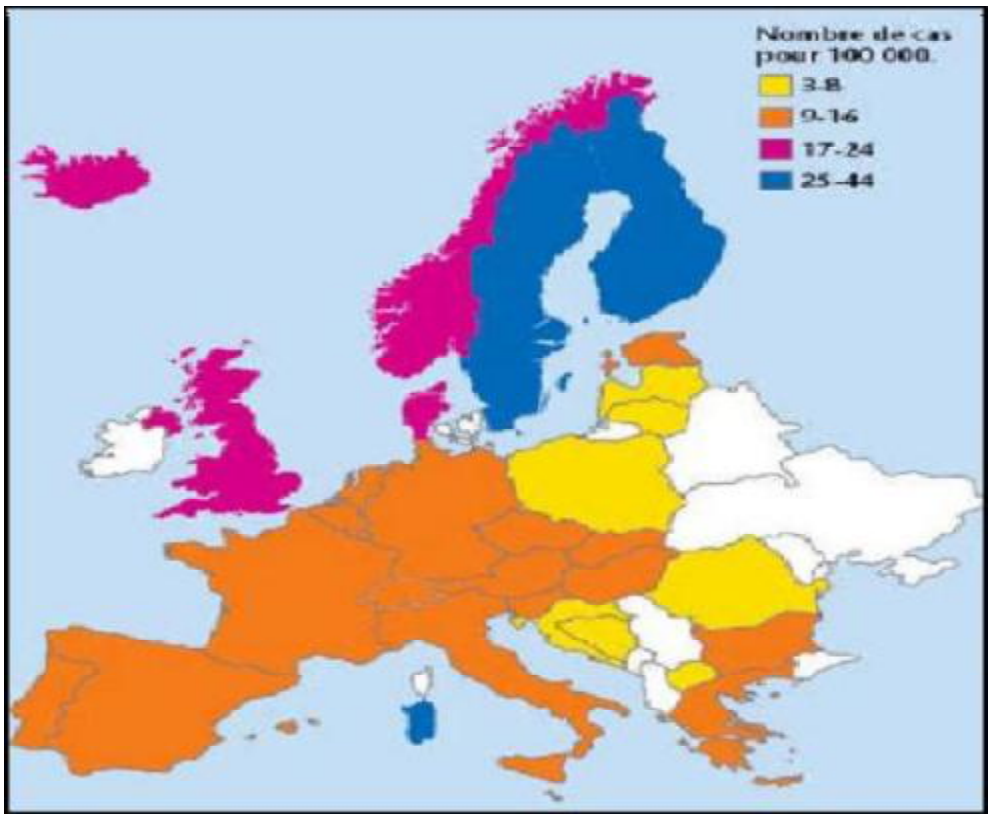


Figure 28 : Incidence du diabète de type 1 de l'enfant en Europe selon Eurobiab.

L'incidence la plus élevée est notée dans la Finlande, suivie par les autres pays scandinaves. Elle demeure globalement plus basse dans le bassin méditerranéen, excepté en Sardaigne dont le taux avoisine celui de la Finlande (37,8 cas pour 100 000 habitants), caractérisée par une susceptibilité génétique forte,

associée à des conditions environnementales modifiées depuis la seconde guerre mondiale une exception qui en fait un terrain d'étude privilégié [30-31].

Ce taux d'incidence du DT1 continue d'augmenter en Europe en moyenne d'environ 3-4% par an, mais l'augmentation n'est pas nécessairement uniforme, montrant des périodes d'accélération de l'incidence de certains registres. Ce modèle de changement suggère que les expositions de risque important diffèrent dans le temps dans différents pays européens.

Selon l'Eurobiab, en France l'âge moyen au diagnostic a été de 10,6 ans. Le sexe ratio était globalement de 1,06 et non significativement différent de la population générale. Le diagnostic est plus souvent fait en hiver et au début du printemps (rapporté aux infections virales saisonnières)..

Les dernières données actualisées en Aquitaine (France) en 2004 font état d'un taux d'incidence à 13,5/100 000 (0-15 ans) contre 8,86 en 1988 [12].

3 - Dans les pays arabes [1,106]:

Pays arabes sont 22 pays, y compris Algérie, Bahreïn, Comores, Djibouti, l'Égypte, L'Irak, la Jordanie, le Koweït, le Liban, la Libye, la Mauritanie, Maroc, Oman, Palestine, Qatar, Arabie Saoudite, Somalie, Soudan, Syrie, Tunisie, Emirats Arabes Unis et le Yémen. Ces pays s'étendent sur environ 5000 miles de la côte atlantique de l'Afrique du Nord à l'ouest à la mer d'Oman et l'océan indien couvrant une superficie de 5.250.000 miles carrés .Ces pays reconnaissent une grande diversité concernant le taux d'incidence, de prévalence et la présentation épidémiologique [106].

Les données d'incidence. Les taux d'incidence actuels selon l'étude de l'OMS DIAMOND.

Tableau 27 : Incidence du diabète de type 1dedans les pays arabes selon l'étude(2006) DIAMOND [1]

Incidence*	Arab countries
Very low (<1)	-
Low (1-4.99)	Oman, Jordan, Palestine
Intermediate (5-9.99)	Egypt, Libya, Tunisia, Morocco, Algeria, Bahrain, Lebanon,Syria
High (10-19.99)	Saudi Arabia, Sudan
Very high (≥20)	Kuwait, Qatar
No data from Somalia, Djibouti, Comoros, Mauritania, Iraq, Yemen, United Arab Emirates	

Tableau 28 : Les études sur la prévalence du diabète de type1chez les enfants<15 ans (2006) [1].

Country	Reference	Year	N of type 1 diabetes x 1000
Algeria	20	1988	0.27
Sudan	9	1989	0.95
Saudi Arabia	6	1980-1982	0.2
Egypt	15	1988	0.01-0.14
Libya (Benghazi)	17	1981-1990	0.24
Libya (Benghazi)	18	1991-2000	0.37

Tableau 29 : La prévalence estimée de diabète de type 1enarabe pays (en milliers)[1]

Countries	1995	2000	2010
Saudi Arabia	6.8	10.9	18.2
Yemen	0.7	2	4.1
Oman	0.9	1.5	2.7
United Arab Emirates	1.2	1.5	1.8
Qatar	0.3	0.4	0.5
Bahrain	0.4	0.5	0.7
Kuwait	8.5	9.2	9.7
Egypt	21.5	36.4	53.5
Libya	3.4	9.1	18.9
Tunisia	6.7	9.5	12.6
Algeria	18.9	27.3	38.6
Morocco	8.9	15.2	21.2
Mauritania	-	-	no data
Sudan	2.2	5.1	9.3
Somalia	0.1	0.1	0.2
Gaza strip	0.8	1.3	2.3
Jordan	4.8	8.8	15.3
Lebanon	2.2	2.3	2.3
Syria	12.9	18.4	26.9
Iraq	7.8	14.2	24.7

4 - Au Maroc :

Au Maroc on note l'absence de données épidémiologiques fiables reflétant la prévalence et l'incidence précises de l'état diabétique. Cependant on estime sur plus d'un million de diabétiques, entre 100.000 et 150.000 cas sont de type I dont au moins 10.000 enfants avec un taux d'incidence de l'ordre de 7/100000(IFD).

Le Maroc comme d'autres pays suit la tendance à l'augmentation du DT1 chez la tranche d'âge 0-5 ans. Dans ce sens, l'expérience de l'hôpital d'enfant à Rabat affirme que l'incidence à triplée entre 1990 et 2005 chez les enfants de moins de 5 ans colligés durant cette période. Durant l'année 2008, 920 enfants diabétiques étaient suivis dans le même centre [33-34].

Dans les pays du Maghreb, l'incidence est d'environ 10/100000 habitants [33-34].

5 - Dans notre série :

Cette étude réalisée chez 183 enfants diabétiques de type 1 a permis d'analyser le profil épidémiologique du diabète type 1 dans notre contexte hospitalier HASSAN II Fès.

Globalement, le nombre de prise en charge diagnostique annuelle a augmenté depuis 2009, avec un accroissement de 60% jusqu'au l'an 2013 .

L'évolution annuelle du nombre d'enfants révélés diabétiques est variable selon l'âge au diagnostic, comme montrée sur la figure 38.

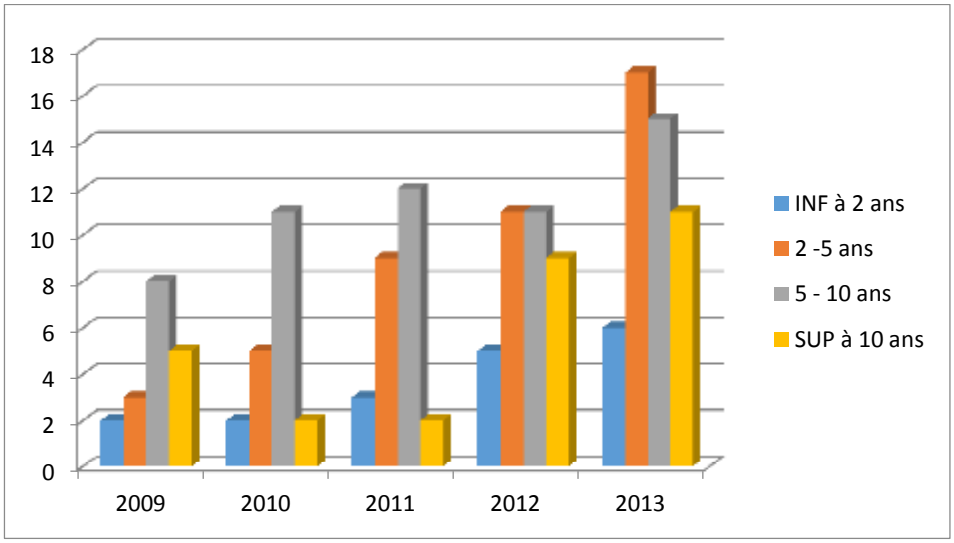


Figure 29: Evolution du nombre de nouveaux diagnostics par tranche d'âge, et par année.

La moyenne d'âge de découverte du diabète chez nos enfants diabétiques était de 6,64±3,81 (ans) avec une médiane de 6 ans. 47% des enfants étaient de sexe masculin (Le sexe ratio=0,87).

Le diagnostic a été établi dans environ 40% en hiver avec deux pics en décembre (16%) et janvier (14%).

Des antécédents familiaux de DT2 étaient retrouvés chez 44% des patients alors que la notion de diabète type1 était retrouvée seulement dans 7% des cas.

Dans notre population d'étude, le mode de révélation du diabète de type 1 reste l'acidocétose inaugurale dans 29,5% avec un taux des formes sévère qui présente 9%.

Les cas d'acidocétoses révélatrices sont encore trop importants, en soulignant toutefois une légère diminution ces dernières années passant de 39% en 2009 à 26% en 2013**(tableau 30) montre la fréquence de L'ACD des nouveaux cas dans différentes séries.**

Tableau 30 : fréquence de l'acidocétose inaugurale dans différentes séries

AUTEURS/Séries	Taille de l'étude en effectif (N)	Fréquence de l'ACD en %
N.Blanc et al (France) [53]	72	54
C .Choleau et al(France) [94]	1000	40
Schober .E et al(Autriche)[86]	3331	37
Germain .H et al(Congo) [99]	93	79
Al Khawri.M et al (KUWAIT) [104]	243	49
Szypowska .A et al(Pologne) [49]	186	26
Quinn.M et al (Boston. USA) [46]	247	44
Abdulrassoul. M et al (Kuwait [93]	677	37,70
Bui. H et al(Canada) [89]	3947	18,60
Levy Marchal et al(EURODIAB) [98]	1260 (24 CENTRES)	40
Al Mgamssi et al (Saoudi Arabia) [84]	230	55,20
Pocecco. M et al(Italie) [101]	73	41
Karges. B et al(Allemagne) [38]	16562 (170 INSTITUS)	20,80
Naeeman. MA et al Arabie Saoudi [102]	373	47
Ting. W .Het al(Taiwan)[103]	304	65
Xin Y(Chine)[45]	203	41,90
AnneHekkala et al (Finland) [91]	2121 (31 DEPART)	26,30
Areta.Rewers(USA) [52]	2824	25,50
Johannat Mallare et al [54]	139	38
Maniatis AK et al(USA) [88]	383	28,40
Neu.A(Allemagne) [90]	14664 (106 INSTITUS)	21,10
Jeremy Kirk et al(UK)[85]	99	27,20

II - Les facteurs liés au mode de révélation par acidocétose:

1- Age :

Age inférieur à 5 ans est associé à l'ACD (p=0,011).

Ce résultat est comparable à ce qui est décrit dans la littérature [35-36-38-39-43-49-53-63-88-91-92-94-101](Tableau 31)

Tableau 31 : Age inférieur à 5 ans & Présence d'une ACD (p)

Age inférieur à 5 ans & Présence d'une ACD (p)	
Notre série	=0,011
Levy Marchal et al(EURODIAB) [63]	<0,0001
Juliet A Usher-Smith et al/[35]	<0,001
N Blanc et al [53]	=0,03
Karges B et al [38]	<0,001
Neu A et al [92]	<0,0001
Anne Hekkala et al [91]	<0,005
Maniatis AK et al [88]	<0,001
Al. FIFI.S.H et al [43]	<0,001
C .Choleau et al [94]	<0 ,01
Olak et al [101]	<0,001
Szypowska .A et al [49]	<0,001

L'intérêt porté à ce groupe d'âge se justifie tout d'abord par l'accroissement accéléré de l'incidence du diabète de type 1 chez les moins de cinq ans (4,8 % en Europe entre 1989 et 1998, et 7,6% en France) [2, 3,12].

Les plus jeunes se distinguent également par leur mode de révélation de la maladie diabétique. La présentation clinique initiale s'écarte du tableau classique et est beaucoup plus bruyante. Il est difficile de mettre en évidence un syndrome polyuro-polydipsique chez un enfant qui n'est pas autonome tant sur l'acquisition de la propreté que sur les prises alimentaires (hydriques) et qui est dans l'incapacité d'exprimer ses doléances. La polyurie est souvent renseignée par le poids des couches. Les symptômes se manifestent spécifiquement par des modifications du

comportement avec phases d'apathie et d'agitation, par des troubles digestifs, par de la fièvre, sans oublier une fréquence accrue d'acidocétose [43]. Le diagnostic est rendu difficile par l'association d'une affection concomitante [44-45]. L'évolution des symptômes est plus rapide [46]. Etant plus sujet à l'acidocétose, il est reconnu que l'œdème cérébral est plus fréquent chez les moins de cinq ans [50, 51], sans pouvoir préciser le mécanisme physiopathologique. En dehors des données physiopathologiques, les jeunes enfants sont aussi plus touchés par l'acidocétose à cause du retard diagnostique, parce qu'il persiste encore des croyances erronées sur le diabète du petit. Le diabète de type 1 reste encore pour de nombreux médecins la pathologie de l'adolescent ou de l'adulte jeune. D'autres particularités du diabète du jeune enfant sont à connaître, notamment le fait que les glycémies à jeun restent très longtemps normales, en raison de très faibles besoins d'insuline la nuit.

La réalisation d'une glycémie à jeun s'avère être un mauvais moyen diagnostique qui retarde la prise en charge, soit par le délai de réalisation ou soit parce qu'elle écarte du diagnostic avec des valeurs faussement normales.

2 - Absence des ATCD familiaux de diabète :

Nous avons retrouvé dans notre population 52 % des antécédents familiaux du diabète, et nous avons pu démontrer une différence significative entre les deux groupes (72%ACD- contre 48%ACD+, p=0,007)(Tableau 32) .

Tableau 32 : ATCD familiaux de diabète & Présence d'une ACD

Notre série	p = 0,007
N Blanc et al [53]	p =0,04
Pinkey et al [105]	p <0,01

Ce modèle de « famille diabétique » [53,65] permet de renforcer l'idée qu'une bonne connaissance des signes précoces du diabète et l'utilisation de moyens diagnostiques simples permettent un diagnostic avant le stade d'acidocétose.

La démonstration faite par Maurizio Vanelli est probante, dans la mesure où le taux d'acidocétoses au diagnostic est passé de 78 % à 12,5 % après huit ans de campagne d'information sur les symptômes précoces du diabète de type 1 [66]. Ces affiches ont été diffusées dans les écoles et dans les cabinets médicaux. Par ailleurs, le matériel de mesure de la glycémie et de la glycosurie avait été mis à disposition des médecins, tout en leur apportant une formation sur les conditions d'utilisation.

3 - Niveau socioéconomique bas :

Il y a eu plus de révélations de diabète de type 1 sous forme acidocétosique chez les enfants de bas niveau socioéconomique (68% des familles du groupe ACD + se considéraient plutôt de bas niveau socioéconomique contre 49% des familles de groupe ACD− ; avec une différence significative ; p=0,037)

Dans la littérature, il est clairement démontré que les familles à situation précaire sont plus à risque [52, 53].

Les études américaines soulignent que de faibles revenus et l'absence de couverture sociale rend l'accès aux soins difficile et majorent le risque d'acidocétose [39 ,54].

Tableau 33 : Bas niveau socioéconomique & Présence d'une ACD

Séries	*p=*
Notre série	=0,037
N Blanc et al [53]	NS
Rosembauer.j[83]	<0,001
Allerta.Rewers[52]	<0,01
Lewis.KR [95]	<0,001
Mallare.JT[54]	0,03

Effectivement, bien que la couverture sociale du RAMED soit considérée comme insuffisante, les enfants en bénéficiant n'ont pas présenté plus d'acidocétoses.

4 - Le retard et les erreurs diagnostiques :

Le retard et l'errance diagnostiques apparaissaient comme les principaux facteurs de risque de survenue d'une acidocétose inaugurale dans la révélation d'un diabète de type 1, soulignant l'importance de l'information des médecins.

Chez les diabétiques révélés par une acidocétose le délai entre la première consultation et l'hospitalisation était plus marqué en moyenne de 2,26 ± 1,4 jours, avec 56% des enfants adressés dans un délai dépassant les 24 heures contre 1,48 ± 1,17 jour pour le groupe ACD− (p =0,001).

Tableau 34 : Retard diagnostique & Présence d'une ACD.

Séries	*p=*
Notre série	0,001
Allerta.Rewers[52]	0,0012
Jeremy kirk[85]	<0,01
N Blanc et al[53]	NS

Les compétences médicales influencent le mode de révélation du DT1 de l'enfant. Le problème est la méconnaissance de la maladie, tant dans la reconnaissance des symptômes que dans la maîtrise de la prise en charge. Le nombre de consultations médicales réalisées avant l'hospitalisation et les erreurs

diagnostiques sont tous deux prédictifs de l'évolution vers une acidocétose inaugurale et de la sévérité de l'affection [53] .

5 - Origine rurale :

Les enfants originaires et habitants dans un milieu rural présentaient plus d'acidocétoses au diagnostic, sans qu'elles soient pour autant plus sévères (p=0,02). En gardant à l'esprit le biais de recrutement, le caractère rétrospectif de l'étude il convient de souligner qu'on ne peut pas avancer l'argument de la ruralité, car les enfants vivant à la campagne ne sont pas plus à risque [35]. En revanche, on peut évoquer l'inégalité d'accès aux soins en raison d'une faible densité médicale.

6 - La durée d'évolution des symptômes :

Elle est significativement différentes entre les deux groupes de comparaison (p=0,02)

Tableau 35 : durée d'évolution des symptômes.

Séries	Durée moyenne d'évolution des symptômes en jours
Notre série	29,76
Rosembauer.J[83]	24
Al Magamsi MS [84]	17,1(3-45)
C.Choleau[94]	15

7 - La présentation clinique :

Le tableau clinique classique dans notre population associait le syndrome polyuro-polydipsique et l'amaigrissement de façon quasi-constante. Au stade d'acidocétose, les troubles digestifs, respiratoires et neurologiques venaient compléter le tableau de manière significative. En l'absence de connaissance des signes

de la maladie, la grande variété des symptômes peut désorienter et alors conduire à des diagnostics erronés.

Ces données sont en accord avec celles de la littérature tant sur la présentation clinique [7,36, 55, 56] que sur l'impact des erreurs diagnostiques [54,58-60].

Ces erreurs diagnostiques sont vécues comme un fléau dans le parcours de soin de l'enfant « nouvellement » diabétique, car elles sont associées à la sévérité de l'acidocétose [53]. Certes, les symptômes du diabète sont banals et non pathognomoniques, mais leur association doit faire évoquer le diagnostic.

III – Les facteurs liés à la sévérité de l'ACD inaugurale :

Notre étude a permis de dégager un seul facteur de risque de l'acidocétose sévère.il s'agit du jeune âge (âge <5 ans ; p=0,008 /âge< 2 ans ; p<<0,0001).

Le sexe, ATCD familiaux de diabète, BNSE, erreurs de diagnostiques, retard diagnostique et le nombre d'enfant de la fratrie restent sans lien significatif avec ACD sévère. Le tableau 36 montre les différents facteurs associés à la sévérité de l'acidocétose décrite dans la littérature :

Tableau 36 : les différents facteurs associés à la sévérité de l'acidocétose décrite dans la littérature

	Facteur lié à la sévérité de l'acidocétose	p	OR
Notre série	Age<5 ans	**0,008**	
	Age< 2 ans	**<<0,0001**	
Neu A et al [92]	Age < 5 ans	<0,001	
Anne Hekkala et al [91]	Age < 2 ans	<0,001	
AbdulRasoul M et al[93]	Age < 5 ans	< 0,0001	
C.Choleau et al [94]	Age > 10 ans	<0,001	
Alerta. Rewers et al [52]	BNSE	<0,001	
	Couverture médicale insuffisante	<0,0001	
	Bas niveau d'éducation des parents	<0,001	
N.Blanc et al [53]	BNSE	0,002	
	Erreurs diagnostiques	0,002	
Rosenbauer.J et al [83]	BNSE	<0,001	3,54
Maniatis ak et al [88]	BNSE	<0,001	6,09

IV - Il faut noter que :

- La tendance actuelle étant à l'augmentation de l'incidence du diabète, il est certain que les médecins généralistes seront de plus en plus concernés par la prise en charge diagnostique. Afin de pallier à la méconnaissance de la maladie diabétique de l'enfant et ainsi éviter un diagnostic erroné ou tardif qui conduirait à l'acidocétose, il faut incontestablement axer la formation des médecins sur les signes cliniques du diabète et la nécessité d'un traitement urgent.
- Il existe un autre impact sur le médecin traitant. Le diabète de type 1 arrivant de plus en plus fréquemment et de plus en plus tôt dans l'enfance. Les médecins vont être amenés à gérer le diabète de l'enfant sur une période plus longue, avec le risque de voir arriver les premières complications micro vasculaires dès l'adolescence.
- La réduction du nombre d'acidocétoses inaugurales passe par un diagnostic précoce, reposant sur une bonne connaissance du diabète de la part des médecins et des familles. Il a été démontré dans la littérature que les pays à forte incidence étaient moins « touchés » par l'acidocétose inaugurale [63] et qu'il y avait moins d'acidocétoses dans les familles aux antécédents de diabète [53, 64].
- La prise en charge thérapeutique des acidocétoses fait l'objet de procédures écrites selon les recommandations de l'ISPAD 2014 [56]. Dans tous les cas, la procédure de prise en charge de l'acidocétose est efficace, car aucune complication aiguë liée à l'acidocétose n'a été retrouvée, mais le traitement doit avant tout être préventif. La prévention de l'œdème cérébral ne repose actuellement que sur la prévention de la survenue d'une acidocétose

Finalement :

- Il faut noter que quelques limites viennent s'opposer à notre étude. Elles sont surtout d'ordre statistique et méthodologique
- Notre recueil des nouveaux cas de DT1 avec acidocétose est loin d'être exhaustif de notre population et l'analyse rétrospective, majoritaire, apporte un biais de sélection majeur. Nous n'avions pas les moyens matériels d'assurer une exhaustivité du recueil de ces paramètres qui étaient souvent manquants dans les dossiers. Des réserves peuvent alors être émises quant à l'interprétation des résultats. La prise en compte de ces limites est nécessaire à la bonne critique de ce travail.
- Cette étude pourrait constituer une nouvelle piste de travail. Elle ouvre effectivement d'autres perspectives.

CONCLUSION

Le diabète sucré est la maladie métabolique endocrinienne la plus fréquente chez l'adulte comme chez l'enfant. C'est une maladie chronique ayant des conséquences sur l'ensemble des activités de la vie avec des complications très lourdes.

D'une part, nous avons pu démontrer le changement du profil épidémiologique avec une proportion d'enfants de moins de cinq ans pris en charge pour un diabète de type 1 qui a fortement crû au fil des années.

Ce glissement vers un diabète infantile risque d'avoir de lourdes conséquences en termes de prise en charge qui sera très spécifique et fortement consommatrice vu les caractéristiques de la maladie chez l'enfant en bas âge cela implique une gestion efficace du diabète limitant non seulement les complications, mais s'associe également à une meilleure qualité de vie pour les enfants et adolescents atteints de diabète ainsi que leurs parents.

D'autre part on a pu identifier quelques facteurs associés à l'acidocétose diabétique inaugurale qui constitue le principal facteur de morbidité et de mortalité dans le diabète de type 1 de l'enfant. Elle est impliquée, en aigu, dans la physiopathologie de l'œdème cérébral. Son effet est également ressenti à long terme, avec un pronostic péjoratif sur les capacités cognitives et sur l'équilibre métabolique.

L'âge inférieur à 5 ans, l'impact du retard et des erreurs diagnostiques et les difficultés d'accès aux soins ou à l'information médicale favorisent l'évolution vers l'acidocétose.

Cela engage principalement les médecins qui évoquent des diagnostics erronés par méconnaissance des signes précoces du diabète, en soulignant que chez les jeunes enfants la démarche diagnostique reste difficile.

Alors qu'il s'agit d'un facteur modifiable, son incidence dans notre population est trop élevée. Le traitement de l'acidocétose doit avant tout être un traitement préventif basé sur un diagnostic précoce du diabète.

Tout doit alors être centré sur l'information des médecins et des familles, afin d'apporter les connaissances nécessaires pour poser le diagnostic de diabète au stade précoce pour réduire autant que possible la fréquence de survenue des acidocétoses inaugurales et ainsi en protéger les enfants qui ont un diabète.

RESUMES

RESUME

Le diabète de type 1 (DT1) est une maladie auto-immune qui représente plus de 90% des diabètes de l'enfant et de l'adolescent. Il constitue une pathologie chronique aux répercussions lourdes sur la qualité de vie de l'enfant et de sa famille.

L'acidocétose est encore trop souvent le mode de révélation du diabète de type 1 de l'enfant. Elle est considérée comme un facteur de gravité à part entière dans la maladie diabétique, avec des complications neurologiques péjoratives. Le défi repose donc sur un diagnostic précoce du diabète afin d'arrêter l'évolution vers l'acidocétose.

Nos principaux objectifs sont :

- Décrire le profil épidémiologique du diabète de type 1 dans notre population.
- Chercher d'éventuels facteurs prédictifs médicaux, sociologiques et économiques dans la survenue de l'acidocétose inaugurale et de sa sévérité, afin de cibler les situations à risque et d'orienter les stratégies de prévention.

Cette étude rétrospective porte sur 183 enfants (53% des filles / 47% des garçons) diagnostiqués diabétiques de type 1 au CHU HASSAN II Fès entre le 01/01/2009 et le 31/12/2013.

La moyenne d'âge de découverte du diabète chez nos enfants diabétiques était de 6,64+/-3,81(ans) avec une médiane de 6 ans ayant des antécédents familiaux de diabète type 2 dans 45% des cas, et de diabète type 1 dans 7%.

57%de nos enfants étaient de bas niveau socioéconomique et 62% étaient non mutualistes (le RAMED 48%) .

Le diagnostic a été établi dans environ 40% en hiver avec deux pics en décembre (16%) et janvier (14%).78% des enfants étaient admis en décompensation acidocétosique avec un syndrome cardinal évoluant sur une durée moyenne de

21±16 jours sans aucune autre complication aigue notée (hypoglycémie sévère, œdème cérébral ou décès).

La durée moyenne d'hospitalisation était 8,5±4,2jours; les enfants diabétiques étaient accompagnés par leurs mères au cours de l'hospitalisation dans 90 ٪ des cas.

Le taux d'acidocétose inaugurale est de 29,5%avec un taux des formes sévère qui atteint 9%.

Nous avons confirmé les enfants de moins de cinq ans comme à risque (p = 0.01), comme il est décrit dans la littérature ; l'impact de l'errance et du retard diagnostiques dans la survenue des acidocétoses avec en moyenne une durée d'évolution des symptômes de 30 ± 15 jours contre 21 ± 15 jours chez le groupe ACD- (p=0,02) ; un délai de prise en charge plus long lié aux erreurs diagnostiques (p=0,001) et à la réalisation d'examens complémentaires inutiles.

Les facteurs socio-économiques limitant l'accès aux soins ou à l'information médicale (faible niveau d'instruction, bas niveau socioéconomique, faible densité médicale) favorisent cette situation de décompensation métabolique.

Il est donc nécessaire de créer des campagnes de prévention et que les médecins y s'investissent tout d'abord en se plaçant comme cible et se rendant disponible à la formation continue, puis comme diffuseur de l'information aux familles.

ABSTRACT

Type 1 diabetes (T1D) is an autoimmune disease which accounts for over 90% of diabetes in children and adolescents. It is a chronic disease with severe impact on the quality of life of the child and his family.

Ketoacidosis is still too often the mode of revelation of type 1 diabetes in children. it is considered a full gravity factor in diabetic disease with neurological complications pejorative.The challenge is based on early diagnosis of diabetes to stop progression to ketoacidosis.

Our main objectives are:

- Describe the epidemiology of type 1 diabetes in our population.
- Search for any medical, sociological and economic predictors in the occurrence of the inaugural ketoacidosis and its severity, to target risk situations and guide prevention strategies.

This retrospective study of 183 children (53% girls / boys 47%) diagnosed with type 1 diabetes at the University Hospital Hassan II Fez between 01/01/2009 and 31/12/2013.

The average age of diabetes discovery in diabetic children was 6.64 +/- 3.81 (years) with a median of 6 years with a family history of type 2 diabetes in 45%,type 1 diabetes in 7% 57% were low socioeconomic level and 62% were non-mutual (RAMED 48%).

The diagnosis was established in about 40% in winter with two peaks in December (16%) and January (14%).

78% of children were admitted with diabetic ketoacidosis after 21 ±16 day's duration of syndrome cardinal.

Furthermore, no other acute complications were noted (Severe hypoglycemia, cerebral edema or death) the average length of hospitalization was 8.5 ± 4.2

days; diabetic children were accompanied by their mothers during hospitalization in 90% of cases.

The inaugural ketoacidosis rate was 29.5% with severe forms of the rate reached 9%.

We confirmed children under five as at risk (p = 0.01), as described in the literature, the impact of wandering and diagnostic delay in the onset of ketoacidosis (p=0, 0012) with an average disease duration of symptoms of 29.76 ± 15.39 days against 21.13 ± 15.08 days in the ACD- group (p = 0.02) a longer period of care related to diagnostic errors (80%, p = 0.001) and the achievement of unnecessary additional tests.

Socioeconomic factors limiting access to care or medical information (low education, low socioeconomic level, and low medical density) favor this metabolic decompensation.

It is therefore necessary to develop prevention campaigns and the doctors there will initially invest by placing a target and making it available for training, then as a broadcaster of information to families.

ملخص

يعتبر مرض السكري نوع 1 أحد أمراض المناعة الذاتية التي تمثل أكثر من 90٪ من مرض السكري لدى الأطفال والمراهقين.

وهو يمثل أحد الأمراض المزمنة ذات الانعكاسات الوخيمة على جودة حياة الطفل وعائلته.

دائما ماتكون حالة الحامض الكيتوني السكري هي الشكل المبدئي لظهور المرض حيث تعتبر عامل خطورة أساسي في هذا الداء بمضاعفاتها العصية الوخيمة ويقوم التحدي على التشخيص المبكر للمرض لإيقاف تطوره لحالة الحامض الكيتوني السكري.

من بين أهدافنا الرئيسية :

- دراسة الحالة الوبائية لمرض السكري نوع 1 بالنسبة لساكنتنا.
- البحث عن العناصر التنبؤية وعوامل الخطر الطبية والسوسيو-إقتصادية في حدوث حالة الحامض الكيتوني السكري وخطورته وذلك لتحديد الحالات الخطيرة وتوجيه إستراتيجيات الوقاية.

يتعلق الأمر بدراسة إستعادية شملت 183 طفل (47٪ بنين و 53٪ فتيات) تم تشخيصهم كمرضى سكري نوع 1 في المركز الإستشفائي الحسن الثاني بفا س في الفترة الممتدة ما بين 01 يناير 2009 و 31 دجنبر 2013 ,متوسط أعمارهم 6.64± 3.81 سنة 45٪ لهم أقرباء مصابون بمرض السكري نوع2 و 7٪ مصابون بمرض السكري نوع 1.

57 ٪ مستواهم السوسيو-اقتصادي منخفض, 62٪ لايتوفرون على تغطية صحية كافية (48٪ RAMED).

تم تشخيص المرض في 40٪ من الحالات في فصل الشتاء مع تسجيل أكبر المعدلات في شهري دجنبر 16٪ ويناير 14٪.

تم قبول 78٪ من المصابين بداء السكري تحت وطأة حالة الحامض الكيتوني السكري بعد مدة متوسطة 21± 16 يوما من التبول و الشرب المفرط بدون تسجيل أي مضاعفات.

سجلت قرابة 30٪ حالة حامض كيتوني في أ ول تشخيص لمرض السكري نوع 1 منها 9٪ من الحالات الحادة.

لقد تمكنا من تأكيد أن الطفل ا لذي عمره أقل من 5 سنوات أكثرعرضة للإصابة بحالة الحامض الكيتوني السكري كما جاء في أدبيات المراجع العلمية.

وأن الغلط أو التأخر قي التشخيص له إنعكاس مباشر في حدوث حالة حامض الكيتوني حيث أن مدة تطور الأعراض بالنسبة للمجموعة (ACD+) وصلت ل30±15يوما في حين كانت عند نضيرتها في المجموعة (ACD-) 21 ±15 (0.002).=p

ومن ناحية أخرى فلقد كان الأجل ما بين أول إستشارة طبية و العلاج الإستشفائي أكبر بالنسبة للمجموعة (ACD+ ; 001, 0=p)وهذا راجع إلى الأغلاط التشخيصية وإجراء بعض الفحوصات التكميلية الغير المجدية.

وتساهم العوامل التي تحد من الولوجية للعلاج والمعلومة الصحية في تفشي هذه الحالة.

في هذا الإطار من الضروري إقامة حملات تحسيسية للوقاية من تطور مرض السكري نوع 1 إلى تكون حالة الحامض الكيتوني السكري وأن يتم مشاركة الأطباء وتكوينهم بإستمرار والإستثمار في هذا الصدد بجعلهم وسيلة للتحسيس وإنتشارالمعلومة الصحية في أوساط العائلات.

BIBLIOGRAPHIE

[1] Diamond Project Group: Incidence and trends of childhood Type 1diabetes worldwide 1990-1999. Diabet Med 2006, 23:857-866.

[2] C. C. Patterson & E. Gyürüs & J. Rosenbauer & O. Cinek & A. Neu &E. Schober & R. C. Parslow & G. Joner & J. Svensson & C. Castell &P. J. Bingley & E. Schoenle & P. Jarosz-Chobot & B. Urbonaité & U. Rothe &C. Krzisnik & C. Ionescu-Tirgoviste & I. Weets & M. Kocova & G. Stipancic &M. Samardzic & C. E. de Beaufort & A Green & G. G. Dahlquist & G. Soltész Trends in childhood type 1 diabetes incidence in Europeduring 1989-2008: evidence of non-uniformity over time in rates of increase.:Diabetologia (2012) 55:2142-2147DOI 10.1007/s00125-012-25718

[3] Patterson CC, Dahlquist GG, Gyurus E, GreenA, Soltesz G. Incidence trends for childhood type 1diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registrationstudy. Lancet 2009: 373: 2027-2033.

[4] The EURODIAB-ACE Study Group. Variation and trends in incidence of childhood diabetes in Europe. Eurodiab ace study group. Lancet 2009;355:873-6.

[5] Sipetic S, Maksimovic J, Vlajinac Hetal.Rising incidence of type 1 diabetes in Belgrade children aged 0-14 years in the period from1982 to 2005. JEndocrinol Invest 2013: 36: 307-312.

[6] Harjutsalo V, Sund R, Knip M, Groop PH.Incidence of type 1 diabetes in Finland. JAMA 2013:310: 427-428.

[7] Skrivarhaug T, Stene LC, Drivvoll AK, Strom H, Joner G, Norwegian Childhood Diabetes Study Group. Incidence of type 1 diabetes in Norway among children aged 0-14 years between 1989 and 2012: has the incidence stopped rising? Results from the Norwegian Childhood Diabetes Registry.Diabetologia 2014: 57: 57-62.

[8] Bruno G, Maule M, Biggeri Aetal.Morethan 20 years of registration of type 1 diabetes in Sardinian children: temporal variations of incidence with age,period of diagnosis, and year of birth. Diabetes 2013:62: 3542-3546.

[9] Cinek O, KulichM, Sumnik Z. The incidence of type1 diabetes in young Czech children stopped rising.Pediatr Diabetes 2012: 13: 559-563.

[10] Kraan JA, Claessen FMAP, Elliott KD et al.Population based incidence of type 1 diabetes in New South Wales Australia 1990-2010 - have we reached a plateau? (Oral Abstract). Pediatr Diabetes 2011: 12(Suppl. 15): 25.

[11] Hermann R, Knip M, Veijola R et al. Temporal changes in the frequencies of HLA genotypes in patients with type 1 diabetes - indication of an increased environmental pressure? Diabetologia 2003:46: 420-425.

[12] P. Barat A. Valade[a],P. Brosselin[b], C. Alberti[b], S. Maurice-Tison[c], C. Lévy-Marchal :Augmentation continue de l'incidence du diabète de l'enfant : expérience française en Aquitaine sur 17 ans.

[13] Fourlanos S, Varney MD, Tait BD et al. The rising incidence of type 1 diabetes is accounted for by cases with lower-risk human leukocyte antigen genotypes.Diabetes Care 2008: 31: 1546-1549.

[14] International Diabetes F. IDF Diabetes Atlas. 6th edn.Brussels, Belgium: International Diabetes F, 2013.)

[15] Harjutsalo V, Sund R, Knip M, Groop PH.Incidence of type 1 diabetes in Finland. JAMA 2013:310: 427-428.) ,

[16] Berhan Y, Waernbaum I, Lind T, Mollsten A,
Dahlquist G, Swedish Childhood Diabetes Study Group. Thirty years of prospective nationwide incidence of childhood type 1 diabetes: the accelerating increase by time tends to level off in Sweden. Diabetes 2011: 60: 577-581

[17] Rawshani A, Landin-OlssonM, Svensson AMet al.The incidence of diabetes among 0-34 year olds in Sweden: new data and better methods. Diabetologia 2014: 57: 1375-1381.)

[18] Newhook LA, Penney S, Fiander J, Dowden J.
Recent incidence of type 1 diabetes mellitus in children 0-14 years in Newfoundland and Labrador, Canada climbs to over 45/100,000: a retrospective time trend study. BMC Res Notes 2012: 5: 628.

[19] Urakami T, Suzuki J, Yoshida A, Saito H, Mugishima H. Incidence of children with slowly progressive form of type 1 diabetes detected by the urine glucose screening at schools in the Tokyo
metropolitan area. Diabetes Res Clin Pract 2008: 80:473-476.

[20] Urakami T, Yoshida A, Suzuki J et al. Differences in prevalence of antibodies to GAD and IA-2 and their titers at diagnosis in children with slowly and rapidly progressive forms of type 1 diabetes.Diabetes Res Clin Pract 2009: 83: 89-93.

[21] Tajima N, Morimoto A. Epidemiology of childhood diabetes mellitus in Japan. Pediatr Endocrinol Rev 2012: 10 (Suppl. 1): 44-50.

[22] Zhao Z, Sun C,Wang C et al.Rapidly rising incidence of childhood type 1 diabetes in Chinese population: epidemiology in Shanghai during 1997-2011. Acta Diabetol 2014: Apr 29. [Epub ahead of print] (PMID: 24777734).

[23] Lin WH, Wang MC, Wang WM et al. Incidence of and mortality from type I diabetes in Taiwan from 1999 through 2010: a nationwide cohort study. PLoS One 2014: 9: e86172.

[24] Casu A, Pascutto C, Bernardinelli L, Songini M: Type 1 diabetes among sardinian children is increasing: the Sardinian diabetes register for children aged 0–14 years (1989–1999). Diabetes Care 2004, 27:1623–1629.

[25] Muntoni S, Fonte MT, Stoduto S, Marietti G, Bizzarri C, Crino A, Ciampalini P, Multari G, Suppa MA, Matteoli MC et al: Incidence of insulin-dependent diabetes mellitus among Sardinian-heritage children born in Lazio region, Italy. Lancet 1997, 349:160–162.

[26]I mkampe AK, Gulliford MC. Trends in type 1diabetes incidence in the UK in 0- to 14-year-olds and in 15- to 34-year-olds, 1991–2008. Diabet Med 2011: 28: 811–814.

[27] Skordis N, Efstathiou E, Kyriakides TC et al.
Epidemiology of type 1 diabetes mellitus in Cyprus: rising incidence at the dawn of the 21st century.Hormones (Athens) 2012: 11: 86–93.

[28]Weets I, Kaufman L, Van der Auwera Betal.
Seasonality in clinical onset of type 1 diabetes in Belgian patients above the age of 10 is restricted to HLA-DQ2/DQ8-negative males, which explains the male to female excess in incidence. Diabetologia 2004:
47: 614–621.

[29] Wandell PE, Carlsson AC. Time trends and gender differences in incidence and prevalence of type 1 diabetes in Sweden. Curr Diabetes Rev 2013: 9:342–349.

[30] Casu A, Pascutto C, Bernardinelli L, Songini M: Type 1 diabetes among sardinian children is increasing: the Sardinian diabetes register for children aged 0-14 years (1989-1999). Diabetes Care 2004, 27:1623-1629.

[31] Muntoni S, Fonte MT, Stoduto S, Marietti G, Bizzarri C, Crino A, Ciampalini P, Multari G, Suppa MA, Matteoli MC et al: Incidence of insulin-dependent diabetes mellitus among Sardinian-heritage children born in Lazio region, Italy. Lancet 1997, 349:160-162.].

[32] Charkaluk ML, Czernichow P, Levy-Marchal C: Incidence data of childhood-onset type I diabetes in France during 1988-1997: the case for a shift toward younger age at onset. Pediatr Res 2002, 52:859-862.

[33] A. Balafrej. Prise en charge de l'enfant diabétique à Rabat. Communication APF Fès le 7.03.09.

[34] Z. Imane, S. Amhager, A. Bennani, A. Balafrej. Épidémiologie du diabète de l'enfant de moins de 5 ans : expérience du service de diabétologie pédiatrique. Diabetes & metabolisme. Elsevier Masson 2010.p28.

[35] Usher-Smith JA, Thompson MJ, Sharp SJ, Walter FM: Factors associated with the presence of diabetic ketoacidosis at diagnosis of diabetes in children and young adults: a systematic review. BMJ 2011, 343:d4092.

[36] Campagne Diabète Enfant et Adolescent. Résultats de l'évaluation de l'observatoire national. [http://www.diabete-france.net/]

[37] Pawlowicz M, Birkholz D, Niedzwiecki M, Balcerska A: Difficulties or mistakes in diagnosing type 1 diabetes in children?--demographic factors influencing delayed diagnosis. Pediatr Diabetes 2009, 10:542-549.

[38] Karges B, Neu A, Hofer SE, Rosenbauer J, Kiess W, Rutschle H, Dost A, Kentrup H, Holl RW: [Frequency and influencing factors of ketoacidosis at diabetes onset in children and adolescents--a long-term study between 1995 and 2009]. Klin Padiatr 2011, 223:70-73.

[39] Rodacki M, Pereira JR, Nabuco de Oliveira AM, Barone B, Mac Dowell R, Perricelli P, Bravo MT, de Oliveira MM, Brum JD, Belem LC et al: Ethnicity and young age influence the frequency of diabetic ketoacidosis at the onset of type 1 diabetes. Diabetes Res Clin Pract 2007, 78:259-262.

[40] Khan N, Couper JJ: Low-birth-weight infants show earlier onset of IDDM. Diabetes Care 1994, 17:653-656.

[41] Sobel A, Grzywa M: [Maternal age at the moment of birth and occurrence of insulin dependent diabetes mellitus (IDDM) in the child]. Pol Arch Med Wewn 1994, 91:274-281.

[42] Jones ME, Swerdlow AJ, Gill LE, Goldacre MJ: Pre-natal and early life risk factors for childhood onset diabetes mellitus: a record linkage study. Int J Epidemiol 1998, 27:444-449.

[43] Al-Fifi SH: The relation of age to the severity of Type I diabetes in children. J Family Community Med 2010, 17:87-90.

[44] Nimri R, Phillip M, Shalitin S: Children diagnosed with diabetes during infancy have unique clinical characteristics. Horm Res 2007, 67:263-267.

[45] Xin Y, Yang M, Chen XJ, Tong YJ, Zhang LH: Clinical features at the onset of childhood type 1 diabetes mellitus in Shenyang, China. J Paediatr Child Health 2010, 46:171-175.

[46] Quinn M, Fleischman A, Rosner B, Nigrin DJ, Wolfsdorf JI: Characteristics at diagnosis of type 1 diabetes in children younger than 6 years. J Pediatr 2006, 148:366-371.

[47] Komulainen J, Kulmala P, Savola K, Lounamaa R, Ilonen J, Reijonen H, Knip M, Akerblom HK: Clinical, autoimmune, and genetic characteristics of very young children with type 1 diabetes. Childhood Diabetes in Finland (DiMe) Study Group. Diabetes Care 1999, 22:1950-1955.

[48] Komulainen J, Lounamaa R, Knip M, Kaprio EA, Akerblom HK: Ketoacidosis at the diagnosis of type 1 (insulin dependent) diabetes mellitus is related to poor residual beta cell function. Childhood Diabetes in Finland Study Group. Arch Dis Child 1996, 75:410-415.

[49] Szypowska A, Skorka A: The risk factors of ketoacidosis in children with newly diagnosed type 1 diabetes mellitus. Pediatr Diabetes 2011, 12:302-306.

[50] Endocrinology and diabetes. Archives of Disease in Childhood 2005, 90:A19-A22.

[51] Rosenbloom AL: Intracerebral crises during treatment of diabetic ketoacidosis. Diabetes Care 1990, 13:22-33.

[52] Rewers A, Klingensmith G, Davis C, Petitti DB, Pihoker C, Rodriguez B, Schwartz ID, Imperatore G, Williams D, Dolan LM et al: Presence of diabetic ketoacidosis at diagnosis of diabetes mellitus in youth: the Search for Diabetes in Youth Study. Pediatrics 2008, 121:e1258-1266.

[53] Blanc N, Lucidarme N, Tubiana-Rufi N: [Factors associated with childhood diabetes manifesting as ketoacidosis and its severity]. Arch Pediatr 2003, 10:320-325.

[54] Mallare JT, Cordice CC, Ryan BA, Carey DE, Kreitzer PM, Frank GR: Identifying risk factors for the development of diabetic ketoacidosis in new onset type 1 diabetes mellitus. Clin Pediatr (Phila) 2003, 42:591-597.

[55] Hamilton DV, Mundia SS, Lister J: Mode of presentation of juvenile diabetes. Br Med J 1976, 2:211-212.

[56]. Chaieb M, Boisson C, Castano L, Chaussain JL, Bougneres PF: [Clinical and biological data affecting insulin-dependent diabetes in French children at the time of its diagnosis]. Arch Fr Pediatr 1989, 46:107-112.

[57]. Wolfsdorf JI, Allgrove J, Craig ME, Edge J, Glaser N,Jain V, Lee WWR, Mungai LNW, Rosenbloom AL,Sperling MA, Hanas R. A Consensus Statement from(ISPAD) the International Society for Pediatric and Adolescent Diabetes: Diabetic ketoacidosis and hyperglycemic hyperosmolar state.Pediatric Diabetes 2014: 15 (Suppl. 20): 154–179.

[58] Craig ME, Wong CH, Alexander J, Maguire AM, Silink M: Delayed referral of new-onset type 1 diabetes increases the risk of diabetic ketoacidosis. Med J Aust 2009, 190:219.

[59] Sundaram PC, Day E, Kirk JM: Delayed diagnosis in type 1 diabetes mellitus. Arch Dis Child 2009, 94:151-152.

[60] Pawlowicz M, Birkholz D, Niedzwiecki M, Balcerska A: Difficulties or mistakes in diagnosing type 1 diabetes mellitus in children? The consequences of delayed diagnosis. Pediatr Endocrinol Diabetes Metab 2008, 14:7-12.

[61]C. Lévy-Marchal, L'augmentation d'incidence du diabète de type 1 : la réalité du diabète de l'enfant ? Médecine des maladies Métaboliques Mai 2010 - Vol. 4 - N°3.

[62] Lévy-Marchal C, Fagot-Campagna A, Daniel M. Surveillance épidémiologique du diabète du diabète de l'enfant. Institut de Veille Sanitaire, novembre 2007.

[63]. Levy-Marchal C, Patterson CC, Green A: Geographical variation of presentation at diagnosis of type I diabetes in children: the EURODIAB study. European and Dibetes. Diabetologia 2001, 44 Suppl 3:B75-80.

[64] Daneman D, Knip M, Kaar ML, Sochett E: Comparison of children with type 1 (insulin-dependent) diabetes in northern Finland and southern Ontario: differences at disease onset. Diabetes Res 1990, 14:123-126.

[65] Blanc N, Polak M, Czernichow P, Tubiana-Rufi N: [Severe ketoacidosis because of delayed diagnosis of diabetes in children. 4 cases to alert physicians]. Arch Pediatr 1997, 4:550-554.

[66] Vanelli M, Chiari G, Ghizzoni L, Costi G, Giacalone T, Chiarelli F: Effectiveness of a prevention program for diabetic ketoacidosis in children. An 8-year study in schools and private practices. Diabetes Care 1999, 22:7-9.

[67] B. Bonnotte, Mise au point : Physiopathologie des maladies auto immunes, La revue de médecine interne 25 (2004) 648–658.

[68] Causes et conséquences de l'activation de l'interféron de type I dans les maladies auto-immunes. Étude dans le modèle du syndrome de Sjögren. Thèse de doctorat en immunologie de l'Université de Paris XI.2012.

[69] . Gepts W: Pathologic anatomy of the pancreas in juvenile diabetes mellitus. Diabetes 1965, 14:619-633.

[70]. Diabète de type 1 : physiopathologie [http://www.memobio.fr/html/bioc/bi_did_ph.html]

[71] . Levy-Marchal C, Papoz L, de Beaufort C, Doutreix J, Froment V, Voirin J, Czernichow P: Clinical and laboratory features of type 1 diabetic children at the time of diagnosis. Diabet Med 1992, 9:279-284.

[72] . Hodgson BM, Ossa AJ, Velasco FN, Urrejola NP, Arteaga LIA: [Clinical picture at the onset of type 1 diabetes mellitus in children]. Rev Med Chil 2006, 134:1535-1540.

[73] . Roche EF, Menon A, Gill D, Hoey H: Clinical presentation of type 1 diabetes. Pediatr Diabetes 2005, 6:75-78.

[74]. Hamilton DV, Mundia SS, Lister J: Mode of presentation of juvenile diabetes. Br Med J 1976, 2:211-212.

[75]. Tenoutasse S, Mouraux T, Dorchy H: [Diabetic ketoacidosis: diagnosis, management, prevention]. Rev Med Brux 2010, 31:S71-76.

[76]. Ghetti S, Lee JK, Sims CE, Demaster DM, Glaser NS: Diabetic ketoacidosis and memory dysfunction in children with type 1 diabetes. J Pediatr 2010, 156:109-114.

[77] . Komulainen J, Lounamaa R, Knip M, Kaprio EA, Akerblom HK: Ketoacidosis at the diagnosis of type 1 (insulin dependent) diabetes mellitus is related to poor residual beta cell function. Childhood Diabetes in Finland Study Group. Arch Dis Child 1996, 75:410-415.

[78] . Lombardo F, Valenzise M, Wasniewska M, Messina MF, Ruggeri C, Arrigo T, De Luca F: Two-year prospective evaluation of the factors affecting honeymoon frequency and duration in children with insulin dependent diabetes mellitus: the key-role of age at diagnosis. Diabetes Nutr Metab 2002, 15:246-251.

[79]. Bowden SA, Duck MM, Hoffman RP: Young children (<5 yr) and adolescents (>12 yr) with type 1 diabetes mellitus have low rate of partial remission: diabetic ketoacidosis is an important risk factor. Pediatr Diabetes 2008, 9:197-201.

[80] Fritsch M, Rosenbauer J, Schober E, Neu A, Placzek K, Holl RW: Predictors of diabetic ketoacidosis in children and adolescents with type 1 diabetes. Experience from a large multicentre database. Pediatr Diabetes 2011, 12:307-312.

[81] Giordano C, Amato MC, Ciresi A, Citarrella R, Mantione L, Accidenti M, Panto F, Guarnotta V, Allotta ML, Criscimanna A et al: Predictors of microvascular complications in type 1 diabetic patients at onset: the role of metabolic memory. Eur J Intern Med 2011, 22:266-274.

[82] Craig ME, Jefferies C, Dabelea D, Balde N, Seth A,Donaghue KC(ISPAD). Definition, epidemiology, and classification of diabetes in children and adolescents.Pediatric Diabetes 2014: 15 (Suppl. 20): 4-17.

[83]) Rosenbauer J[1], Icks A, Giani GClinical characteristics and predictors of severe ketoacidosis at onset of type 1 diabetes mellitus in children in a North Rhine-Westphalian region, Germany.J Pediatr Endocrinol Metab. 2002 Sep-Oct;15(8):1137-45.

[84] Al-Magamsi MS[1], Habib HS.Clinical presentation of childhood type 1 diabetes mellitus in the Al-Madina region of Saudi Arabia.Pediatr Diabetes. 2004 Jun; 5(2):95-8

[85]) P C B Sundaram, E Day, J M W Kirk . Delayed diagnosis in type 1 diabetes mellitus

[86] Schober E[1], Rami B, Waldhoer T; Austrian Diabetes Incidence Study Group.Diabetic ketoacidosis at diagnosis in Austrian children in 1989-2008: a population-based analysis.Diabetologia. 2010 Jun; 53(6):1057-61. doi: 10.1007/s00125-010-1704-1. Epub 2010 Mar 7.

[87]) Pawłowicz M[1], Birkholz D, Niedźwiecki M, Balcerska ADifficulties or mistakes in diagnosing type 1 diabetes in children?--demographic factors influencing delayed diagnosis.Pediatr Diabetes. 2009 Dec;10(8):542-9. doi: 10.1111/j.1399-5448.2009.00516.x. Epub 2009 May 28.

[88] Maniatis AK[1], Goehrig SH, Gao D, Rewers A, Walravens P, Klingensmith GJ.Increased incidence and severity of diabetic ketoacidosis among uninsured children with newly diagnosed type 1 diabetes mellitus.Pediatr Diabetes. 2005 Jun; 6(2):79-83.

[89] Bui H[1], To T, Stein R, Fung K, Daneman D.Is diabetic ketoacidosis at disease onset a result of missed diagnosis?J Pediatr. 2010 Mar; 156(3):472-7. doi: 10.1016/j.jpeds.2009.10.001. Epub 2009 Dec 3.

[90]. Ketoacidosis at diabetes onset is still frequent in children and adolescents: a multicenter analysis of 14,664 patients from 106 institutions.Diabetes Care. 2009 Sep;32(9):1647-8. doi: 10.2337/dc09-0553. Epub 2009 Jun 23

[91]) Ketoacidosis at Diagnosis of Type 1 Diabetes in Children in Northern Finland Temporal changes over 20 years Anne Hekkala, MD1, Mikael Knip, MD, PHD23 and Riitta Veijola, MD, PHD1

[92]Neu A[1], Willasch A, Ehehalt S, Hub R, Ranke MB; DIARY Group Baden-Wuerttemberg.Ketoacidosis at onset of type 1 diabetes mellitus in children--frequency and clinical presentation.Pediatr Diabetes. 2003 Jun;4(2):77-81

[93] Abdul-Rasoul M[1], Al-Mahdi M, Al-Qattan H, Al-Tarkait N, Alkhouly M, Al-Safi R, Al-Shawaf F, Mahmoud HKetoacidosis at presentation of type 1 diabetes in children in Kuwait: frequency and clinical characteristics.Pediatr Diabetes. 2010 Aug; 11(5):351-6. doi: 10.1111/j.1399-5448.2009.00600.x.

[94] C. Choleau[1], J. Maitre[2], J.-J. Robert[2], M. Cahane[1], M. Cahane[3] Fréquence et circonstances de l'acidocétose inaugurale en France, à partir de 1 000 nouveaux cas de diabète de type 1 diagnostiqués dans 139 services de pédiatri

[95]: Lewis KR[1], Clark C, Velarde MC.10.1111/cen.12350. Epub 2013 Nov 19.Socioeconomic factors associated with pediatric diabetic ketoacidosis admissions in Southern West Virginia.
Clin Endocrinol (Oxf). 2014 Aug;81(2):218-21. Doi

[96] Jackson W[1], Hofman PL, Robinson EM, Elliot RB, Pilcher CC, Cutfield WSThe changing presentation of children with newly diagnosed type 1 diabetes mellitus.Pediatr Diabetes. 2001 Dec; 2(4):154-9.

.[97] Rosenbauer, J (Rosenbauer, J); Icks, A (Icks, A); Giani, G (Giani, G) Clinical characteristics and predictors of severe ketoacidosis at onset of type 1 diabetes mellitus in children in a North Rhine-Westphalian region, Germany JOURNAL OF PEDIATRIC ENDOCRINOLOGY & METABOLISM Volume: 15 Issue: 8 Pages: 1137-1145

[98] Lévy-Marchal C[1], Patterson CC, Green A; EURODIAB ACE Study Group. Europe and Diabetes.Geographical variation of presentation at diagnosis of type I diabetes in children: the EURODIAB study. European and Dibetes. Diabetologia. 2001 Oct;44 Suppl 3:B75-80.

[99] Monabeka HG[1], Mbika-Cardorelle A, Moyen G.[Ketoacidosis in children and teenagers in Congo]. Sante. 2003 Jul-Sep;13(3):139-41.110/100

[100] Pocecco M[1], Nassimbeni G. [Distribution of new cases of insulin-dependent diabetes mellitus (IDDM) by age, sex, seasonality, and clinical characteristics at onset in youngsters from the Friuli Venezia Giulia region from 1987 to 1990]. Pediatr Med Chir. 1993 Sep-Oct;15(5):489-92.

[101] Olak-Białoń B[1], Deja G, Jarosz-Chobot P, Buczkowska EO.[The occurrence and analysis of chosen risk factors of DKA among children with new onset of DMT1].)Pediatr Endocrinol Diabetes Metab. 2007;13(2):85-90.

[102] Naeem MA[1], Al-Alem HA, Al-Dubayee MS, Al-Juraibah FN, Omair A, Al-Ruwaili AS, Al-Saleh AM.Characteristics of pediatric diabetic ketoacidosis patients in Saudi Arabia. Saudi Med J. 2015 Jan;36(1):20-5. doi: 10.15537/smj.2015.1.9763.

[103] Ting WH[1], Huang CY, Lo FS, Hung CM, Chan CJ, Li HJ, Lin CH, Lee HC, Lee YJ.Clinical and laboratory characteristics of type 1 diabetes in children and adolescents: experience from a medical center. Acta Paediatr Taiwan. 2007 May-Jun;48(3):119-24.

[104])) al Khawari M[1], Shaltout A, Qabazard M, Abdella N, al Moemen J, al-Mazidi Z, Mandani F, Moussa MA.Incidence and severity of ketoacidosis in childhood-onset diabetes in Kuwait. Kuwait Diabetes Study Group. Diabetes Res Clin Pract. 1997 Mar;35(2-3):123-8.

[105] Pinkey JH[1], Bingley PJ, Sawtell PA, Dunger DB, Gale EA Presentation and progress of childhood diabetes mellitus: a prospective population-based study. The Bart's-Oxford Study Group. Diabetologia. 1994 Jan;37(1):70-4.

[106] Mohamed A.Abdulah.Epidemiology of type 1 diabetes mellitus among Arab children .Saudi Med J 2005; Vol. 26 (6): 911-917.

ANNEXES

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Pediatric Diabetes

ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Definition, epidemiology, and classification of diabetes in children and adolescents

Craig ME, Jefferies C, Dabelea D, Balde N, Seth A, Donaghue KC. Definition, epidemiology, and classification of diabetes in children and adolescents. Pediatric Diabetes 2014: 15 (Suppl. 20): 4–17.

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Key words: adolescent – child – epidemiology – type 1 diabetes

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1-3).

Executive summary and Recommendations

- Diagnostic criteria for diabetes are based on laboratory measurement of plasma glucose concentrations and the presence or absence of symptoms (E). Finger prick blood glucose level (BGL) testing should not be used to diagnose diabetes (E).
- A marked elevation of the blood glucose level confirms the diagnosis. If ketones are present in blood or urine, treatment is urgent, and the child should be referred the same day to avoid the development of ketoacidosis (A).
- The diagnosis of diabetes should not be based on a single plasma glucose concentration. If the diagnosis is in doubt, continued observation with fasting and/or 2 h postprandial blood glucose levels and/or an oral glucose tolerance test (OGTT) may be required (E). However, an OGTT is not needed and should not be performed if diabetes can be diagnosed using fasting, random, or postprandial criteria as excessive hyperglycemia can result (E).
- Hyperglycemia detected under conditions of stress, such as acute infection, trauma, surgery, respiratory distress, circulatory, or other stress may be transitory and requires treatment but should not in itself be regarded as diagnostic of diabetes (E).
- The possibility of other types of diabetes should be considered in the child who has negative diabetes-associated autoantibodies and (B):
  - An autosomal dominant family history of diabetes.
  - Diabetes diagnosed in the first 6 months of life.
  - Mild fasting hyperglycemia [5.5–8.5 mmol (100–150 mg/dL)], which does not progress, especially if young, non-obese, and asymptomatic.
  - Associated conditions such as deafness, optic atrophy, or syndromic features.
  - A history of exposure to drugs known to be toxic to β cells or cause insulin resistance.
- The differentiation between type 1, type 2, monogenic, and other forms of diabetes has important implications for both treatment and

education (E). Diagnostic tools, which may assist in confirming the diabetes type if the diagnosis is unclear, include:

  - Diabetes-associated autoantibodies: Glutamic acid decarboxylase 65 autoantibodies (GAD); tyrosine phosphatase-like insulinoma antigen 2 (IA2); insulin autoantibodies (IAA); and β-cell-specific zinc transporter 8 autoantibodies (ZnT8). The presence of one of more of these antibodies confirms the diagnosis of type 1 diabetes (A).
  - OGTT (A).
  - Haemoglobin A1c (HbA1c) (B).

- Molecular genetic testing can help define the diagnosis and treatment of children with suspected monogenic diabetes. All patients diagnosed with diabetes in the first 6 months of life should have immediate molecular genetic testing to define their subtype of neonatal diabetes mellitus (NDM), as type 1 diabetes is extremely rare in this subgroup (B). Beyond the age of 6 months, genetic testing should be limited to those with negative autoantibodies (particularly if measured at diagnosis), who have clinical features suggestive of monogenic diabetes who on clinical grounds are likely to be positive (E).

Definition and description

The term diabetes mellitus describes a complex metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Inadequate insulin secretion and/or diminished tissue responses to insulin in the complex pathways of hormone action result in deficient insulin action on target tissues, which leads to abnormalities of carbohydrate, fat, and protein metabolism. Impaired insulin secretion and/or action may coexist in the same patient (1, 2).

While the etiology of diabetes is heterogeneous, most cases of diabetes can be classified into two broad etiopathogenetic categories (discussed in further detail below): type 1 diabetes, which is characterized by an absolute deficiency of insulin secretion; or type 2 diabetes, which results from a combination of resistance to insulin action and an inadequate compensatory insulin secretory response. While type 1 diabetes remains the most common form of diabetes in young people in many populations, especially those of Caucasian background, type 2 diabetes has become an increasingly important public health concern globally, see the ISPAD guideline on type 2 diabetes (3).

Diagnostic criteria for diabetes in childhood and adolescence

Diagnostic criteria for diabetes are based on blood glucose measurements and the presence or absence of symptoms (1, 4). Different methods can be used to diagnose diabetes (Table 1) and in the absence of unequivocal hyperglycemia, must be confirmed by repeat testing.

- Diabetes in young people usually presents with characteristic symptoms such as polyuria, polydipsia, nocturia, enuresis, weight loss – which may be accompanied by polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also accompany chronic hyperglycemia.
- In its most severe form, ketoacidosis or less commonly non-ketotic hyperosmolar syndrome may develop and lead to stupor, coma and in the absence of effective treatment, death.
- If symptoms are present, urinary 'dipstick' testing for glycosuria and ketonuria, or measurement of glucose and ketones using a bedside glucometer, provides a simple and sensitive screening tool. If the blood glucose level is elevated, then prompt referral to a center with experience in managing children with diabetes is essential. Waiting another day specifically to confirm the hyperglycemia is unnecessary and if

Table 1. Criteria for the diagnosis of diabetes mellitus (1, 2)

i Classic symptoms of diabetes or hyperglycemic crisis, with plasma glucose concentration ≥11.1 mmol/L (200 mg/dL) or

ii Fasting plasma glucose ≥7.0 mmol/L (≥126 mg/dL). Fasting is defined as no caloric intake for at least 8 h* or

iii Two hour postload glucose ≥11.1 mmol/L (≥200 mg/dL) during an OGTT*.

- The test should be performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water or 1.75 g/kg of body weight to a maximum of 75 g or

iv HbA1c >6.5%†

- The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay

HbA1c, hemoglobin A1c; OGTT, oral glucose tolerance test
*In the absence of unequivocal hyperglycemia, the diagnosis of diabetes based on these criteria should be confirmed by repeat testing.
†A value of less than 6.5% does not exclude diabetes diagnosed using glucose tests. The role of HbA1c alone in diagnosing type 1 diabetes in children is unclear.

ketones are present in blood or urine, treatment is urgent, because ketoacidosis can evolve rapidly.
- A formal plasma glucose measurement is required to confirm the diagnosis; this should be based on laboratory glucose oxidase estimation rather than a capillary blood glucose monitor.
- Scenarios where the diagnosis of diabetes may be unclear include:

  ◦ Absence of symptoms, for example, hyperglycemia detected incidentally or in children participating in screening studies
  ◦ Presence of mild/atypical symptoms of diabetes
  ◦ Hyperglycemia detected under conditions of acute infective, traumatic, circulatory, or other stress, which may be transitory and should not be regarded as diagnostic of diabetes.

In these situations, the diagnosis of diabetes should not be based on a single plasma glucose concentration and continued observation with fasting and 2 h postprandial blood glucose levels and/or an OGTT may be required to confirm the diagnosis.

- An OGTT is not required and should not be performed if diabetes can be diagnosed using fasting, random, or postprandial criteria as excessive hyperglycemia can result. It is rarely indicated in making the diagnosis of type 1 diabetes in childhood and adolescence, but may be useful in diagnosing other forms such as type 2 diabetes, monogenic diabetes, or cystic fibrosis related diabetes (CFRD). If doubt remains, periodic retesting should be undertaken until the diagnosis is established.
- HbA1c can be used as a diagnostic test for diabetes providing that stringent quality assurance tests are in place and assays are standardized to criteria aligned to the international reference values, and there are no conditions present which preclude its accurate measurement (2, 5). However, in rapidly evolving diabetes, such as the development of type 1 diabetes in some children, HbA1c may not be significantly elevated despite classic symptoms of diabetes.

Impaired glucose tolerance and impaired fasting glucose

Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) are intermediate stages in the natural history of disordered carbohydrate metabolism between normal glucose homeostasis and diabetes (2). IFG and IGT are not interchangeable and represent different abnormalities of glucose regulation or different stages in the progression of dysglycemia. IFG is a measure of disturbed carbohydrate metabolism in the basal state while IGT is a dynamic measure of carbohydrate intolerance after a standardized glucose load. IFG and IGT are not clinical entities in their own right; patients with IFG and/or IGT are referred to as having 'prediabetes' indicating their relatively high risk for development of diabetes and cardiovascular disease.

IFG and IGT may be associated with the metabolic syndrome, the features of which include obesity (particularly abdominal or visceral obesity), dyslipidemia [high triglyceride and/or low-high-density lipoprotein (HDL)], and hypertension. IFG and IGT can be observed as intermediate stages in any of the disease processes listed in Table 2 (etiologic classification of diabetes).

Individuals who meet criteria for IGT or IFG may be euglycemic in their daily lives as shown by normal or near-normal HbA1c, and those with IGT may manifest hyperglycemia only when challenged with an OGTT.

Categories of fasting plasma glucose (FPG) are defined as follows:

- FPG <5.6 mmol/L (100 mg/dL) = normal fasting glucose.
- FPG 5.6–6.9 mmol/L (100–125 mg/dL) = IFG.
- FPG ≥ 7.0 mmol/L (126 mg/dL) = provisional diagnosis of diabetes (the diagnosis must be confirmed, as described in Table 1).

The corresponding categories when the OGTT is used are as follows:

- Two hour postload glucose <7.8 mmol/L (140 mg/dL) = normal glucose tolerance.
- Two hour postload glucose 7.8–<11.1 mmol/L (140–200 mg/dL) = IGT.
- Two hour postload glucose ≥ 11.1 mmol/L (200 mg/dL) = provisional diagnosis of diabetes (the diagnosis must be confirmed, as described above).

Classification of diabetes and other categories of glucose regulation

The type of diabetes assigned to a young person at diagnosis is typically based on their characteristics at presentation, however, increasingly the ability to make a clinical diagnosis has been hampered by factors including the increasing prevalence of overweight in young people with type 1 diabetes (6, 7) and the presence of diabetic ketoacidosis (DKA) in some young people at diagnosis of type 2 diabetes (8, 9). In addition, the presentation of a familial form of mild diabetes during adolescence should raise the suspicion of monogenic diabetes, which accounts for 1–4% of pediatric diabetes cases (10–13).

The etiological classification of diabetes is shown in Table 2, which is based on the American Diabetes

Table 2. Etiological classification of diabetes

I. Type 1
β-Cell destruction, usually leading to absolute insulin deficiency
A. Immune mediated
B. Idiopathic

II. Type 2
May range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance

III. Other specific types

A. Genetic defects of β-cell function
1. Chromosome 12, *HNF1A* (MODY3)
2. Chromosome 7, *GCK* (MODY2)
3. Chromosome 20, *HNF4B* (MODY1)
4. Other rare forms of MODY including:
   Chromosome 13, *IPF-1* (MODY4);
   Chromosome 17, *HNF1B* (MODY5);
   Chromosome 2, *NEUROD1* (MODY6);
   Chromosome 2, *KLF11* (MODY7);
   Chromosome 9, *CEL* (MODY8);
   Chromosome 7, *PAX4* (MODY9)
5. TNDM (most commonly *PLAGL1/HYMAI* imprinting defect on 6q24)
6. PNDM (most commonly *KCNJ11* gene encoding Kir6.2 subunit of beta-cell KATP channel)
7. Mitochondrial DNA mutation
8. Others

B. Genetic defects in insulin action
1. Type A insulin resistance
2. Leprechaunism
3. Rabson–Mendenhall syndrome
4. Lipoatrophic diabetes
5. Others

C. Diseases of the exocrine pancreas
1. Pancreatitis
2. Trauma/pancreatectomy
3. Neoplasia
4. Cystic fibrosis
5. Hemochromatosis
6. Fibrocalculous pancreatopathy
7. Others

D. Endocrinopathies
1. Acromegaly
2. Cushing's syndrome
3. Glucagonoma
4. Phaeochromocytoma
5. Hyperthyroidism
6. Somatostatinoma
7. Aldosteronoma
8. Others

E. Drug- or chemical-induced
1. Vacor
2. Pentamidine
3. Nicotinic acid
4. Glucocorticoids
5. Thyroid hormone
6. Diazoxide
7. β-Adrenergic agonists
8. Thiazides
9. Dilantin
10. α-Interferon
11. Others

F. Infections
1. Congenital rubella
2. Cytomegalovirus
3. Enterovirus
4. Others

G. Uncommon forms of immune-mediated diabetes
1. 'Stiff-man' syndrome
2. Anti-insulin receptor antibodies
3. Autoimmune polyendocrine syndrome (APS) types I and II
4. IPEX
5. Others

H. Other genetic syndromes sometimes associated with diabetes
1. Down syndrome
2. Klinefelter syndrome
3. Turner syndrome
4. Wolfram syndrome
5. Friedreich's ataxia
6. Huntington's chorea
7. Laurence–Moon–Biedl syndrome
8. Myotonic dystrophy
9. Porphyria
10. Prader–Willi syndrome
11. Others

IV. Gestational diabetes mellitus (GDM)

CEL, carboxyl ester lipase; HNF, hepatocyte nuclear factor; IPEX, immunodysregulation polyendocrinopathy enteropathy X-linked syndrome; IPF, insulin promoter factor; *KLF11*, Kruppel-like factor 11; MODY, maturity-onset diabetes of the young; *PAX4*, Paired Domain gene 4.
Individuals with any form of diabetes may or may not require insulin treatment at various stages of their disease. Such use of insulin does not, of itself, classify the diabetes type.

Association classification (2). Some forms, including specific drug-, hormone-, or toxin-induced forms of diabetes, are rarely observed in young people. In Africa and South Asia, atypical forms of diabetes may occur in older children, adolescents, and young adults. These include ketosis-prone atypical diabetes, malnutrition-related diabetes, and fibrocalculous pancreatic disease (14, 15).

The differentiation between type 1, type 2, monogenic, and other forms of diabetes has important

implications for both therapeutic decisions and educational approaches. Diagnostic tools, which may assist in confirming the diabetes type, include:

- Diabetes-associated autoantibodies: the presence of GAD, IA2, IAA, and/or ZnT8 confirms the diagnosis of type 1 diabetes, as one and usually more of these autoantibodies are present in 85–90% of individuals when fasting hyperglycemia is initially detected (16).
- An elevated fasting C-peptide level can distinguish young people with non-autoimmune, insulin resistant type 2 diabetes from type 1 diabetes (17). However, as there is considerable overlap in insulin or C-peptide measurements between type 1 and type 2 diabetes in the first year after diagnosis, C-peptide measurements are not recommended in the acute phase. If patients are insulin treated, measuring C-peptide when the glucose is sufficiently high (>8 mmol/L) to stimulate C peptide will detect if endogenous insulin secretion is still present. This is rare beyond the remission phase (2–3 yr) in children with type 1 diabetes.

The possibility of other types of diabetes should be considered in the child who has no autoantibodies and:

- an autosomal dominant family history of diabetes;
- diabetes diagnosed in the first 6 months of life;
- mild fasting hyperglycemia [5.5–8.5 mmol (100–150 mg/dL)], which does not progress, especially if young, non-obese, and asymptomatic;
- associated conditions such as deafness, optic atrophy, or syndromic features; and
- a history of exposure to drugs known to be toxic to β cells or cause insulin resistance.

Characteristic features of youth onset type 1 diabetes in comparison with type 2 diabetes and monogenic diabetes are shown in Table 3. Type 2 diabetes is more completely discussed in the ISPAD guidelines on type 2 diabetes (3) and monogenic diabetes (18).

Regardless of the type of diabetes, however, the child who presents with severe hyperglycemia, ketonemia, and metabolic derangements will require insulin therapy initially to reverse the metabolic abnormalities.

Pathogenesis of type 1 diabetes

Type 1 diabetes is characterized by chronic immune-mediated destruction of pancreatic β-cells, leading to partial, or in most cases, absolute insulin deficiency. The majority of cases (type 1A) result from autoimmune mediated pancreatic β-cell destruction, which occurs at a variable rate, and becomes clinically symptomatic when approximately 90% of pancreatic β-cells are destroyed. The etiology is multifactorial, however, the specific roles for genetic susceptibility, environmental factors, the immune system, and β-cells in the pathogenic processes underlying type 1 diabetes remain unclear.

Diabetes-associated autoantibodies, which are serological markers of β-cell autoimmunity, include GAD, IA2, IAA, and ZnT8 (16). The expression of these antibodies is age-dependent, with IAA and ZnT8 more commonly expressed in children aged <10 yr, while GAD and IA-2 are associated with older age and GAD with female gender (19).

Susceptibility to autoimmune type 1 diabetes is determined by multiple genes; with more than 60 risk loci identified by genome-wide association studies (20). Human leukocyte antigen (HLA) genotype confers approximately 50% of risk (21, 22); in the Caucasian population, specific combinations of HLA DR and DQ alleles determine genetic susceptibility (23). The highest-risk haplotypes are DRB1*03:01-DQA1*05:01-DQB1*02:01 and DRB1*04-DQA1*03:01-DQB1*03:02 (also expressed as DR3/DR4 or DQ2/DQ8 using the former serological designation). Haplotypes conferring protection from type 1 diabetes are DRB1*15:01-DQA1*01:02-DQB1*06:02, DRB1*14:01-DQA1*01:01-DQB*05:03, and DRB1*07:01-DQA1*02:01-DQB1*03:03 (24). For individuals who are heterozygotes for the two highest risk HLA haplotypes (DR3/4), the odds ratio is 30 for development of islet autoimmunity and type 1 diabetes (24), however, <10% of those with HLA conferred diabetes susceptibility genes progress to clinical disease (25).

Individuals at increased risk of developing type 1 diabetes can be identified by a combination of diabetes-associated autoantibodies, genetic markers, intravenous glucose tolerance test (IVGTT) and/or OGTT (26–30).

The environmental triggers (infective and/or chemical) which initiate pancreatic β-cell destruction remain largely unknown, but the process usually begins months to years before the manifestation of clinical symptoms (28, 31, 32). Enterovirus infection has been associated with development of both islet autoimmunity and type 1 diabetes in many populations (33, 34) and enteroviruses have been detected in the islets of individuals with diabetes (35–37).

When the clinical presentation is typical of type 1 diabetes but antibodies are absent, then the diabetes is classified as type 1B (idiopathic). Most cases are of African or Asian ancestry, however, other forms of diabetes, including type 2 and monogenic diabetes, should also be considered (as shown in Table 2). In geographical areas where type 1 diabetes occurs with lower incidence, there is a higher rate of DKA at presentation (38).

Table 3. Clinical characteristics of type 1, type 2 and monogenic diabetes in children and adolescents

Characteristic	Type 1	Type 2	Monogenic
Genetics	Polygenic	Polygenic	Monogenic
Age of onset	6 months to young adulthood	Usually pubertal (or later)	Often postpubertal except *GCK* and NDM
Clinical presentation	Most often acute, rapid	Variable; from slow, mild (often insidious) to severe	Variable (may be incidental in *GCK*)
Associations			
Autoimmunity	Yes	No	No
Ketosis	Common	Uncommon	Common in NDM, rare in other forms
Obesity	Population frequency	Increased frequency	Population frequency
Acanthosis nigricans	No	Yes	No
Frequency (% of all diabetes in young people)	Usually >90%	Most countries <10% (Japan 60–80%)	1–4%
Parent with diabetes	2–4%	80%	90%

Epidemiology of type 1 diabetes

In most western countries, type 1 diabetes accounts for over 90% of childhood and adolescent diabetes, while across the lifespan, type 1 diabetes accounts for 5–10% of individuals with diabetes. Overall, approximately 80 000 children under 15 yr are estimated to develop type 1 diabetes annually worldwide (39). Type 2 diabetes is becoming more common and accounts for a significant proportion of youth onset diabetes in certain at-risk populations (3), but population-based epidemiological data are more limited compared with type 1 diabetes.

Older epidemiological incidence studies define the 'onset of type 1 diabetes' by the date of the first insulin injection because of the variable time between the onset of symptoms and diagnosis (40), while current guidelines define diabetes based on abnormal test results (as shown in Table 1).

Type 1 diabetes incidence varies greatly between different countries, within countries, and between different ethnic populations (Figure 1), with the highest incidence rates observed in Finland (41), Northern Europe (42–44), and Canada (45). There is an approximate 20-fold difference in the disease incidence among Caucasians living in Europe (25), and incidence rates are correlated with the frequency of HLA susceptibility genes in the general population (46, 47).

Of the estimated approximately 500 000 children living with type 1 diabetes, approximately 26% are from Europe, and 22% from North America and the Caribbean region (39). In Asia, the incidence of type 1 diabetes is very low, Japan approximately 2 per 100 000 person-years (48); China (Shanghai) 3.1 per 100 000 (49); Taiwan approximately 5 per 100 000 (50) and has a different and unique HLA association compared with Caucasians (51–54). In addition, there is a distinct slowly progressive form of type 1 diabetes in Japan, which represents approximately one third of cases of type 1 diabetes (55, 56). Mean annual incidence rates for childhood type 1 diabetes (<age 15 yr) comparing different countries globally are shown in Fig. 1.

A seasonal variation in the presentation of new cases is well described, with the peak being in the winter months, whereas other reports demonstrate higher rates in warmer seasons (49) or variation from year to year (57–59). In addition, development of islet autoimmunity also demonstrates seasonal variation, as does the association between month of birth and risk of type 1 diabetes (60, 61).

In contrast to most autoimmune disorders, which disproportionately affect females, gender differences in the incidence of type 1 diabetes are found in some, but not all, populations. However, a male gender bias is generally observed in older adolescents and young adults (59, 62, 63).

A rise in type 1 diabetes incidence has been observed globally in recent decades (41, 43, 49, 50, 57–59, 64–72). In some reports there has been a disproportionately greater increase in those under the age of 5 yr (64, 73) and in developing countries or those undergoing economic transition in recent decades (64, 68). There is evidence for a plateau in incidence in some countries in recent years (41, 43, 69, 74, 75). The rising incidence of type 1 diabetes is associated with an increased proportion of individuals with low-risk HLA genotypes in some populations (76–78), suggesting an increasing role for environmental factors in the disease etiology.

Familial aggregation accounts for approximately 10% of cases of type 1 diabetes (79), but more than 20% when accounting for the extended family history (80), however, there is no recognizable pattern of inheritance. The risk of diabetes to an identical twin of a patient with type 1 diabetes is <40% (25, 81); for a sibling the risk is approximately 4% by age 20 yr (82, 83) and 9.6% by age 60 yr (49); compared with 0.5% for

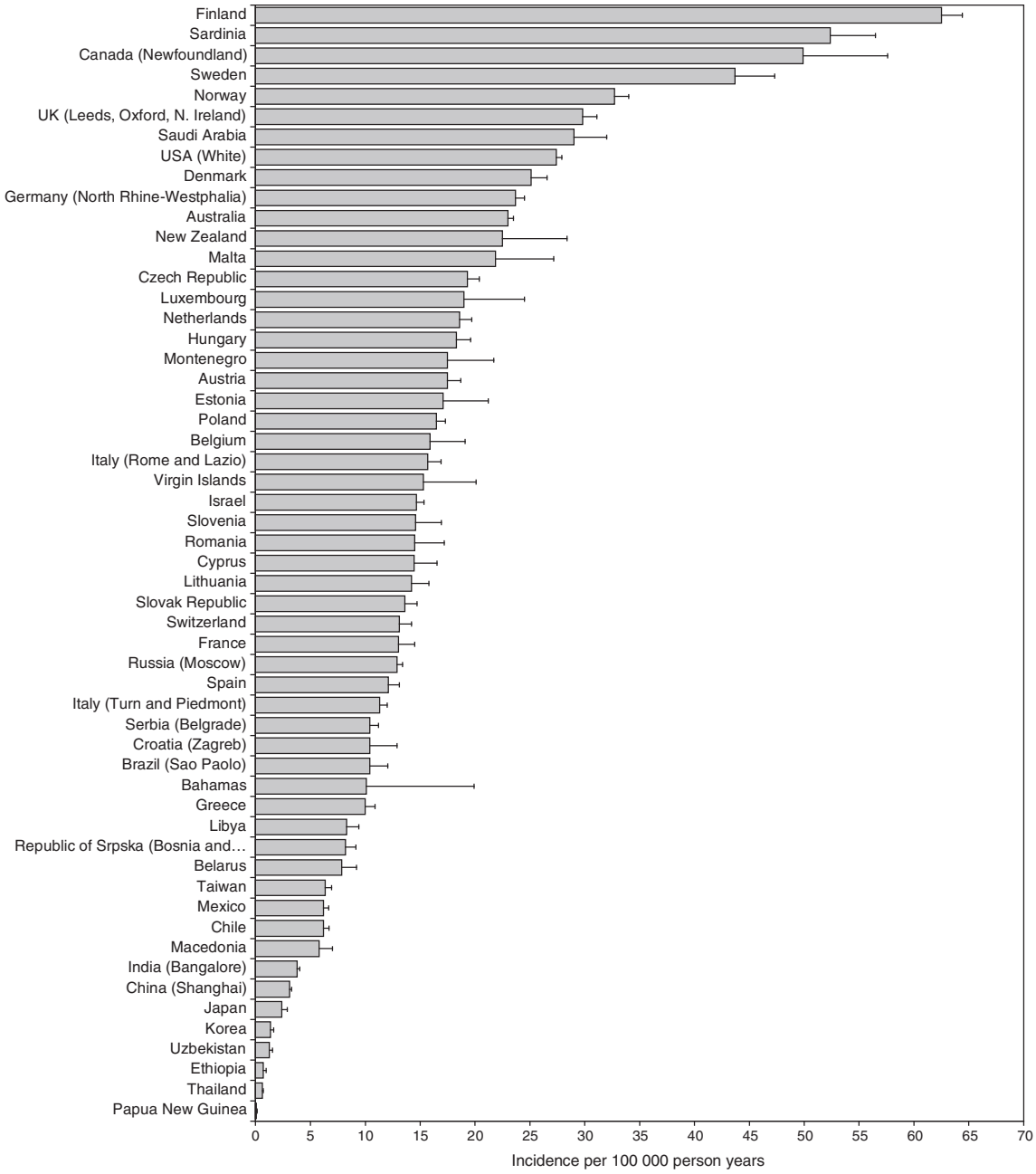

Fig. 1. Global mean annual incidence rates of type 1 diabetes in children and adolescents aged 0–14 yr. Only countries in which the study period included data from 2000 onwards are shown [adapted from the International Federation atlas (39)].

the general population. The cumulative risk of diabetes by age 15 is greater in HLA-identical DR3-DQ2/DR4-DQ8 siblings (17 vs. 6% in those sharing one haplotype or none) (84). The risk is also higher in siblings of probands diagnosed at younger age, paternal young-onset diabetes, male sex, and older parental age (82, 84, 85).

Type 1 diabetes is two to three times more common in the offspring of diabetic men (3.6–8.5%) compared with diabetic women (1.3–3.6%) (85–90). The cumulative risk of type 1 diabetes is approximately 4% for offspring of adult onset (15–39 yr) type 1 diabetes (91), with a similar recurrence risk in the offspring of mothers and fathers.

Monogenic diabetes

A familial form of mild, non-ketotic diabetes presenting during adolescence or early adulthood (92, 93),

originally termed maturity-onset diabetes of the young (MODY), is now recognized as a group of disorders which result from dominantly acting heterozygous mutations in genes important for the development or function of β cells (93, 94). Despite the classical description of MODY as a disorder with onset before 25 yr of age, autosomal dominant inheritance and non-ketotic diabetes mellitus (94, 95), it is clear that there is considerable overlap in the presentation of type 1, type 2, and monogenic diabetes. With the increased recognition of type 2 diabetes in young people, many will meet all of the 'classical' criteria for monogenic diabetes, but may initially be classified as having type 2 diabetes (96). Certain clinical characteristics should alert the clinician to the possibility of monogenic diabetes, as outlined in Table 3.

It is now considered more appropriate to define monogenic diabetes by its genetic subgroups, as shown in Table 2.

The most common form is associated with mutations in the transcription factor hepatocyte nuclear factor-1α (*HNF1A*, also known as MODY3). Mutations in the glucokinase gene (*GCK*) and *HNF4A* contribute to the majority of remaining cases, while rare forms result from mutations in other transcription factors, including *HNF1B*, insulin promoter factor (*IPF*)-*1*, and *NeuroD1* (Table 2) (2, 94); for further detail see The ISPAD guideline on Monogenic Diabetes (18).

Within the diagnostic groups of monogenic diabetes, there is great variation in the degree of hyperglycemia, need for insulin, and risk for future complications.

Making a specific molecular diagnosis helps predict the expected clinical course of the disease, guide the most appropriate management for an individual, and has important implications for family members, enabling genetic counseling and extended genetic testing in other diabetic family members, whose diabetes may eventually be reclassified (97).

Neonatal diabetes

Type 1 diabetes rarely presents in the first year of life, particularly before age 6 months (98, 99), and in very young infants is most likely to be due to mutations in the transcription factor FOXP3 as part of the immunodysregulation polyendocrinopathy enteropathy X-linked syndrome (IPEX) syndrome (100). A monogenic form of diabetes in the first 6 months of life is known as NDM, although cases may present as late 9–12 months of age (101–103). An alternative term, 'monogenic diabetes of infancy' has therefore been suggested to account for the fact that many cases are diagnosed beyond the neonatal period (104), but NDM is still widely used.

This rare condition (approximately 1 in 100 000–400 000 births) may be associated with intrauterine growth retardation, a consequence of prenatal insulin deficiency (105, 106), as well a as range of associated extra-pancreatic clinical features.

Approximately half of NDM cases will require lifelong treatment to control hyperglycemia (permanent NDM (PNDM)). In the remaining cases, diabetes remits within weeks or months (transient NDM (TNDM)), although may relapse later in life.

Approximately two thirds of cases of TNDM are caused by abnormalities in an imprinted region on chromosome 6q24 (107, 108). The majority of remaining cases result from activating mutations in either of the genes encoding the two subunits of the ATP-sensitive potassium (K_{ATP}) channel of the β-cell membrane (*KCNJ11*, encoding the Kir6.2 subunit, or *ABCC8*, encoding the SUR1 subunit) (109). Although diabetes is transient during infancy, permanent diabetes appears in 50–60% of patients later in life, typically around puberty (110).

PNDM is associated with activating mutations of *KCNJ11* and *ABCC8* (111, 112) and mutations in the insulin gene (*INS*) (113–117) and less commonly, *GCK* (118, 119) and the transcription factor for pancreatic development, *PDX1* (120). In addition, a range of syndromic forms of diabetes may present during infancy. Further details of the genetic basis of NDM are provided in the chapter on The diagnosis and management of monogenic diabetes in children and adolescents (18).

Mitochondrial diabetes

Mitochondrial diabetes is commonly associated with sensorineural deafness and is characterized by progressive non-autoimmune β-cell failure (121, 122). Maternal transmission of mutated mitochondrial DNA (mtDNA) can result in maternally inherited diabetes. The most common mutation occurs at position 3243 in the tRNA leucine gene, leading to an A-to-G transition (123, 124).

Mitochondrial diabetes may present with variable phenotypes, ranging from acute onset with or without ketoacidosis, to a more gradual onset resembling type 2 diabetes. The disease typically presents in young adults (121), but can occur in children and adolescents, who have a lower prevalence of hearing loss compared with adults (125).

Cystic fibrosis and diabetes

CFRD is the most common comorbidity associated with cystic fibrosis (CF). The pathophysiology of CFRD is primarily due to insulin deficiency, along with glucagon deficiency and variable insulin resistance (particularly during acute illness, secondary to infections and medications such as bronchodilators and glucocorticoids). Other contributory factors include the need for high caloric intake, delayed

gastric emptying, altered intestinal motility, and liver disease (126).

CF is associated with a progressive deterioration in glucose tolerance as individuals grow older, including indeterminate glycemia followed by IGT and finally diabetes. Early CFRD is characterized by normal fasting glucose levels, but over time fasting hyperglycemia develops.

CFRD typically presents in adolescence and early adulthood (127), but may occur at any age including infancy. The presentation may be asymptomatic, insidious, associated with poor weight gain (128), or precipitated by insulin resistance associated with infection/use of glucocorticoids. Detection rates for CFRD vary with screening practices (129). The onset of CFRD is defined as the date a person with CF first meets diabetes diagnostic criteria, even if hyperglycemia subsequently abates.

The onset of CFRD is a poor prognostic sign, and was associated with increased morbidity and mortality reported prior to implementation of routine screening for CFRD and early use of insulin therapy (130). Poorly controlled CFRD interferes with immune responses to infection and promotes protein catabolism (129, 131).

Annual screening for CFRD should commence by age 10 yr in all CF patients who do not have CFRD. Screening should be performed using the 2-h 75 g (1.75 g/kg) OGTT. A more comprehensive discussion can be found in the ISPAD guideline on CFRD (132).

Diabetes induced by drugs and toxins

A range of pharmacological agents impair insulin secretion (e.g., propranolol), and/or action (e.g., glucocorticoids, antipsychotic agents), while others (e.g., pentamidine) can cause permanent β-cell damage (2, 133, 134).

In neurosurgery, large doses of dexamethasone are frequently used to prevent cerebral edema. The additional stress of surgery may add to the drug-induced insulin resistance, and cause a relative insulin deficiency, sufficient to cause transient diabetes. Hyperglycemia may be exacerbated if large volumes of intravenous dextrose are given for management of diabetes insipidus. An intravenous insulin infusion is the optimal method to control the hyperglycemia, which is usually transient.

In oncology, protocols which employ L-asparaginase, high dose glucocorticoids, cyclosporin, or tacrolimus (FK506) may be associated with diabetes. L-Asparaginase usually causes a reversible form of diabetes (135). Tacrolimus and cyclosporin may cause a permanent form of diabetes possibly due to islet cell destruction (136). Often the diabetes is cyclical and associated with the chemotherapy cycles, especially if associated with large doses of glucocorticoids.

Following organ transplantation, diabetes most frequently occurs with the use of high dose glucocorticoids and tacrolimus; the risk is increased in patients with preexisting obesity (137–139).

Diabetes can also be induced by the use of atypical antipsychotics including olanzapine, risperidol, quetiapine, and ziprasidone, which may be associated with weight gain. In children and adolescents, use of antipsychotics was associated with a more than threefold increased risk of non-autoimmune diabetes, and the risk was significantly higher with increasing cumulative dose (140). Among Canadian youth with medication-induced diabetes, risk factors for type 2 diabetes (family history of type 2 diabetes, obesity, non-caucasian ethnicity, and acanthosis nigricans) were less commonly observed than in youth with type 2 diabetes (141).

Stress hyperglycemia

Stress hyperglycemia has been reported in up to 5% of children presenting to an emergency department, in association with acute illness/sepsis; traumatic injuries, febrile seizures, burns, and elevated body temperature (>39°C) (142–145). However, the incidence of severe hyperglycemia (≥16.7 mmol/L or 300 mg/dL) was <1% and almost two thirds of patients had received glucose-influencing interventions before evaluation, suggesting the etiology may at least in part be iatrogenic (146).

The reported incidence of progression to overt diabetes varies from 0 to 32% (145, 147–152). Children with incidental hyperglycemia without a serious concomitant illness were more likely to develop diabetes than those with a serious illness (150). As would be expected, testing for diabetes-associated autoantibodies had a high positive and negative predictive value for the development of type 1 diabetes in children with stress hyperglycemia (150). In children who have sustained severe burns, insulin resistance may persist for up to 3 yr later (144).

Conflicts of interest

The authors have declared no conflicts of interest.

References

1. World Health Organisation. Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia: Report of a WHO/IDF Consultation. Geneva, Switzerland: World Health Organisation, 2006.
2. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014: 37 (Suppl. 1): S81–S90.
3. Zeitler P, Fu J, Tandon N et al. Type 2 diabetes in the child and adolescent. Pediatr Diabetes 2014: 15 (Suppl. 20): 26–46.

4. American Diabetes Association. Standards of medical care in diabetes – 2014. Diabetes Care 2014: 37 (Suppl. 1): S14–S80.
5. World Health Organization. Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus. Geneva, Switzerland: World Health Organization, 2011.
6. Islam ST, Abraham A, Donaghue KC et al. Plateau of adiposity in Australian children diagnosed with type 1 diabetes: a 20-year study. Diabet Med 2014: 31: 686–690.
7. Kapellen TM, Gausche R, Dost A et al. Children and adolescents with type 1 diabetes in Germany are more overweight than healthy controls: results comparing DPV database and CrescNet database. J Pediatr Endocrinol Metab 2014: 27: 209–214.
8. Rewers A, Klingensmith G, Davis C et al. Presence of diabetic ketoacidosis at diagnosis of diabetes mellitus in youth: the Search for Diabetes in Youth Study. Pediatrics 2008: 121: e1258–e1266.
9. Dabelea D, Rewers A, Stafford JM et al. Trends in the prevalence of ketoacidosis at diabetes diagnosis: the SEARCH for diabetes in youth study. Pediatrics 2014: 133: e938–e945.
10. Fendler W, Borowiec M, Baranowska-Jazwiecka A et al. Prevalence of monogenic diabetes amongst Polish children after a nationwide genetic screening campaign. Diabetologia 2012: 55: 2631–2635.
11. Irgens HU, Molnes J, Johansson BB et al. Prevalence of monogenic diabetes in the population-based Norwegian Childhood Diabetes Registry. Diabetologia 2013: 56: 1512–1519.
12. Pihoker C, Gilliam LK, Ellard S et al. Prevalence, characteristics and clinical diagnosis of maturity onset diabetes of the young due to mutations in HNF1A, HNF4A, and glucokinase: results from the SEARCH for Diabetes in Youth. J Clin Endocrinol Metab 2013: 98: 4055–4062.
13. Galler A, Stange T, Muller G et al. Incidence of childhood diabetes in children aged less than 15 years and its clinical and metabolic characteristics at the time of diagnosis: data from the Childhood Diabetes Registry of Saxony, Germany. Horm Res Paediatr 2010: 74: 285–291.
14. Gill GV, Mbanya JC, Ramaiya KL, Tesfaye S. A sub-Saharan African perspective of diabetes. Diabetologia 2009: 52: 8–16.
15. Barman KK, Premalatha G, Mohan V. Tropical chronic pancreatitis. Postgrad Med J 2003: 79: 606–615.
16. Watkins RA, Evans-Molina C, Blum JS, Dimeglio LA. Established and emerging biomarkers for the prediction of type 1 diabetes: a systematic review. Transl Res 2014: 164: 110–121.
17. Dabelea D, Pihoker C, Talton JW et al. Etiological approach to characterization of diabetes type: the SEARCH for Diabetes in Youth Study. Diabetes Care 2011: 34: 1628–1633.
18. Rubio-Cabezas O, Hattersley A, Njolstad P et al. The diagnosis and management of monogenic diabetes in children and adolescents. Pediatr Diabetes 2014: 15 (Suppl. 20): 47–64.
19. Howson JM, Stevens H, Smyth DJ et al. Evidence that HLA class I and II associations with type 1 diabetes, autoantibodies to GAD and autoantibodies to IA-2, are distinct. Diabetes 2011: 60: 2635–2644.
20. Barrett JC, Clayton DG, Concannon P et al. Genome-wide association study and meta-analysis find that over 40 loci affect risk of type 1 diabetes. Nat Genet 2009: 41: 703–707.
21. Noble JA, Valdes AM, Cook M, Klitz W, Thomson G, Erlich HA. The role of HLA class II genes in insulin-dependent diabetes mellitus: molecular analysis of 180 Caucasian, multiplex families. Am J Hum Genet 1996: 59: 1134–1148.
22. Lambert AP, Gillespie KM, Thomson G et al. Absolute risk of childhood-onset type 1 diabetes defined by human leukocyte antigen class II genotype: a population-based study in the United Kingdom. J Clin Endocrinol Metab 2004: 89: 4037–4043.
23. Nguyen C, Varney MD, Harrison LC, Morahan G. Definition of high-risk type 1 diabetes HLA-DR and HLA-DQ types using only three single nucleotide polymorphisms. Diabetes 2013: 62: 2135–2140.
24. Erlich H, Valdes AM, Noble J et al. HLA DR-DQ haplotypes and genotypes and type 1 diabetes risk: analysis of the type 1 diabetes genetics consortium families. Diabetes 2008: 57: 1084–1092.
25. Knip M. Pathogenesis of type 1 diabetes: implications for incidence trends. Horm Res Paediatr 2011: 76 (Suppl. 1): 57–64.
26. Aly TA, Ide A, Jahromi MM et al. Extreme genetic risk for type 1A diabetes. Proc Natl Acad Sci U S A 2006: 103: 14074–14079.
27. Steck AK, Wong R, Wagner B et al. Effects of non-HLA gene polymorphisms on development of islet autoimmunity and type 1 diabetes in a population with high-risk HLA-DR, DQ genotypes. Diabetes 2012: 61: 753–758.
28. Ziegler AG, Rewers M, Simell O et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. JAMA 2013: 309: 2473–2479.
29. Bonifacio E, Krumsiek J, Winkler C, Theis FJ, Ziegler AG. A strategy to find gene combinations that identify children who progress rapidly to type 1 diabetes after islet autoantibody seroconversion. Acta Diabetol 2014: 51: 403–411.
30. DPT-1 Study Group. Effects of insulin in relatives of patients with type 1 diabetes mellitus. N Engl J Med 2002: 346: 1685–1691.
31. Verge CF, Gianani R, Kawasaki E et al. Prediction of type I diabetes in first-degree relatives using a combination of insulin, GAD, and ICA512bdc/IA-2 autoantibodies. Diabetes 1996: 45: 926–933.
32. Skyler JS, Krischer JP, Wolfsdorf J et al. Effects of oral insulin in relatives of patients with type 1 diabetes: the diabetes prevention trial – type 1. Diabetes Care 2005: 28: 1068–1076.
33. Yeung G, Rawlinson WD, Craig ME. Enterovirus infection and type 1 diabetes mellitus – a systematic review of molecular studies. BMJ 2011: 342: d35.
34. Laitinen OH, Honkanen H, Pakkanen O et al. Coxsackievirus B1 is associated with induction of beta-cell autoimmunity that portends type 1 diabetes. Diabetes 2014: 63: 446–455.
35. Richardson SJ, Willcox A, Bone AJ, Foulis AK, Morgan NG. The prevalence of enteroviral

capsid protein vp1 immunostaining in pancreatic islets in human type 1 diabetes. Diabetologia 2009: 52: 1143–1151.
36. Dotta F, Censini S, van Halteren AG et al. Coxsackie B4 virus infection of beta cells and natural killer cell insulitis in recent-onset type 1 diabetic patients. Proc Natl Acad Sci U S A 2007: 104: 5115–5120.
37. Richardson SJ, Leete P, Bone AJ, Foulis AK, Morgan NG. Expression of the enteroviral capsid protein VP1 in the islet cells of patients with type 1 diabetes is associated with induction of protein kinase R and downregulation of Mcl-1. Diabetologia 2013: 56: 185–193.
38. Usher-Smith JA, Thompson MJ, Sharp SJ, Walter FM. Factors associated with the presence of diabetic ketoacidosis at diagnosis of diabetes in children and young adults: a systematic review. BMJ 2011: 343: d4092.
39. International Diabetes F. IDF Diabetes Atlas. 6th edn. Brussels, Belgium: International Diabetes F, 2013.
40. Diamond Project Group. Incidence and trends of childhood type 1 diabetes worldwide 1990-1999. Diabet Med 2006: 23: 857–866.
41. Harjutsalo V, Sund R, Knip M, Groop PH. Incidence of type 1 diabetes in Finland. JAMA 2013: 310: 427–428.
42. Berhan Y, Waernbaum I, Lind T, Mollsten A, Dahlquist G, Swedish Childhood Diabetes Study Group. Thirty years of prospective nationwide incidence of childhood type 1 diabetes: the accelerating increase by time tends to level off in Sweden. Diabetes 2011: 60: 577–581.
43. Skrivarhaug T, Stene LC, Drivvoll AK, Strom H, Joner G, Norwegian Childhood Diabetes Study Group. Incidence of type 1 diabetes in Norway among children aged 0-14 years between 1989 and 2012: has the incidence stopped rising? Results from the Norwegian Childhood Diabetes Registry. Diabetologia 2014: 57: 57–62.
44. Rawshani A, Landin-Olsson M, Svensson AM et al. The incidence of diabetes among 0-34 year olds in Sweden: new data and better methods. Diabetologia 2014: 57: 1375–1381.
45. Newhook LA, Penney S, Fiander J, Dowden J. Recent incidence of type 1 diabetes mellitus in children 0-14 years in Newfoundland and Labrador, Canada climbs to over 45/100,000: a retrospective time trend study. BMC Res Notes 2012: 5: 628.
46. Ilonen J, Reijonen H, Green A et al. Geographical differences within finland in the frequency of HLA-DQ genotypes associated with type 1 diabetes susceptibility. Eur J Immunogenet 2000: 27: 225–230.
47. Kukko M, Virtanen SM, Toivonen A et al. Geographical variation in risk HLA-DQB1 genotypes for type 1 diabetes and signs of beta-cell autoimmunity in a high-incidence country. Diabetes Care 2004: 27: 676–681.
48. Tajima N, Morimoto A. Epidemiology of childhood diabetes mellitus in Japan. Pediatr Endocrinol Rev 2012: 10 (Suppl. 1): 44–50.
49. Zhao Z, Sun C, Wang C et al. Rapidly rising incidence of childhood type 1 diabetes in Chinese population: epidemiology in Shanghai during 1997-2011. Acta Diabetol 2014: Apr 29. [Epub ahead of print] (PMID: 24777734).
50. Lin WH, Wang MC, Wang WM et al. Incidence of and mortality from type I diabetes in Taiwan from 1999 through 2010: a nationwide cohort study. PLoS One 2014: 9: e86172.
51. Park Y. Why is type 1 diabetes uncommon in Asia? Ann N Y Acad Sci 2006: 1079: 31–40.
52. Park YS, Wang CY, Ko KW et al. Combinations of HLA DR and DQ molecules determine the susceptibility to insulin-dependent diabetes mellitus in Koreans. Hum Immunol 1998: 59: 794–801.
53. Ikegami H, Fujisawa T, Kawabata Y, Noso S, Ogihara T. Genetics of type 1 diabetes: similarities and differences between Asian and Caucasian populations. Ann N Y Acad Sci 2006: 1079: 51–59.
54. Sugihara S. Genetic susceptibility of childhood type 1 diabetes mellitus in Japan. Pediatr Endocrinol Rev 2012: 10 (Suppl. 1): 62–71.
55. Urakami T, Suzuki J, Yoshida A, Saito H, Mugishima H. Incidence of children with slowly progressive form of type 1 diabetes detected by the urine glucose screening at schools in the Tokyo metropolitan area. Diabetes Res Clin Pract 2008: 80: 473–476.
56. Urakami T, Yoshida A, Suzuki J et al. Differences in prevalence of antibodies to GAD and IA-2 and their titers at diagnosis in children with slowly and rapidly progressive forms of type 1 diabetes. Diabetes Res Clin Pract 2009: 83: 89–93.
57. Imkampe AK, Gulliford MC. Trends in type 1 diabetes incidence in the UK in 0- to 14-year-olds and in 15- to 34-year-olds, 1991-2008. Diabet Med 2011: 28: 811–814.
58. Jarosz-Chobot P, Polanska J, Szadkowska A et al. Rapid increase in the incidence of type 1 diabetes in Polish children from 1989 to 2004, and predictions for 2010 to 2025. Diabetologia 2011: 54: 508–515.
59. Skordis N, Efstathiou E, Kyriakides TC et al. Epidemiology of type 1 diabetes mellitus in Cyprus: rising incidence at the dawn of the 21st century. Hormones (Athens) 2012: 11: 86–93.
60. Laron Z, Lewy H, Wilderman I et al. Seasonality of month of birth of children and adolescents with type 1 diabetes mellitus in homogenous and heterogeneous populations. Isr Med Assoc J 2005: 7: 381–384.
61. Kahn HS, Morgan TM, Case LD et al. Association of type 1 diabetes with month of birth among U.S. youth: the SEARCH for Diabetes in Youth Study. Diabetes Care 2009: 32: 2010–2015.
62. Weets I, Kaufman L, Van der Auwera B et al. Seasonality in clinical onset of type 1 diabetes in Belgian patients above the age of 10 is restricted to HLA-DQ2/DQ8-negative males, which explains the male to female excess in incidence. Diabetologia 2004: 47: 614–621.
63. Wandell PE, Carlsson AC. Time trends and gender differences in incidence and prevalence of type 1 diabetes in Sweden. Curr Diabetes Rev 2013: 9: 342–349.
64. Patterson CC, Dahlquist GG, Gyurus E, Green A, Soltesz G. Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new

cases 2005-20: a multicentre prospective registration study. Lancet 2009: 373: 2027–2033.
65. Schober E, Waldhoer T, Rami B, Hofer S. Incidence and time trend of type 1 and type 2 diabetes in Austrian children 1999-2007. J Pediatr 2009: 155: 190-3 e1.
66. Haynes A, Bulsara MK, Bower C, Jones TW, Davis EA. Cyclical variation in the incidence of childhood type 1 diabetes in Western Australia (1985-2010). Diabetes Care 2012: 35: 2300–2302.
67. Derraik JG, Reed PW, Jefferies C, Cutfield SW, Hofman PL, Cutfield WS. Increasing incidence and age at diagnosis among children with type 1 diabetes mellitus over a 20-year period in Auckland (New Zealand). PLoS One 2012: 7: e32640.
68. Sipetic S, Maksimovic J, Vlajinac H et al. Rising incidence of type 1 diabetes in Belgrade children aged 0-14 years in the period from 1982 to 2005. J Endocrinol Invest 2013: 36: 307–312.
69. Bruno G, Maule M, Biggeri A et al. More than 20 years of registration of type 1 diabetes in Sardinian children: temporal variations of incidence with age, period of diagnosis, and year of birth. Diabetes 2013: 62: 3542–3546.
70. Lipman TH, Levitt Katz LE, Ratcliffe SJ et al. Increasing incidence of type 1 diabetes in youth: twenty years of the Philadelphia Pediatric Diabetes Registry. Diabetes Care 2013: 36: 1597–1603.
71. Tran F, Stone M, Huang CY et al. Population-based incidence of diabetes in Australian youth aged 10-18 yr: increase in type 1 diabetes but not type 2 diabetes. Pediatr Diabetes 2014: Mar 17. doi: 10.1111/pedi.12131. [Epub ahead of print].
72. Lawrence JM, Imperatore G, Dabelea D et al. Trends in incidence of type 1 diabetes among non-Hispanic White youth in the United States, 2002-2009. Diabetes 2014: Jun 4. pii: DB_131891. [Epub ahead of print].
73. Gyurus EK, Patterson C, Soltesz G. Twenty-one years of prospective incidence of childhood type 1 diabetes in Hungary – the rising trend continues (or peaks and highlands?). Pediatr Diabetes 2012: 13: 21–25.
74. Cinek O, Kulich M, Sumnik Z. The incidence of type 1 diabetes in young Czech children stopped rising. Pediatr Diabetes 2012: 13: 559–563.
75. Kraan JA, Claessen FMAP, Elliott KD et al. Population based incidence of type 1 diabetes in New South Wales Australia 1990-2010 - have we reached a plateau? (Oral Abstract). Pediatr Diabetes 2011: 12 (Suppl. 15): 25.
76. Hermann R, Knip M, Veijola R et al. Temporal changes in the frequencies of HLA genotypes in patients with type 1 diabetes – indication of an increased environmental pressure? Diabetologia 2003: 46: 420–425.
77. Gillespie KM, Bain SC, Barnett AH et al. The rising incidence of childhood type 1 diabetes and reduced contribution of high-risk HLA haplotypes. Lancet 2004: 364: 1699–1700.
78. Fourlanos S, Varney MD, Tait BD et al. The rising incidence of type 1 diabetes is accounted for by cases with lower-risk human leukocyte antigen genotypes. Diabetes Care 2008: 31: 1546–1549.
79. Hemminki K, Li X, Sundquist J, Sundquist K. Familial association between type 1 diabetes and other autoimmune and related diseases. Diabetologia 2009: 52: 1820–1828.
80. Parkkola A, Harkonen T, Ryhanen SJ, Ilonen J, Knip M. Extended family history of type 1 diabetes and phenotype and genotype of newly diagnosed children. Diabetes Care 2012: 36: 348–354.
81. Olmos P, A'Hern R, Heaton DA et al. The significance of the concordance rate for type 1 (insulin-dependent) diabetes in identical twins. Diabetologia 1988: 31: 747–750.
82. Harjutsalo V, Podar T, Tuomilehto J. Cumulative incidence of type 1 diabetes in 10,168 siblings of Finnish young-onset type 1 diabetic patients. Diabetes 2005: 54: 563–569.
83. Steck AK, Barriga KJ, Emery LM, Fiallo-Scharer RV, Gottlieb PA, Rewers MJ. Secondary attack rate of type 1 diabetes in Colorado families. Diabetes Care 2005: 28: 296–300.
84. Gillespie KM, Aitken RJ, Wilson I, Williams AJ, Bingley PJ. Early onset of diabetes in the proband is the major determinant of risk in HLA DR3-DQ2/DR4-DQ8 siblings. Diabetes 2014: 63: 1041–1047.
85. Gillespie KM, Gale EA, Bingley PJ. High familial risk and genetic susceptibility in early onset childhood diabetes. Diabetes 2002: 51: 210–214.
86. Green A, Schober E, Christov V et al. Familial risk of type 1 diabetes in European children. Diabetologia 1998: 41: 1151–1156.
87. Dorman JS, Steenkiste AR, O'Leary LA, McCarthy BJ, Lorenzen T, Foley TP. Type 1 diabetes in offspring of parents with type 1 diabetes: the tip of an autoimmune iceberg? Pediatr Diabetes 2000: 1: 17–22.
88. El Hashimy M, Angelico MC, Martin BC, Krolewski AS, Warram JH. Factors modifying the risk of IDDM in offspring of an IDDM parent. Diabetes 1995: 44: 295–299.
89. Lorenzen T, Pociot F, Stilgren L et al. Predictors of IDDM recurrence risk in offspring of Danish IDDM patients. Danish IDDM Epidemiology and Genetics Group. Diabetologia 1998: 41: 666–673.
90. Warram JH, Krolewski AS, Gottlieb MS, Kahn CR. Differences in risk of insulin-dependent diabetes in offspring of diabetic mothers and diabetic fathers. N Engl J Med 1984: 311: 149–152.
91. Harjutsalo V, Lammi N, Karvonen M, Groop PH. Age at onset of type 1 diabetes in parents and recurrence risk in offspring. Diabetes 2010: 59: 210–214.
92. Tattersall R. Maturity-onset diabetes of the young: a clinical history. Diabet Med 1998: 15: 11–14.
93. Fajans SS, Bell GI. MODY: history, genetics, pathophysiology, and clinical decision making. Diabetes Care 2011: 34: 1878–1884.
94. Fajans SS, Bell GI, Polonsky KS. Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. N Engl J Med 2001: 345: 971–980.
95. Tattersall RB, Fajans SS. A difference between the inheritance of classical juvenile-onset and maturity-onset type diabetes of young people. Diabetes 1975: 24: 44–53.

96. Awa WL, Schober E, Wiegand S et al. Reclassification of diabetes type in pediatric patients initially classified as type 2 diabetes mellitus: 15 years follow-up using routine data from the German/Austrian DPV database. Diabetes Res Clin Pract 2011: 94: 463–467.
97. Murphy R, Ellard S, Hattersley AT. Clinical implications of a molecular genetic classification of monogenic beta-cell diabetes. Nat Clin Pract Endocrinol Metab 2008: 4: 200–213.
98. Edghill EL, Dix RJ, Flanagan SE et al. HLA genotyping supports a nonautoimmune etiology in patients diagnosed with diabetes under the age of 6 months. Diabetes 2006: 55: 1895–1898.
99. Iafusco D, Stazi MA, Cotichini R et al. Permanent diabetes mellitus in the first year of life. Diabetologia 2002: 45: 798–804.
100. Rubio-Cabezas O, Minton JA, Caswell R et al. Clinical heterogeneity in patients with FOXP3 mutations presenting with permanent neonatal diabetes. Diabetes Care 2009: 32: 111–116.
101. Rubio-Cabezas O, Flanagan SE, Damhuis A, Hattersley AT, Ellard S. KATP channel mutations in infants with permanent diabetes diagnosed after 6 months of life. Pediatr Diabetes 2012: 13: 322–325.
102. Rubio-Cabezas O, Edghill EL, Argente J, Hattersley AT. Testing for monogenic diabetes among children and adolescents with antibody-negative clinically defined Type 1 diabetes. Diabet Med 2009: 26: 1070–1074.
103. Mohamadi A, Clark LM, Lipkin PH, Mahone EM, Wodka EL, Plotnick LP. Medical and developmental impact of transition from subcutaneous insulin to oral glyburide in a 15-yr-old boy with neonatal diabetes mellitus and intermediate DEND syndrome: extending the age of KCNJ11 mutation testing in neonatal DM. Pediatr Diabetes 2010: 11: 203–207.
104. Massa O, Iafusco D, D'Amato E et al. KCNJ11 activating mutations in Italian patients with permanent neonatal diabetes. Hum Mutat 2005: 25: 22–27.
105. Iafusco D, Massa O, Pasquino B et al. Minimal incidence of neonatal/infancy onset diabetes in Italy is 1:90,000 live births. Acta Diabetol 2012: 49: 405–408.
106. von Muhlendahl KE, Herkenhoff H. Long-term course of neonatal diabetes. N Engl J Med 1995: 333: 704–708.
107. Temple IK, Gardner RJ, Mackay DJ, Barber JC, Robinson DO, Shield JP. Transient neonatal diabetes: widening the understanding of the etiopathogenesis of diabetes. Diabetes 2000: 49: 1359–1366.
108. Gardner RJ, Mackay DJ, Mungall AJ et al. An imprinted locus associated with transient neonatal diabetes mellitus. Hum Mol Genet 2000: 9: 589–596.
109. Flanagan SE, Patch AM, Mackay DJ et al. Mutations in ATP-sensitive K+ channel genes cause transient neonatal diabetes and permanent diabetes in childhood or adulthood. Diabetes 2007: 56: 1930–1937.
110. Temple IK, Shield JP. 6q24 transient neonatal diabetes. Rev Endocr Metab Disord 2010: 11: 199–204.
111. Gloyn AL, Cummings EA, Edghill EL et al. Permanent neonatal diabetes due to paternal germline mosaicism for an activating mutation of the KCNJ11 Gene encoding the Kir6.2 subunit of the beta-cell potassium adenosine triphosphate channel. J Clin Endocrinol Metab 2004: 89: 3932–3935.
112. Massa O, Iafusco D, D'Amato E et al. KCNJ11 activating mutations in Italian patients with permanent neonatal diabetes. Hum Mutat 2005: 25: 22–27.
113. Colombo C, Porzio O, Liu M et al. Seven mutations in the human insulin gene linked to permanent neonatal/infancy-onset diabetes mellitus. J Clin Invest 2008: 118: 2148–2156.
114. Edghill EL, Flanagan SE, Patch AM et al. Insulin mutation screening in 1,044 patients with diabetes: mutations in the INS gene are a common cause of neonatal diabetes but a rare cause of diabetes diagnosed in childhood or adulthood. Diabetes 2008: 57: 1034–1042.
115. Polak M, Dechaume A, Cave H et al. Heterozygous missense mutations in the insulin gene are linked to permanent diabetes appearing in the neonatal period or in early infancy: a report from the French ND (Neonatal Diabetes) Study Group. Diabetes 2008: 57: 1115–1119.
116. Støy J, Edghill EL, Flanagan SE et al. Insulin gene mutations as a cause of permanent neonatal diabetes. Proc Natl Acad Sci U S A 2007: 104: 15040–15044.
117. Garin I, Edghill EL, Akerman I et al. Recessive mutations in the INS gene result in neonatal diabetes through reduced insulin biosynthesis. Proc Natl Acad Sci U S A 2010: 107: 3105–3110.
118. Njolstad PR, Sovik O, Cuesta-Munoz A et al. Neonatal diabetes mellitus due to complete glucokinase deficiency. N Engl J Med 2001: 344: 1588–1592.
119. Rubio-Cabezas O, Ellard S. Diabetes mellitus in neonates and infants: genetic heterogeneity, clinical approach to diagnosis, and therapeutic options. Horm Res Paediatr 2013: 80: 137–146.
120. Stoffers DA, Zinkin NT, Stanojevic V, Clarke WL, Habener JF. Pancreatic agenesis attributable to a single nucleotide deletion in the human IPF1 gene coding sequence. Nat Genet 1997: 15: 106–110.
121. Guillausseau PJ, Dubois-Laforgue D, Massin P et al. Heterogeneity of diabetes phenotype in patients with 3243 bp mutation of mitochondrial DNA (maternally inherited diabetes and deafness or MIDD). Diabetes Metab 2004: 30: 181–186.
122. Laloi-Michelin M, Meas T, Ambonville C et al. The clinical variability of maternally inherited diabetes and deafness is associated with the degree of heteroplasmy in blood leukocytes. J Clin Endocrinol Metab 2009: 94: 3025–3030.
123. Reardon W, Ross RJ, Sweeney MG et al. Diabetes mellitus associated with a pathogenic point mutation in mitochondrial DNA. Lancet 1992: 340: 1376–1379.
124. van den Ouweland JM, Lemkes HH, Ruitenbeek W et al. Mutation in mitochondrial tRNA(Leu)(UUR) gene in a large pedigree with maternally transmitted type II diabetes mellitus and deafness. Nat Genet 1992: 1: 368–371.
125. Mazzaccara C, Iafusco D, Liguori R et al. Mitochondrial diabetes in children: seek and you will find it. PLoS One 2012: 7: e34956.
126. Rana M, Munns CF, Selvadurai H, Donaghue KC, Craig ME. Cystic fibrosis-related diabetes in children-gaps in the evidence? Nat Rev Endocrinol 2010: 6: 371–378.

127. Rana M, Munns CF, Selvadurai HC, et al. Increased detection of cystic-fibrosis-related diabetes in Australia. Arch Dis Child 2011: 96: 823–826.
128. Hameed S, Morton JR, Jaffe A et al. Early glucose abnormalities in cystic fibrosis are preceded by poor weight gain. Diabetes Care 2010: 33: 221–226.
129. Waugh N, Royle P, Craigie I et al. Screening for cystic fibrosis-related diabetes: a systematic review. Health Technol Assess 2012: 16 iii–iv, 1–179.
130. Moran A, Dunitz J, Nathan B, Saeed A, Holme B, Thomas W. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. Diabetes Care 2009: 32: 1626–1631.
131. Moran A, Milla C, Ducret R, Nair KS. Protein metabolism in clinically stable adult cystic fibrosis patients with abnormal glucose tolerance. Diabetes 2001: 50: 1336–1343.
132. Moran A, Pillay K, Becker D, Acerini CL. Management of cystic fibrosis related diabetes in children and adolescents. Pediatr Diabetes 2014: 15 (Suppl. 20): 65–76.
133. Berne C, Pollare T, Lithell H. Effects of antihypertensive treatment on insulin sensitivity with special reference to ACE inhibitors. Diabetes Care 1991: 14 (Suppl. 4): 39–47.
134. Vestri HS, Maianu L, Moellering DR, Garvey WT. Atypical antipsychotic drugs directly impair insulin action in adipocytes: effects on glucose transport, lipogenesis, and antilipolysis. Neuropsychopharmacology 2007: 32: 765–772.
135. Pui CH, Burghen GA, Bowman WP, Aur RJ. Risk factors for hyperglycemia in children with leukemia receiving L-asparaginase and prednisone. J Pediatr 1981: 99: 46–50.
136. Drachenberg CB, Klassen DK, Weir MR et al. Islet cell damage associated with tacrolimus and cyclosporine: morphological features in pancreas allograft biopsies and clinical correlation. Transplantation 1999: 68: 396–402.
137. Al Uzri A, Stablein DM, Cohn A. Posttransplant diabetes mellitus in pediatric renal transplant recipients: a report of the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS). Transplantation 2001: 72: 1020–1024.
138. Maes BD, Kuypers D, Messiaen T et al. Posttransplantation diabetes mellitus in FK-506-treated renal transplant recipients: analysis of incidence and risk factors. Transplantation 2001: 72: 1655–1661.
139. First MR, Gerber DA, Hariharan S, Kaufman DB, Shapiro R. Posttransplant diabetes mellitus in kidney allograft recipients: incidence, risk factors, and management. Transplantation 2002: 73: 379–386.
140. Bobo WV, Cooper WO, Stein CM et al. Antipsychotics and the risk of type 2 diabetes mellitus in children and youth. JAMA Psychiatry 2013: 70: 1067–1075.
141. Amed S, Dean H, Sellers EA et al. Risk factors for medication-induced diabetes and type 2 diabetes. J Pediatr 2011: 159: 291–296.
142. Bhisitkul DM, Morrow AL, Vinik AI, Shults J, Layland JC, Rohn R. Prevalence of stress hyperglycemia among patients attending a pediatric emergency department. J Pediatr 1994: 124: 547–551.
143. Valerio G, Franzese A, Carlin E, Pecile P, Perini R, Tenore A. High prevalence of stress hyperglycaemia in children with febrile seizures and traumatic injuries. Acta Paediatr 2001: 90: 618–622.
144. Gauglitz GG, Herndon DN, Kulp GA, Meyer WJ III, Jeschke MG. Abnormal insulin sensitivity persists up to three years in pediatric patients post-burn. J Clin Endocrinol Metab 2009: 94: 1656–1664.
145. Saz EU, Ozen S, Simsek Goksen D, Darcan S. Stress hyperglycemia in febrile children: relationship to prediabetes. Minerva Endocrinol 2011: 36: 99–105.
146. Weiss SL, Alexander J, Agus MS. Extreme stress hyperglycemia during acute illness in a pediatric emergency department. Pediatr Emerg Care 2010: 26: 626–632.
147. Herskowitz RD, Wolfsdorf JI, Ricker AT et al. Transient hyperglycemia in childhood: identification of a subgroup with imminent diabetes mellitus. Diabetes Res 1988: 9: 161–167.
148. Schatz DA, Kowa H, Winter WE, Riley WJ. Natural history of incidental hyperglycemia and glycosuria of childhood. J Pediatr 1989: 115: 676–680.
149. Vardi P, Shehade N, Etzioni A et al. Stress hyperglycemia in childhood: a very high risk group for the development of type I diabetes. J Pediatr 1990: 117: 75–77.
150. Herskowitz-Dumont R, Wolfsdorf JI, Jackson RA, Eisenbarth GS. Distinction between transient hyperglycemia and early insulin-dependent diabetes mellitus in childhood: a prospective study of incidence and prognostic factors. J Pediatr 1993: 123: 347–354.
151. Bhisitkul DM, Vinik AI, Morrow AL et al. Prediabetic markers in children with stress hyperglycemia. Arch Pediatr Adolesc Med 1996: 150: 936–941.
152. Shehadeh N, On A, Kessel I et al. Stress hyperglycemia and the risk for the development of type 1 diabetes. J Pediatr Endocrinol Metab 1997: 10: 283–286.

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ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

The diagnosis and management of monogenic diabetes in children and adolescents

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1-3).

Executive summary and Recommendations

- Monogenic diabetes is uncommon, accounting for ~1–4% of pediatric diabetes cases (B).
- All patients diagnosed with diabetes in the first 6 months of life should have immediate molecular genetic testing to define their subtype of monogenic neonatal diabetes mellitus (NDM), as type 1 diabetes is extremely rare in this subgroup (B). In patients diagnosed between 6 and 12 months of age, testing for NDM should be limited to those without islet antibodies as the majority of patients in this age group have type 1 diabetes (B).
- The molecular genetic diagnosis of NDM will give information on which patients have a potassium channel mutation and can be treated with high dose sulfonylureas and which patients have transient neonatal diabetes mellitus (TNDM), which will resolve but may later relapse. In addition the diagnosis will inform other likely features, e. g., pancreatic exocrine failure and developmental delay (B).
- The diagnosis of maturity-onset diabetes of the young (MODY) should be suspected in cases with:
  - A family history of diabetes in one parent and first degree relatives of that affected parent in patients who lack the characteristics of type 1 diabetes [no islet autoantibodies, low or no insulin requirements 5 yr after diagnosis (stimulated C-peptide >200 pmol/L)] and lack the characteristics type 2 diabetes (marked obesity, acanthosis nigricans).

  - Mild stable fasting hyperglycemia which does not progress. Such cases should be tested for glucokinase (*GCK*) gene mutations, which is the commonest cause of persistent, incidental hyperglycemia in the pediatric population (B).

- Specific features can suggest subtypes of MODY, such as renal developmental disease or renal cysts (HNF1B-MODY) and macrosomia and/or neonatal hypoglycemia (HNF4A-MODY) (C).
- In familial autosomal dominant symptomatic diabetes, mutations in the hepatocyte nuclear factor 1α (*HNF1A*) gene (HNF1A-MODY) should be considered as the first diagnostic possibility, while mutations in the *GCK* gene are the most common cause in the absence of symptoms or marked hyperglycemia (B).
- Results of genetic testing should be reported and presented to families in a clear and unambiguous manner, as results may have a major effect on clinical management (E).
- Referral to a specialist in monogenic diabetes or an interested clinical genetics unit is recommended when predictive testing of asymptomatic individuals is requested (E).
- Some forms of MODY diabetes are sensitive to sulfonylureas, such as HNF1A-MODY and HNF4A-MODY (B).
- Mild fasting hyperglycemia due to GCK-MODY is not progressive during childhood; patients do not develop complications (B) and do not respond to low dose insulin or oral agents (C), so should not receive treatment.

Introduction

Monogenic diabetes results from one or more defects in a single gene. The disease may be inherited within families as a dominant, recessive, or non-Mendelian trait or may present as a spontaneous case due to a *de novo* mutation. Well over 40 different genetic subtypes of monogenic diabetes have been identified to date, each having a typical phenotype and a specific pattern of inheritance.

A familial form of mild diabetes presenting during adolescence or in early adulthood was first described many years ago (1, 2). Even though diabetes presented in young patients, the disease clinically resembled elderly onset non-insulin dependent diabetes and the newly recognized subtype of familial diabetes became known by the acronym MODY (3). As MODY patients passed on the disease to their offspring following an autosomal dominant pattern of inheritance, it was quickly suspected that it might be a monogenic disorder (4). MODY is by far the commonest type of monogenic diabetes. All currently known subtypes of MODY are caused by dominantly acting heterozygous mutations in genes important for the development or function of β cells (1, 5). Over the last few years, however, a number of forms of monogenic diabetes clinically and genetically different from MODY have been identified (6). Some patients harbor dominant mutations arising *de novo* (i.e., not inherited from parents) so family history suggesting a monogenic condition is lacking (7–9). These facts, along with a widespread lack of awareness, hinder clinical diagnosis so that the majority of children with genetically proven monogenic diabetes are initially misdiagnosed as having type 1 (10–12) or, less commonly, type 2 diabetes (13). Although monogenic diabetes is uncommon, it accounts for 1–4% of pediatric diabetes cases (14–16).

Clinical relevance of diagnosing monogenic diabetes

Identification of children with monogenic diabetes usually improves their clinical care. Making a specific molecular diagnosis helps predict the expected clinical course of the disease and guide the most appropriate management in a particular patient, including pharmacological treatment. Furthermore, it has important implications for the family as it enables genetic counseling and frequently triggers extended genetic testing in other diabetic family members, whose diabetes may eventually be reclassified.

Selecting candidates for molecular testing

In contrast to type 1 and type 2 diabetes, where there is no single diagnostic test, molecular genetic testing is both sensitive and specific for diagnosing monogenic diabetes. Genetic testing is currently available in many countries around the world and should be strongly considered in patients with suspected monogenic diabetes (see below). Appropriate informed consent/assent must be prospectively obtained from the patient and his/her legal guardians. Genetic testing for some conditions is available free of charge on a research basis in certain academic institutions (e.g., www.diabetesgenes.org, http://monogenicdiabetes.uchicago.edu, http://www.pediatria.umed.pl/team/en/contact, www.mody.no, and http://www.euro-wabb.org/en/european-genetic-diagnostic-laboratories).

Next-generation sequencing enables the simultaneous analysis of multiple genes at a lower cost and may become a feasible alternative to traditional genetic testing in the near future (17–20). In the meantime, a judicious approach to selecting candidates for molecular testing is required. The simplest way of maximizing the cost-effectiveness of traditional genetic testing is by

increasing its positive yield through a reasoned selection of the appropriate gene(s) for analysis according to the patient's clinical, immunological, and/or biochemical phenotype (21, 22). This process may be relatively easy to undertake when clinical features directly pointing to a specific syndrome are present, but results may be very difficult to achieve when diabetes is the only manifestation of the monogenic disorder.

When to suspect a diagnosis of type 1 diabetes in children may not be correct?

Features in children initially thought to have type 1 diabetes that suggest a possible diagnosis of monogenic diabetes are shown below. Except for age of diagnosis less than 6 months, none of these are pathognomonic and should be considered together rather than in isolation:

1 Diabetes presenting before 6 months of age as type 1 diabetes is extremely rare in this age-group (2, 23).
2 Family history of diabetes in one parent and other first degree relatives of that affected parent.
3 Absence of islet autoantibodies, especially if measured at diagnosis.
4 Preserved β-cell function, with low insulin requirements and detectable C-peptide (either in blood or urine) over an extended partial remission phase (5 yr after diagnosis).

When to suspect a diagnosis of type 2 diabetes in children may not be correct?

In young people, type 2 diabetes often presents around puberty and the majority are obese. A number of features that should suggest monogenic diabetes are listed below:

1 Absence of severe obesity.
2 Lack of acanthosis nigricans and/or other markers of metabolic syndrome.
3 Ethnic background with a low prevalence of type 2 diabetes, e.g., European Caucasian.
4 Strong family history of diabetes without obesity.

Interpretation of genetic findings

Despite the obvious clinical benefits derived from an increased awareness and more widely available genetic diagnostic services, care needs to be exercised in the interpretation of genetic findings (24). The way the clinician interprets the genetic report will have a major effect on the further clinical management of the patient and his/her family. Therefore, it is crucial that the results are presented in a clear and unambiguous way to ensure that both clinicians and patients receive adequate and understandable information. Specific recommendations describing the information that should be included in the molecular genetics laboratory report for MODY testing have been published (25). These include the method used for mutation screening, whether the mutation is novel and if so, evidence for its pathogenicity, and information about the likelihood of the disease being inherited by the offspring. Referral to a specialist unit (diabetes genetics or clinical genetics) is recommended when predictive testing of asymptomatic individuals is requested.

Specific subtypes of monogenic diabetes and their management

The different forms of monogenic diabetes can be classified according to the main pathogenic mechanism into two separate groups (26): genetic defects of insulin secretion and genetic defects of insulin action. In children, the majority of cases result from mutations in genes causing β cell loss or dysfunction although diabetes can rarely occur from mutations resulting in very severe insulin resistance. From a clinical perspective, clinical scenarios when a diagnosis of monogenic diabetes should be considered include:

1 Diabetes presenting before 6 months of age (NDM).
2 Autosomal dominant familial mild hyperglycemia or diabetes.
3 Diabetes associated with extrapancreatic features.
4 Monogenic insulin resistance syndromes.

NDM diabetes diagnosed within the first 6–12 months of life

The clinical presentation of autoimmune type 1 diabetes is exceedingly rare before age 6 months (23, 27). Even though autoantibodies against β-cell antigens may be occasionally found in very young diabetic infants (23), it is now accepted that *FOXP3* mutations, and not type 1 diabetes, will account for most of these cases (28). Therefore, all patients diagnosed under 6 months should have genetic testing for monogenic NDM. Some cases of monogenic diabetes can be diagnosed between 6 and 12 months (12, 29, 30) although the vast majority of these patients have type 1 diabetes.

Many patients with NDM are born small for gestational age, which reflects a prenatal deficiency of insulin secretion as insulin exerts potent growth-promoting effects during intrauterine development (31). Approximately half will require lifelong treatment to control hyperglycemia - permanent neonatal diabetes mellitus (PNDM). In the remaining cases, diabetes will remit within a few weeks or months

- transient neonatal diabetes mellitus (TNDM), although it might relapse later in life. In both situations, diabetes presents more frequently as an isolated condition, but some patients show a variety of associated extra-pancreatic clinical features pointing to a particular gene, which may help guide genetic testing (Table 1).

The genetic basis of TNDM has been mostly uncovered: approximately two thirds of cases are caused by abnormalities in an imprinted region on chromosome 6q24 (32, 33), with activating mutations in either of the genes encoding the two subunits of the ATP-sensitive potassium (K_{ATP}) channel of the β-cell membrane (*KCNJ11* or *ABCC8*) causing the majority of the remaining cases (34). A minority of cases of TNDM is caused by mutations in other genes, including *HNF1B* (35), *INS* (preproinsulin gene) (36), etc. In contrast, the genetic abnormality responsible for up to 30% of PNDM cases remains unknown, although the commonest known cause in outbred populations are mutations in the K_{ATP} channel or *INS* genes (37, 38). If parents are related, Wolcott–Rallison syndrome or homozygous mutations in the *GCK* gene are the most common etiologies (37).

Transient neonatal diabetes from imprinting anomalies on 6q24

Anomalies at the 6q24 locus, spanning two candidate genes *PLAGL1* and *HYMAI*, are the single most common cause of neonatal diabetes and always result in TNDM (39). In normal circumstances, this region is maternally imprinted so that only the allele inherited from the father is expressed. TNDM is ultimately associated with overexpression of the imprinted genes (40), with three different molecular mechanisms identified to date: paternal uniparental disomy of chromosome 6 (either complete or partial; it accounts for 50% of sporadic TNDM cases), unbalanced paternal duplication of 6q24 (found in most familial cases), and abnormal methylation of the maternal allele (found in some sporadic cases) (41). Methylation defects may affect only the 6q24 locus or may arise in the context of a generalized hypomethylation syndrome along with other clinical features including congenital heart defects, brain malformations, etc. (42). Some cases of TNDM secondary to multiple methylation defects are caused by recessively acting mutations in *ZFP57*, a gene on chromosome 6p involved in the regulation of DNA methylation (43).

Patients with 6q24 abnormalities are born with severe intrauterine growth retardation and develop severe but non-ketotic hyperglycemia very early on, usually during the first week of life (41, 44). Despite the severity of the initial presentation, the insulin dose can be tapered quickly so that the majority of patients do not require any treatment by a median age of 12 wk. One third of patients show macroglossia and, more rarely, an umbilical hernia is present. During remission, transient hyperglycemia may occur during intercurrent illnesses (45). Over time, diabetes relapses in at least 50–60% of patients, usually around puberty, although recurrences have been reported as young as 4 yr of age. Relapse clinically resembles early-onset type 2 diabetes and is characterized by a loss of the first-phase insulin secretion. Insulin therapy is not always necessary (there is usually some response to oral sulfonylureas) and, if needed, insulin doses required tend to be lower than in patients with type 1 diabetes.

The phases described above do not present irremediably in every patient. Interestingly, some mutation carrier relatives develop type 2 diabetes or gestational diabetes in adulthood without any evidences of having had neonatal diabetes, suggesting that other genetic or epigenetic factors may influence the clinical expression alterations of chromosome 6q24 (32).

The role of genetic counseling depends on the underlying molecular mechanism. Uniparental disomy of chromosome 6 is generally sporadic and therefore the risk of recurrence in siblings and offspring is low. When paternal duplication of the 6q24 region is found, males have a 50% chance of transmitting the mutation and the disease to their children. In contrast, females will pass on the duplication but their children will not develop the disease. In this case, TNDM may recur in the next generation as their asymptomatic sons pass on the molecular defect to their own children. Some methylation defects (i.e., *ZFP57* mutations) show an autosomal recessive inheritance and hence the recurrence risk is 25% for siblings and almost negligible for the offspring of a patient.

Neonatal diabetes due to mutations in the K_{ATP} channel genes

K_{ATP} channels are hetero-octameric complexes formed by four pore-forming Kir6.2 subunits and four SUR1 regulatory subunits, encoded by the genes *KCNJ11* and *ABCC8*, respectively (46). They regulate insulin secretion by linking intracellular metabolic state to the β-cell membrane electrical activity. Any increase in the intracellular metabolic activity induces an increase in the ATP/ADP ratio within the pancreatic β-cell which makes the K_{ATP} channels close, and leads to the cell membrane depolarization which ultimately triggers insulin secretion (47). Activating mutations in *KCNJ11* or *ABCC8*, which prevent K_{ATP} channel closure and hence insulin secretion in response to hyperglycemia, are the most common cause of PNDM (7, 48–51) and the second most common cause of TNDM (34).

The majority of patients with mutations in *KCNJ11* have PNDM rather than TNDM (90 vs. 10%). In

Table 1. Monogenic subtypes of neonatal and infancy-onset diabetes (modified from reference 37)

Gene	Locus	Inheritance	Other clinical features	References
Abnormal pancreatic development				
PLAGL1/HYMAI	6q24	Variable (imprinting)	TNDM ± macroglossia ± umbilical hernia	(33)
ZFP57	6p22.1	Recessive	TNDM (multiple hypomethylation syndrome) ± macroglossia ± developmental delay ± umbilical defects ± congenital heart disease	(43)
PDX1	13q12.1	Recessive	PNDM + pancreatic agenesis (steatorrhea)	(173)
PTF1A	10p12.2	Recessive	PNDM + pancreatic agenesis (steatorrhea) + cerebellar hypoplasia/aplasia + central respiratory dysfunction	(174)
PTF1A enhancer	10p12.2	Recessive	PNDM + pancreatic agenesis without CNS features	(89)
HNF1B	17q21.3	Dominant	TNDM + pancreatic hypoplasia and renal cysts	(35)
RFX6	6q22.1	Recessive	PNDM + intestinal atresia + gall bladder agenesis	(175)
GATA6	18q11.1-q11.2	Dominant	PNDM + pancreatic agenesis + congenital heart defects + biliary abnormalities	(90)
GATA4	8p23.1	Dominant	PNDM + pancreatic agenesis + congenital heart defects	(176)
GLIS3	9p24.3-p23	Recessive	PNDM + congenital hypothyroidism + glaucoma + hepatic fibrosis + renal cysts	(177)
NEUROG3	10q21.3	Recessive	PNDM + enteric anendocrinosis (malabsorptive diarrhea)	(178)
NEUROD1	2q32	Recessive	PNDM + cerebellar hypoplasia + visual impairment + deafness	(179)
PAX6	11p13	Recessive	PNDM + microphthalmia + brain malformations	(180)
MNX1	7q36.3	Recessive	PNDM + developmental delay + sacral agenesis + imperforate anus	(181) (175)
NKX2-2	20p11.22	Recessive	PNDM + developmental delay + hypotonia + short stature + deafness + constipation	(182)
Abnormal β-cell function				
KCNJ11	11p15.1	Spontaneous or dominant	PNDM/TNDM ± DEND	(7)
ABCC8	11p15.1	Spontaneous, dominant or recessive	TNDM/PNDM ± DEND	(48)
INS	11p15.5	Recessive	Isolated PNDM or TNDM	(36)
GCK	7p15-p13	Recessive	Isolated PNDM	(83)
SLC2A2 (GLUT2)	3q26.1-q26.3	Recessive	Fanconi–Bickel syndrome: PNDM + hypergalactosemia, liver dysfunction	(183)
SLC19A2	1q23.3	Recessive	Roger's syndrome: PNDM + thiamine-responsive megaloblastic anemia, sensorineural deafness	(184)
Destruction of β cells				
INS	11p15.5	Spontaneous or dominant	Isolated PNDM	(9)
EIF2AK3	2p11.2	Recessive	Wolcott–Rallison syndrome: PNDM + skeletal dysplasia + recurrent liver dysfunction	(77)
IER3IP1	18q21.2	Recessive	PNDM + microcephaly + lissencephaly + epileptic encephalopathy	(185)
FOXP3	Xp11.23-p13.3	X-linked, recessive	IPEX syndrome (autoimmune enteropathy, eczema, autoimmune hypothyroidism, and elevated IgE)	(186)
WFS1	4p16.1	Recessive	PNDM* + optic atrophy ± diabetes insipidus ± deafness	(126)

CNS, central nervous system; DEND, developmental delay, epilepsy, and neonatal diabetes syndrome; IgE, immunoglobulin; IPEX, immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome; TNDM; transient neonatal diabetes mellitus.
*The mean age of diagnosis among patients with *WFS1* mutations is approximately 5 yr (129).

contrast, mutations in *ABCC8* cause TNDM more frequently (~66%) (48, 52). There are no significant differences between the two subtypes of neonatal diabetes regarding the severity of intrauterine growth retardation or the age at diagnosis of diabetes (34, 53). Patients with K_{ATP} channel mutations typically show milder intrauterine growth retardation and are diagnosed slightly later than patients with 6q24 abnormalities, indicating a less severe insulin deficiency during the last months of intrauterine development and at the time birth. In K_{ATP}-TNDM patients, diabetes usually remits later and relapses earlier than in 6q24-TNDM (34).

Presenting clinical features in patients with K_{ATP} channel activating mutations suggest insulin dependency, with low or undetectable C-peptide levels and frequent presentation with diabetic ketoacidosis (54). In addition to diabetes, about 20% of patients with mutations in *KCNJ11* were initially found to present with associated neurological features (7, 54, 55) in keeping with the expression of K_{ATP} channels in neurons and muscle cells (47, 56). The most severe defect included marked developmental delay and early-onset epilepsy and became known as DEND (developmental delay, epilepsy, and neonatal diabetes) syndrome. An intermediate DEND syndrome characterized by neonatal diabetes and less severe developmental delay without epilepsy is more common. Neurological features were considered less frequent and usually milder in patients with mutations in *ABCC8* (48, 49). However, a recent study suggested that mild neurodevelopmental abnormalities, including developmental coordination disorder (particularly visual-spatial dyspraxia) or attention deficits, might be found on detailed testing in all patients with K_{ATP} channel mutations (57).

Approximately 90% of patients with activating mutations in the K_{ATP} channel genes can be transferred from insulin onto sulfonylurea tablets (58, 59). Transfer usually improves glycemic control without increasing the risk of hypoglycemia. The doses required are high when calculated on a per kg body weight basis compared with adults with type 2 diabetes, typically needing around 0.5 mg/kg/d of glibenclamide, although doses as high as 2.3 mg/kg/d have been occasionally reported (60, 61). Many patients have been able to progressively reduce the dose of sulfonylurea after transition while maintaining excellent glycemic control (58, 62). The only side effects reported to date are transient diarrhea and staining of the teeth (63, 64). Some brain imaging studies have shown that sulfonylurea drugs may penetrate blood–brain barrier (65, 66) and very interesting case reports suggest that sulfonylureas may partially improve some of the neurological symptoms (67–70).

Activating mutations in *KCNJ11* causing neonatal diabetes are always heterozygous. As about 90% of these mutations arise *de novo*, there is usually no family history of neonatal diabetes (71) but familial cases show an autosomal dominant inheritance. Recurrence risk for the offspring of an affected patient is 50%. This is also true for most patients with activating mutations in *ABCC8*. However, some patients are homozygous or compound heterozygous for two different mutations and neonatal diabetes is recessively inherited (49). In this case, the risk of neonatal diabetes for future siblings is 25% but almost inexistent for the offspring. Germline mosaicism (mutations present in the gonads but not detectable in blood) has been reported in several families (71) and hence unaffected parents of a child with an apparently *de novo* mutation should be advised that the recurrence risk in siblings is low but not negligible.

Neonatal diabetes due to mutations in *INS* gene

Heterozygous coding mutations in the *INS* gene are the second most common cause of PNDM after K_{ATP} channel mutations (9, 53, 72, 73). The mutation usually results in a misfolded proinsulin molecule that is trapped and accumulated in the endoplasmic reticulum, leading to endoplasmic reticulum stress and β-cell apoptosis (74).

The severity of intrauterine growth retardation in patients with heterozygous *INS* mutations is similar to that of patients with K_{ATP} channel mutations. In contrast, diabetes presents at a slightly later age although the ranges overlap greatly and patients do not present with neurological features as a direct consequence of the mutation (53).

The majority of heterozygous *INS* mutations are sporadic *de novo* mutations. Only about 20% of probands have a positive family history of autosomal dominant neonatal diabetes (53). Occasionally, *INS* mutations cause permanent diabetes after 6 months of age and therefore genetic testing should be considered in certain situations, especially in patients with antibody-negative type 1 diabetes (12, 73, 75, 76).

In addition to heterozygous *INS* mutations, homozygous or compound heterozygous mutations causing neonatal diabetes have also been described (36). Biallelic mutations do not cause slowly progressive β-cell destruction but result in a lack of insulin biosynthesis before and after birth, which explains much lower birth weights and earlier presentation of diabetes in affected children. As the disease is recessively inherited, there is a 25% recurrence risk in siblings but, in the absence of consanguinity, a very low risk for the offspring of a patient.

Wolcott–Rallison syndrome

Biallelic mutations in *EIF2AK3* (eukaryotic translation initiation factor alpha 2-kinase 3) cause a rare

autosomal recessive syndrome characterized by early-onset diabetes mellitus, spondyloepiphyseal dysplasia, and recurrent hepatic and/or renal dysfunction (77, 78). *EIF2AK3* encodes a protein involved in the regulation of the endoplasmic reticulum stress response. Pancreatic development is rather normal in the absence of the functional protein but misfolded proteins accumulate within the endoplasmic reticulum after birth and eventually induce β-cell apoptosis. Although diabetes usually manifests during infancy, it might not present until 3–4 yr of age. Diabetes may be the first clinical manifestation of the syndrome and therefore this diagnosis needs to be considered in children with PNDM especially if parental consanguinity is present or the patient originates from a highly inbred population (79, 80). As the disease is recessively inherited, there is a 25% recurrence risk in siblings but in the absence of consanguinity, a very low risk for the offspring of a patient.

Neonatal diabetes due to *GCK* mutations

The enzyme glucokinase is considered the glucose sensor of the β cells, as it catalyzes the rate-limiting step of glucose phosphorylation and therefore enables the β cell to respond appropriately to the degree of glycemia (81). Heterozygous mutations in the *GCK* gene produce familial mild non-progressive hyperglycemia (see below). However, complete glucokinase deficiency secondary to mutations in both alleles, either homozygous or compound heterozygous, prevents the β cells from secreting insulin in response to hyperglycemia (82, 83). For this reason, patients present with severe intrauterine growth retardation, are usually diagnosed with diabetes during the first few days of life, and require exogenous insulin therapy. Apart from diabetes, patients do not show any relevant extrapancreatic features.

GCK is responsible for not more than 2–3% of cases of PNDM overall (37). This type of PNDM is inherited in a recessive manner so the recurrence risk for future siblings is 25%. This diagnosis should be strongly considered in probands born to parents with asymptomatic mild hyperglycemia and therefore measuring fasting blood glucose in the parents of any child with neonatal diabetes, even when there is no known consanguinity or family history of diabetes, is often recommended. Sulfonylurea treatment has been tested with no clear effect (P. R. N. and A. T. H., unpublished observations).

IPEX syndrome

Mutations in the *FOXP3* gene are responsible for the IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked) syndrome (84, 85). This is the only well-established form of PNDM that is associated with β-cell autoimmunity and pancreatic islet autoantibodies. Among male infants who present with diabetes, immune deficiency, and/or life-threatening infection, mutations in *FOXP3* should be considered. Treatment with immunosuppressive agents (sirolimus or steroids) is recommended (86, 87). Alternatively, allogeneic bone marrow transplantation with reduced-intensity conditioning should be considered (88).

Other causes of neonatal diabetes

The clinical features in other causes of neonatal and infancy-onset diabetes are shown in Table 1. Pancreatic scanning is unreliable in neonates and so it is best to use functional tests of exocrine pancreatic function (fecal elastase and fecal fats) when assessing if pancreatic aplasia is present (89, 90). Apart from K_{ATP} channel neonatal diabetes, all other causes need to be treated with subcutaneous insulin. Patients with pancreatic aplasia/hypoplasia will also require exocrine pancreatic supplements.

Genetic testing should be performed as soon as diabetes is diagnosed in a child aged less than 6 months

Genetic testing will allow diagnosis of a specific type of monogenic diabetes in over 80% of patients whose diabetes is diagnosed before the age of 6 months. As discussed above, this will influence treatment as well as prediction of clinical features. This means that molecular genetic testing is now recommended at the time of diabetes diagnosis in child aged less than 6 months. It is no longer necessary to wait to see if the diabetes resolves or for other features to develop, as major labs will offer comprehensive testing of all NDM subtypes as well as very rapid testing of subtypes that alter treatment.

Autosomal dominant familial mild hyperglycemia or diabetes (MODY)

The different genetic subtypes of MODY differ in age of onset, pattern of hyperglycemia, and response to treatment. Most of them cause isolated diabetes and therefore may be misdiagnosed as either familial type 1 or type 2 diabetes (10, 13, 91). Although the classic criteria for MODY include family history of diabetes, sporadic *de novo* mutations in a number of causative genes have been reported (92).

Three genes are responsible for the majority of MODY cases (*GCK*, *HNF1A*, and *HNF4A*) and will be described in some detail below (see also Table 2). However, up to 13 different genes have been reported to cause autosomal dominant non-insulin dependent diabetes but these are so unusual they do not need to be

Table 2. Common subtypes of MODY and associated clinical features

Gene	Locus	Clinical features	Treatment	References
HNF4A	20q12-q13.1	Macrosomia and neonatal hypoglycemia, renal Fanconi syndrome (mutation specific)	Sulfonylurea	(187)
GCK	7p15-p13	Mild asymptomatic hyperglycemia	Nil/diet	(188)
HNF1A	12q24.2	Renal glucosuria	Sulfonylurea	(189)
HNF1B	17q12	Renal developmental abnormalities, genital tract malformations	Insulin	(190)

MODY, maturity-onset diabetes of the young.

tested for in children with diabetes except in a research setting or when there are additional phenotypes such as pancreatic exocrine dysfunction (93).

Mild fasting hyperglycemia due to glucokinase gene mutations (*GCK*-MODY, MODY2)

The incidental finding of mild hyperglycemia (5.5–8 mmol/L or 100–145 mg/dL) in otherwise asymptomatic children and adolescents raises the possibility that these patients subsequently develop type 1 or type 2 diabetes. In the absence of concomitant pancreatic autoimmunity, the risk of future type 1 diabetes is minimal (94) and a significant proportion will have a heterozygous mutation in *GCK* (95, 96). In peripubertal children and adolescents, the lack of obesity or other signs of insulin resistance should raise concern about a diagnosis of type 2 diabetes.

GCK-MODY is the commonest subtype of monogenic diabetes in the pediatric diabetes clinic and its clinical phenotype is remarkably homogeneous among patients. In contrast to other subtypes of monogenic diabetes, GCK-MODY patients regulate insulin secretion adequately but around a slightly higher set point than normal subjects. As a result, they show non-progressive mild hyperglycemia from birth (97). Their hemoglobin A1c (HbA1c) is mildly elevated but usually below 7.5% (98). Despite the mild fasting hyperglycemia, there is usually a small increment in blood glucose during an oral glucose tolerance test (<60 mg/dL or <3.5 mmol/L) (99), although this should not be considered an absolute criterion because of the variability of the oral glucose tolerance test (OGTT). As the degree of hyperglycemia is not high enough to cause osmotic symptoms, most cases are usually diagnosed incidentally when blood glucose is measured for any other reason. Very often, the affected parent remains undiagnosed or has been misdiagnosed with early-onset type 2 diabetes. Measuring fasting glucose in apparently unaffected parents is important when considering a diagnosis of a glucokinase mutation.

As blood glucose does not deteriorate significantly over time, this subtype of monogenic diabetes is rarely associated with chronic microvascular or macrovascular complications of diabetes (100, 101) and patients do not generally require any treatment (102). Of note, the presence of a *GCK* mutation does not protect against the concurrent development of polygenic type 2 diabetes later in life, which occurs at a similar prevalence than in the general population (103). GCK-PNDM may manifest in GCK-MODY families since in the setting of consanguinity or a second *de novo* mutation.

Familial diabetes due to HNF1A-MODY (MODY3) and HNF4A-MODY (MODY1)

The possibility of monogenic diabetes should be considered whenever a parent of a diabetic child has diabetes, even if they are thought to have type 1 or type 2 diabetes. HNF1A-MODY is the most common form of monogenic diabetes that results in familial symptomatic diabetes, with heterozygous *HNF1A* mutations being about 10 times more frequent than heterozygous mutations in *HNF4A* (104). Therefore, HNF1A-MODY is the first diagnostic possibility to be considered in families with autosomal dominant symptomatic diabetes.

In both HNF1A-MODY and HNF4A-MODY, glucose intolerance usually becomes evident during adolescence or early adulthood. In the early stages of the disease, fasting blood glucose may be normal but patients tend to show a large increment in blood glucose (>80 mg/dL or 5 mmol/L) after meals or at 2 h during an OGTT (99). Patients with HNF1A-MODY demonstrate impaired incretin effect and inappropriate glucagon responses to OGTT (105). Over time, fasting hyperglycemia and osmotic symptoms (polyuria and polydipsia) present but patients rarely develop ketosis because some residual insulin secretion persists for many years. Chronic complications of diabetes are frequent and their development is related to the degree of metabolic control (106). The frequency of microvascular complications (retinopathy, nephropathy, and neuropathy) is similar to that of patients with type 1 and type 2 diabetes. *HNF1A* mutations are associated with an increased frequency of cardiovascular disease (107).

Mutations in *HNF1A* show a high penetrance so that 63% of mutation carriers develop diabetes before 25 yr of age, 79% before age 35 and 96% before 55 yr (6). The age at diagnosis of diabetes is partly determined by the location of the mutation within the gene (108, 109). Patients with mutations affecting the terminal exons (8–10) are diagnosed, on average, 8 yr later than those with mutations in exons 1–6. On the other hand, exposure to maternal diabetes *in utero* (when the mutation is maternally inherited) brings forward the age at onset of diabetes by about 12 yr (99). In the pediatric population, diabetes in *HNF4A* mutation carriers tend to appear at a similar age to patients with mutations in *HNF1A* (16).

There are some differential clinical characteristics between patients with mutations in *HNF4A* and *HNF1A* that can help decide which gene should be considered first in a particular family.

- Patients with *HNF1A* mutations typically have a low renal threshold for glucose reabsorption due to impaired renal tubular transport of glucose and may present postprandial glycosuria before developing significant hyperglycemia (110).
- In addition to diabetes, carriers of the R76W mutation in *HNF4A* present with an atypical form of Fanconi syndrome including hypercalciuria and nephrocalcinosis (111).
- About 50% of *HNF4A* mutation carriers are macrosomic at birth and 15% have diazoxide-responsive neonatal hyperinsulinemic hypoglycemia (112). In this case, hyperinsulinism typically remits during infancy and patients develop diabetes from adolescence (113, 114). Recently, hyperinsulinemic hypoglycemia has also been reported in *HNF1A* mutation carriers (115) but this is very uncommon.

Patients with both HNF1A- and HNF4A-MODY can initially be treated with diet although they will have marked postprandial hyperglycemia with high carbohydrate food (99). Most patients will need pharmacological treatment as they show progressive deterioration in glycemic control. They are extremely sensitive to sulfonylureas (116), which usually allow a better glycemic control than that achieved on insulin, especially in children and young adults (117). The initial dose should be low (one-quarter of the normal starting dose in adults) to avoid hypoglycemia. As long as the patients do not have problems with hypoglycemia, they can be maintained on low-dose sulfonylureas (e.g., 20–40 mg gliclazide daily) for decades (118, 119). If there is hypoglycemia despite dose titration of a once or twice daily sulfonylurea preparation, a slow release preparation or meal time doses with a short-acting agent such as nateglinide may be considered (120, 121). A recent randomized controlled trial comparing a glucagon-like peptide (GLP-1) agonist with a sulfonylurea demonstrated lower fasting glucose in those treated with the GLP-1 agonist (122).

Genetic syndromes associated with diabetes

A monogenic disorder should be considered in any child with diabetes associated with multi-system extrapancreatic features (123). These syndromes may either cause neonatal diabetes (Table 1) or present later in life (see below). The online Mendelian inheritance in Man website (www.ncbi.nlm.nih.gov/omim or www.omim.org) can help with clinical features and to know if the gene for a particular syndrome has been defined and hence molecular genetic testing is available. Genetic testing for some of these conditions is available on a research basis at www.euro-wabb.org (124). The most common syndromes usually presenting beyond infancy are described in some detail below.

Diabetes insipidus, diabetes mellitus, optic atrophy, and deafness syndrome (Wolfram syndrome)

The association of diabetes with progressive optic atrophy below 16 yr of age is diagnostic of this autosomal recessive syndrome (125). Non-autoimmune insulin-deficient diabetes is usually the first manifestation of the disease and presents at a mean age of 6 yr, although may present anytime from early-infancy (126, 127). Patients require insulin treatment from diagnosis. Other typical clinical features, such as sensorineural deafness, central diabetes insipidus, urinary tract dilatations, and neurological symptoms develop later in a variable order even within the same family. Many patients with Wolfram Syndrome (WFS) are initially diagnosed as having type 1 diabetes; subsequent loss of vision, which occurs approximately 4 yr after diabetes diagnosis, may be misdiagnosed as diabetic retinopathy (128, 129). Patients WFS die at a median age of 30 yr, mainly from neurodegenerative complications.

At least 90% of patients harbor recessively acting mutations in the *WFS1* gene (130, 131). A second variant of the syndrome has recently been described in association with mutations in *CISD2* (132). Patients with this rare variant do not develop diabetes insipidus but present with additional symptoms including bleeding diathesis and peptic ulcer disease.

Renal cysts and diabetes syndrome (*HNF1B*-MODY or MODY5)

Although initially described as a rare subtype of familial diabetes, it is now clear that patients with heterozygous mutations in *HNF1B* rarely present with isolated diabetes (133). In contrast, renal developmental disorders (especially renal cysts and renal dysplasia) are present in almost all patients

with *HNF1B* mutations or gene deletions (8) and constitute the main presentation in children, even in the absence of diabetes (134). Genital-tract malformations (particularly uterine abnormalities), hyperuricemia and gout can also occur, as well as abnormal liver function tests (133). Diabetes develops later, typically during adolescence or early adulthood (135, 136), although transient neonatal diabetes has been reported in a few cases (35, 137). In addition to insulin deficiency related to pancreatic hypoplasia (138), patients also show some degree of hepatic insulin resistance (139), which explains why they do not respond adequately to sulfonylurea treatment and require early insulin therapy (6). Moreover, mutation carriers have lower exocrine pancreatic function with reduced fecal elastase; this involves both ductal and acinar cells (140). Therefore, the phenotype of renal cysts and diabetes (RCAD) patients is highly variable even within families sharing the same *HNF1B* mutation and therefore this diagnosis should be considered not only in the diabetes clinic but also in other clinics (nephrology, urology, gynecology, etc.). In patients found to have renal cysts, imaging of the pancreas is indicated, as the absence of the pancreatic body and/or tail is highly indicative of HNF1B-MODY (141). Fecal elastase should also be measured, as this is always abnormal in patients with HNF1B-MODY (140). Importantly, a family history of renal disease or diabetes is not essential to prompt genetic testing, as spontaneous mutations and deletions of this gene are common (one third to two thirds of cases) (8, 134).

Mitochondrial diabetes

Diabetes due to mitochondrial mutations and deletions is rarely seen in the pediatric age group as the vast majority of patients develop diabetes as young or middle-aged adults. The most common form of mitochondrial diabetes is caused by the m.3243A>G mutation in mitochondrial DNA. Diabetes onset is usually insidious but approximately 20% of patients have an acute presentation, even in diabetic ketoacidosis (142). Although it typically presents in adulthood, some cases have been reported in adolescents with a high degree of heteroplasmy (143, 144). Mitochondrial diabetes should be suspected in patients presenting with diabetes and sensorineural hearing loss inherited from mother's side. Interestingly, the same m.3243A>G mutation also causes a much more severe clinical syndrome known as MELAS (myopathy, encephalopathy, lactic acidosis, and stroke) (145).

Patients with mitochondrial diabetes may respond initially to diet or oral hypoglycemic agents but often require insulin treatment within months or years. Metformin should be avoided as it interferes with mitochondrial function and may trigger episodes of lactic acidosis (146).

The penetrance of diabetes in mutation carriers depends on the age considered, but is estimated to be above 85% at 70 yr (142). Affected males do not transmit the disease to their offspring. In contrast, females transmit the mutation to all their children, although some may not develop the disease (6). In addition to the m.3243A>G mutation, early-onset diabetes (even in infancy) has been reported in other less common mitochondrial disorders such as Kearns–Sayre syndrome (147) and Pearson syndrome (148).

Diabetes secondary to monogenic diseases of the exocrine pancreas

Heterozygous mutations in *CEL*, which encodes a pancreatic lipase, cause an autosomal dominant disorder of pancreatic exocrine insufficiency and diabetes (93). Importantly, the exocrine component of the syndrome is initiated already in childhood, 10–30 yr before diabetes develops, and can be revealed by lowered fecal elastase and/or pancreatic lipomatosis (149, 150). Other autosomal dominant monogenic diseases affecting mainly the exocrine pancreas that can lead to diabetes sooner or later include cystic fibrosis (*CFTR*) (151), hereditary pancreatitis (*PRSS1* and *SPINK1*) (152), and pancreatic agenesis/hypoplasia (*GATA6*) (90).

Monogenic insulin resistance syndromes

The key features of insulin resistance syndromes are moderate to severe acanthosis nigricans associated with either severely increased insulin concentrations or increased insulin requirements (depending on whether the patient has diabetes already), usually in the absence of a corresponding degree of obesity. Three different groups have been proposed based on the pathogenesis of the disease: primary insulin signaling defects, insulin resistance secondary to adipose tissue abnormalities, and insulin resistance as a feature of complex syndromes (153). Clinical and biochemical characterization of patients with severe insulin resistance may be used to guide genetic testing, as it happens with monogenic β-cell diabetes (Table 3). However, diabetes associated with monogenic severe insulin resistance is far less common than monogenic β-cell failure, especially in prepubertal children as hyperglycemia is usually a late event in the natural history of these disorders (154). As ovarian hyperandrogenism usually is the commonest presentation in adolescents, there is a gender bias in the diagnosis. The most relevant disorders are briefly described below.

Table 3. Classification of syndromes of severe insulin resistance (modified from reference 154)

Insulin resistance syndrome subtype		Gene (inheritance)	Leptin	Adiponectin	Other clinical features
Primary insulin signaling defects	Receptor defect	*INSR* (AR or AD)	Decreased	Normal or elevated	No dyslipidemia
	Post receptor defects	*AKT2*, *TBC1D4* (AD)			No fatty liver
Adipose tissue abnormalities	Monogenic obesity	*MC4R* (AD)	Increased (low in *LEP*)		Tall stature (*MC4R*)
		LEP, *LEPR*, *POMC* (AR)			Hypogonadism (*LEP*)
		Others			Hypoadrenalism (*POMC*)
	Congenital generalized lipodystrophy	*AGPAT2*, *BSCL2* (AR)	Decreased	Decreased	Severe dyslipidemia (high triglycerides, low HDL cholesterol)
		Others			Fatty liver
	Partial lipodystrophy	*LMNA*, *PPARG*, *PIK3R1* (AD)	Variable		Myopathy and cardiomyopathy (*LMNA*)
		Others			Pseudoacromegaly (*PPARG*)
					SHORT syndrome with partial lipodystrophy, insulin resistance and diabetes (PIK3R1)
Complex syndromes	Alström	*ALMS1* (AR)			
	Bardet–Biedl	*BBS1* to *BBS18* (mostly AR)			
	DNA damage repair disorders	*WRN* (AR)			
		BLM (AR)			
	Primordial dwarfism	*PCNT* (AR)			

AD, autosomal dominant; AR, autosomal recessive; HDL, high-density lipoprotein; SHORT, short stature, hypermobility of joints, ocular depression, Rieger's anomaly, and teething delay syndrome.

Primary insulin signaling defects due to mutations in the insulin receptor gene

Insulin receptor (*INSR*) gene mutations are responsible for a number of rare insulin resistance syndromes (155). Leptin levels are low, but adiponectin levels are normal or elevated as insulin normally inhibits adiponectin secretion. The most common form is type A insulin resistance syndrome, which is usually diagnosed in non-obese female adolescents with severe acanthosis nigricans and hyperandrogenism (polycystic ovarian syndrome) and may show autosomal dominant or autosomal recessive inheritance. Mutations in both alleles of *INSR* are also responsible for the more severe Donohue syndrome (formerly known as Leprechaunism) and Rabson–Mendenhall syndrome. The presenting complaint is failure to thrive, with impaired linear growth and weight gain, associated to overgrowth of soft tissues. Postprandial hyperglycemia may be severe but is usually accompanied by fasting hypoglycemia.

Metabolic control in patients with *INSR* mutations remains poor and long-term diabetes complications are frequent. Insulin sensitizers may be tried initially but most patients need extraordinarily high doses of insulin, with limited effect (155). As an alternative therapeutic method for young children, recombinant human insulin-like growth factor (IGF-I) has been reported to improve both fasting and postprandial glycemia although long-term effects on survival remain unclear (156).

Monogenic lipodystrophies

Lipodystrophies are characterized by a selective lack of adipose tissue, which results in decreased adipokines levels and insulin resistance (157). Mutations in either *AGPAT2* or *BSCL* account for approximately 80% of cases of congenital generalized lipodystrophy (Berardinelli–Seip syndrome) (158). This is a recessive disorder characterized by an almost complete absence of subcutaneous and visceral fat with abdominal distention due hepatic steatosis, which may evolve to hepatic fibrosis. Diabetes usually becomes apparent in early adolescence. In contrast, familial partial lipodystrophy is usually recognized after puberty in patients with loss of subcutaneous fat from the extremities and lower trunk and progressive accumulation of subcutaneous adipose tissue in the face and around the neck. Visceral fat is greatly increased. In addition to hyperinsulinemia, hypertriglyceridemia, and decreased high-density lipoprotein (HDL) cholesterol, patients also show signs of hyperandrogenism and sometimes pseudoacromegalic growth of soft tissues. Diabetes usually appears in late adolescence or early adulthood. Heterozygous mutations in *LMNA* or *PPARG* account for approximately 50% of cases (157). Two recent causes of lipodystrophy and multisystem disease are: (i) subcutaneous lipodystrophy and diabetes, deafness, mandibular hypoplasia, and hypogonadism in males associated with a specific mutation in POLD1, a universal DNA polymerase (159) and (ii) SHORT (short stature, hypermobility of joints, ocular depression, Rieger´s anomaly, and teething delay) syndrome with partial lipodystrophy, in which IR and diabetes were caused by a hot spot mutation in *PIK3R1* encoding p85 that has a central role in the insulin-signaling pathway (160).

Dietary advice with a low-fat, sometimes hypocaloric diet is the mainstay of treating lipodystrophies as it can have a dramatic effect on metabolic derangements.

In partial lipodystrophy, insulin sensitizers such as metformin and glitazones may be initially effective (161) but glitazones can cause further accumulation of fat in the face and neck (154). Patients with severe congenital lipodystrophy greatly benefit from treatment with recombinant leptin (162). In partial lipodystrophy, leptin replacement has limited value with improvement of hypertriglyceridemia but not hyperglycemia (163).

Ciliopathy-related insulin resistance and diabetes

Alström syndrome (ALMS). This autosomal recessive disorder shares symptoms with Bardet–Biedl syndrome (BBS) (see below), including progressive visual impairment related to cone–rod dystrophy, sensorineural hearing loss, obesity, and diabetes mellitus. It can be distinguished from the latter syndrome by the lack of polydactyly and hypogonadism and by the absence of cognitive impairment (164). More than 60% of individuals with ALMS develop cardiomyopathy. The syndrome is caused by mutations within the *ALMS1* gene of unknown function (165). Patients ALMS usually show many features of the metabolic syndrome including acanthosis nigricans, hyperlipidemia, hyperuricemia, hypertension, and slowly progressive insulin-resistant diabetes (166). Lifestyle intervention can initially ameliorate the metabolic abnormalities (167).

Bardet–Biedl syndrome. This disorder is characterized by intellectual disability, progressive visual impairment due to cone–rod dystrophy, polydactyly, obesity, diabetes mellitus, renal dysplasia, hepatic fibrosis, and hypogonadism. Obesity is found in almost every patient, while diabetes affects less than 50% (168). While the syndrome shares some similarities with Lawrence–Moon syndrome, these two disorders can be distinguished by the presence of paraplegia and the absence of polydactyly, obesity, and diabetes mellitus in Lawrence–Moon syndrome. Terms such as Lawrence–Moon–Bardet–Biedl or Lawrence–Moon–Biedl syndrome should therefore be avoided. BBS has been linked to 18 different genetic loci, referred to as *BBS1* to *BBS18* (169, 170). The majority of cases are autosomal recessive (171), but triallelic inheritance has been reported (172). Genetic diagnostic laboratories and detailed clinical recommendations for patients with ALMS and BBS are present at http://www.euro-wabb.org.

Conclusions

Advances in molecular genetics have led to the identification of genes associated with many clinically identified subgroups of diabetes. Molecular genetic testing is being used as a diagnostic tool that can help define the diagnosis and treatment of children with diabetes. As these tests are expensive, diagnostic genetic testing should be limited to those patients who are likely to harbor a mutation on clinical grounds.

Conflicts of interest

The authors have declared no conflicts of interest.

References

1. Fajans SS, Bell GI. MODY: history, genetics, pathophysiology, and clinical decision making. Diabetes Care 2011: 34: 1878–1884.
2. Tattersall R. Maturity-onset diabetes of the young: a clinical history. Diabet Med 1998: 15: 11–14.
3. Tattersall RB, Fajans SS. A difference between the inheritance of classical juvenile-onset and maturity-onset type diabetes of young people. Diabetes 1975: 24: 44–53.
4. Tattersall RB. Mild familial diabetes with dominant inheritance. Q J Med 1974: 43: 339–357.
5. Fajans SS, Bell GI, Polonsky KS. Molecular mechanisms and clinical pathophysiology of maturity-onset diabetes of the young. N Engl J Med 2001: 345: 971–980.
6. Murphy R, Ellard S, Hattersley AT. Clinical implications of a molecular genetic classification of monogenic beta-cell diabetes. Nat Clin Pract Endocrinol Metab 2008: 4: 200–213.
7. Gloyn AL, Pearson ER, Antcliff JF et al. Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 and permanent neonatal diabetes. N Engl J Med 2004: 350: 1838–1849.
8. Bellanné-Chantelot C, Clauin S, Chauveau D et al. Large genomic rearrangements in the hepatocyte nuclear factor-1beta (TCF2) gene are the most frequent cause of maturity-onset diabetes of the young type 5. Diabetes 2005: 54: 3126–3132.
9. Støy J, Edghill EL, Flanagan SE et al. Insulin gene mutations as a cause of permanent neonatal diabetes. Proc Natl Acad Sci U S A 2007: 104: 15040–15044.
10. Møller AM, Dalgaard LT, Pociot F, Nerup J, Hansen T, Pedersen O. Mutations in the hepatocyte nuclear factor-1alpha gene in Caucasian families originally classified as having type I diabetes. Diabetologia 1998: 41: 1528–1531.
11. Lambert AP, Ellard S, Allen LI et al. Identifying hepatic nuclear factor 1alpha mutations in children and young adults with a clinical diagnosis of type 1 diabetes. Diabetes Care 2003: 26: 333–337.
12. Rubio-Cabezas O, Edghill EL, Argente J, Hattersley AT. Testing for monogenic diabetes among children and adolescents with antibody-negative clinically defined Type 1 diabetes. Diabet Med 2009: 26: 1070–1074.
13. Awa WL, Schober E, Wiegand S et al. Reclassification of diabetes type in pediatric patients initially classified as type 2 diabetes mellitus: 15 years follow-up using routine data from the German/Austrian DPV database. Diabetes Res Clin Pract 2011: 94: 463–467.

14. Fendler W, Borowiec M, Baranowska-Jazwiecka A et al. Prevalence of monogenic diabetes amongst Polish children after a nationwide genetic screening campaign. Diabetologia 2012: 55: 2631–2635.
15. Irgens HU, Molnes J, Johansson BB et al. Prevalence of monogenic diabetes in the population-based Norwegian Childhood Diabetes Registry. Diabetologia 2013: 56: 1512–1519.
16. Pihoker C, Gilliam LK, Ellard S et al. Prevalence, characteristics and clinical diagnosis of maturity onset diabetes of the young due to mutations in HNF1A, HNF4A, and glucokinase: results from the SEARCH for Diabetes in Youth. J Clin Endocrinol Metab 2013: 98: 4055–4062.
17. Bonnefond A, Philippe J, Durand E et al. Highly sensitive diagnosis of 43 monogenic forms of diabetes or obesity through one-step PCR-based enrichment in combination with next-generation sequencing. Diabetes Care 2014: 37: 460–467.
18. Ellard S, Lango Allen H, De Franco E et al. Improved genetic testing for monogenic diabetes using targeted next-generation sequencing. Diabetologia 2013: 56: 1958–1963.
19. Gao R, Liu Y, Gjesing AP et al. Evaluation of a target region capture sequencing platform using monogenic diabetes as a study-model. BMC Genet 2014: 15: 13.
20. Johansson S, Irgens H, Chudasama KK et al. Exome sequencing and genetic testing for MODY. PLoS One 2012: 7: e38050.
21. Greeley SA, John PM, Winn AN et al. The cost-effectiveness of personalized genetic medicine: the case of genetic testing in neonatal diabetes. Diabetes Care 2011: 34: 622–627.
22. Naylor RN, John PM, Winn AN et al. Cost-effectiveness of MODY genetic testing: translating genomic advances into practical health applications. Diabetes Care 2014: 37: 202–209.
23. Iafusco D, Stazi MA, Cotichini R et al. Permanent diabetes mellitus in the first year of life. Diabetologia 2002: 45: 798–804.
24. Rubio-Cabezas O. Diagnosing monogenic diabetes: common misinterpretations of genetic findings. Pediatr Diabetes 2009: 10: 497–499.
25. Ellard S, Bellanne-Chantelot C, Hattersley AT. European Molecular Genetics Quality Network Mg. Best practice guidelines for the molecular genetic diagnosis of maturity-onset diabetes of the young. Diabetologia 2008: 51: 546–553.
26. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014: 37 (Suppl. 1): S81–S90.
27. Edghill EL, Dix RJ, Flanagan SE et al. HLA genotyping supports a nonautoimmune etiology in patients diagnosed with diabetes under the age of 6 months. Diabetes 2006: 55: 1895–1898.
28. Rubio-Cabezas O, Minton JA, Caswell R et al. Clinical heterogeneity in patients with FOXP3 mutations presenting with permanent neonatal diabetes. Diabetes Care 2009: 32: 111–116.
29. Rubio-Cabezas O, Flanagan SE, Damhuis A, Hattersley AT, Ellard S. KATP channel mutations in infants with permanent diabetes diagnosed after 6 months of life. Pediatr Diabetes 2012: 13: 322–325.
30. Mohamadi A, Clark LM, Lipkin PH, Mahone EM, Wodka EL, Plotnick LP. Medical and developmental impact of transition from subcutaneous insulin to oral glyburide in a 15-yr-old boy with neonatal diabetes mellitus and intermediate DEND syndrome: extending the age of KCNJ11 mutation testing in neonatal DM. Pediatr Diabetes 2010: 11: 203–207.
31. Gicquel C, Le Bouc Y. Hormonal regulation of fetal growth. Horm Res 2006: 65 (Suppl. 3): 28–33.
32. Temple IK, Gardner RJ, Mackay DJ, Barber JC, Robinson DO, Shield JP. Transient neonatal diabetes: widening the understanding of the etiopathogenesis of diabetes. Diabetes 2000: 49: 1359–1366.
33. Gardner RJ, Mackay DJ, Mungall AJ et al. An imprinted locus associated with transient neonatal diabetes mellitus. Hum Mol Genet 2000: 9: 589–596.
34. Flanagan SE, Patch AM, Mackay DJ et al. Mutations in ATP-sensitive K+ channel genes cause transient neonatal diabetes and permanent diabetes in childhood or adulthood. Diabetes 2007: 56: 1930–1937.
35. Yorifuji T, Kurokawa K, Mamada M et al. Neonatal diabetes mellitus and neonatal polycystic, dysplastic kidneys: phenotypically discordant recurrence of a mutation in the hepatocyte nuclear factor-1beta gene due to germline mosaicism. J Clin Endocrinol Metab 2004: 89: 2905–2908.
36. Garin I, Edghill EL, Akerman I et al. Recessive mutations in the INS gene result in neonatal diabetes through reduced insulin biosynthesis. Proc Natl Acad Sci U S A 2010: 107: 3105–3110.
37. Rubio-Cabezas O, Ellard S. Diabetes mellitus in neonates and infants: genetic heterogeneity, clinical approach to diagnosis, and therapeutic options. Horm Res Paediatr 2013: 80: 137–146.
38. Russo L, Iafusco D, Brescianini S et al. Permanent diabetes during the first year of life: multiple gene screening in 54 patients. Diabetologia 2011: 54: 1693–1701.
39. Mackay D, Bens S, Perez de Nanclares G, Siebert R, Temple IK. Clinical utility gene card for: transient neonatal diabetes mellitus, 6q24-related. Eur J Hum Genet 2014: Feb 26. doi: 10.1038/ejhg.2014.27.
40. Ma D, Shield JP, Dean W et al. Impaired glucose homeostasis in transgenic mice expressing the human transient neonatal diabetes mellitus locus, TNDM. J Clin Invest 2004: 114: 339–348.
41. Temple IK, Shield JP. Transient neonatal diabetes, a disorder of imprinting. J Med Genet 2002: 39: 872–875.
42. Mackay DJ, Boonen SE, Clayton-Smith J et al. A maternal hypomethylation syndrome presenting as transient neonatal diabetes mellitus. Hum Genet 2006: 120: 262–269.
43. Mackay DJ, Callaway JL, Marks SM et al. Hypomethylation of multiple imprinted loci in individuals with transient neonatal diabetes is associated with mutations in ZFP57. Nat Genet 2008: 40: 949–951.
44. Docherty LE, Kabwama S, Lehmann A et al. Clinical presentation of 6q24 transient neonatal diabetes mellitus (6q24 TNDM) and genotype-phenotype correlation in an international cohort of patients. Diabetologia 2013: 56: 758–762.

45. Shield JP, Temple IK, Sabin M et al. An assessment of pancreatic endocrine function and insulin sensitivity in patients with transient neonatal diabetes in remission. Arch Dis Child Fetal Neonatal Ed 2004: 89: F341–F343.
46. McTaggart JS, Clark RH, Ashcroft FM. The role of the KATP channel in glucose homeostasis in health and disease: more than meets the islet. J Physiol 2010: 588 (Pt 17): 3201–3209.
47. Ashcroft FM. ATP-sensitive potassium channelopathies: focus on insulin secretion. J Clin Invest 2005: 115: 2047–2058.
48. Babenko AP, Polak M, Cavé H et al. Activating mutations in the ABCC8 gene in neonatal diabetes mellitus. N Engl J Med 2006: 355: 456–466.
49. Ellard S, Flanagan SE, Girard CA et al. Permanent neonatal diabetes caused by dominant, recessive, or compound heterozygous SUR1 mutations with opposite functional effects. Am J Hum Genet 2007: 81: 375–382.
50. Flanagan SE, Edghill EL, Gloyn AL, Ellard S, Hattersley AT. Mutations in KCNJ11, which encodes Kir6.2, are a common cause of diabetes diagnosed in the first 6 months of life, with the phenotype determined by genotype. Diabetologia 2006: 49: 1190–1197.
51. Vaxillaire M, Populaire C, Busiah K et al. Kir6.2 mutations are a common cause of permanent neonatal diabetes in a large cohort of French patients. Diabetes 2004: 53: 2719–2722.
52. Proks P, Arnold AL, Bruining J et al. A heterozygous activating mutation in the sulphonylurea receptor SUR1 (ABCC8) causes neonatal diabetes. Hum Mol Genet 2006: 15: 1793–1800.
53. Edghill EL, Flanagan SE, Patch AM et al. Insulin mutation screening in 1,044 patients with diabetes: mutations in the INS gene are a common cause of neonatal diabetes but a rare cause of diabetes diagnosed in childhood or adulthood. Diabetes 2008: 57: 1034–1042.
54. Hattersley AT, Ashcroft FM. Activating mutations in Kir6.2 and neonatal diabetes: new clinical syndromes, new scientific insights, and new therapy. Diabetes 2005: 54: 2503–2513.
55. Gloyn AL, Diatloff-Zito C, Edghill EL et al. KCNJ11 activating mutations are associated with developmental delay, epilepsy and neonatal diabetes syndrome and other neurological features. Eur J Hum Genet 2006: 14: 824–830.
56. Clark RH, McTaggart JS, Webster R et al. Muscle dysfunction caused by a KATP channel mutation in neonatal diabetes is neuronal in origin. Science 2010: 329: 458–461.
57. Busiah K, Drunat S, Vaivre-Douret L et al. Neuropsychological dysfunction and developmental defects associated with genetic changes in infants with neonatal diabetes mellitus: a prospective cohort study. Lancet Diabetes Endocrinol 2013: 1: 199–207.
58. Pearson ER, Flechtner I, Njolstad PR et al. Switching from insulin to oral sulfonylureas in patients with diabetes due to Kir6.2 mutations. N Engl J Med 2006: 355: 467–477.
59. Rafiq M, Flanagan SE, Patch AM et al. Effective treatment with oral sulfonylureas in patients with diabetes due to sulfonylurea receptor 1 (SUR1) mutations. Diabetes Care 2008: 31: 204–209.
60. Sagen JV, Raeder H, Hathout E et al. Permanent neonatal diabetes due to mutations in KCNJ11 encoding Kir6.2: patient characteristics and initial response to sulfonylurea therapy. Diabetes 2004: 53: 2713–2718.
61. Greeley SA, Tucker SE, Naylor RN, Bell GI, Philipson LH. Neonatal diabetes mellitus: a model for personalized medicine. Trends Endocrinol Metab 2010: 21: 464–472.
62. Klupa T, Skupien J, Mirkiewicz-Sieradzka B et al. Efficacy and safety of sulfonylurea use in permanent neonatal diabetes due to KCNJ11 gene mutations: 34-month median follow-up. Diabetes Technol Ther 2010: 12: 387–391.
63. Codner E, Flanagan S, Ellard S, García H, Hattersley AT. High-dose glibenclamide can replace insulin therapy despite transitory diarrhea in early-onset diabetes caused by a novel R201L Kir6.2 mutation. Diabetes Care 2005: 28: 758–759.
64. Kumaraguru J, Flanagan SE, Greeley SA et al. Tooth discoloration in patients with neonatal diabetes after transfer onto glibenclamide: a previously unreported side effect. Diabetes Care 2009: 32: 1428–1430.
65. Mlynarski W, Tarasov AI, Gach A et al. Sulfonylurea improves CNS function in a case of intermediate DEND syndrome caused by a mutation in KCNJ11. Nat Clin Pract Neurol 2007: 3: 640–645.
66. Fendler W, Pietrzak I, Brereton MF et al. Switching to sulphonylureas in children with iDEND syndrome caused by KCNJ11 mutations results in improved cerebellar perfusion. Diabetes Care 2013: 36: 2311–2316.
67. Battaglia D, Lin YW, Brogna C et al. Glyburide ameliorates motor coordination and glucose homeostasis in a child with diabetes associated with the KCNJ11/S225T, del226-232 mutation. Pediatr Diabetes 2012: 13: 656–660.
68. Gurgel LC, Crispim F, Noffs MH, Belzunces E, Rahal MA, Moises RS. Sulfonylrea treatment in permanent neonatal diabetes due to G53D mutation in the KCNJ11 gene: improvement in glycemic control and neurological function. Diabetes Care 2007: 30: e108.
69. Koster JC, Cadario F, Peruzzi C, Colombo C, Nichols CG, Barbetti F. The G53D mutation in Kir6.2 (KCNJ11) is associated with neonatal diabetes and motor dysfunction in adulthood that is improved with sulfonylurea therapy. J Clin Endocrinol Metab 2008: 93: 1054–1061.
70. Slingerland AS, Nuboer R, Hadders-Algra M, Hattersley AT, Bruining GJ. Improved motor development and good long-term glycaemic control with sulfonylurea treatment in a patient with the syndrome of intermediate developmental delay, early-onset generalised epilepsy and neonatal diabetes associated with the V59M mutation in the KCNJ11 gene. Diabetologia 2006: 49: 2559–2563.
71. Edghill EL, Gloyn AL, Goriely A et al. Origin of de novo KCNJ11 mutations and risk of neonatal diabetes for subsequent siblings. J Clin Endocrinol Metab 2007: 92: 1773–1777.

72. Colombo C, Porzio O, Liu M et al. Seven mutations in the human insulin gene linked to permanent neonatal/infancy-onset diabetes mellitus. J Clin Invest 2008: 118: 2148–2156.
73. Polak M, Dechaume A, Cave H et al. Heterozygous missense mutations in the insulin gene are linked to permanent diabetes appearing in the neonatal period or in early infancy: a report from the French ND (Neonatal Diabetes) Study Group. Diabetes 2008: 57: 1115–1119.
74. Eizirik DL, Cardozo AK, Cnop M. The role for endoplasmic reticulum stress in diabetes mellitus. Endocr Rev 2008: 29: 42–61.
75. Bonfanti R, Colombo C, Nocerino V et al. Insulin gene mutations as cause of diabetes in children negative for five type 1 diabetes autoantibodies. Diabetes Care 2009: 32: 123–125.
76. Molven A, Ringdal M, Nordbo AM et al. Mutations in the insulin gene can cause MODY and autoantibody-negative type 1 diabetes. Diabetes 2008: 57: 1131–1135.
77. Delépine M, Nicolino M, Barrett T, Golamaully M, Lathrop GM, Julier C. EIF2AK3, encoding translation initiation factor 2-alpha kinase 3, is mutated in patients with Wolcott-Rallison syndrome. Nat Genet 2000: 25: 406–409.
78. Senée V, Vattem KM, Delépine M et al. Wolcott-Rallison syndrome: clinical, genetic, and functional study of EIF2AK3 mutations and suggestion of genetic heterogeneity. Diabetes 2004: 53: 1876–1883.
79. Habeb AM, Flanagan SE, Deeb A et al. Permanent neonatal diabetes: different aetiology in Arabs compared to Europeans. Arch Dis Child 2012: 97: 721–723.
80. Rubio-Cabezas O, Patch AM, Minton JA et al. Wolcott-Rallison syndrome is the most common genetic cause of permanent neonatal diabetes in consanguineous families. J Clin Endocrinol Metab 2009: 94: 4162–4170.
81. Matschinsky FM. Glucokinase, glucose homeostasis, and diabetes mellitus. Curr Diab Rep 2005: 5: 171–176.
82. Njolstad PR, Sagen JV, Bjorkhaug L et al. Permanent neonatal diabetes caused by glucokinase deficiency: inborn error of the glucose-insulin signaling pathway. Diabetes 2003: 52: 2854–2860.
83. Njølstad PR, Søvik O, Cuesta-Muñoz A et al. Neonatal diabetes mellitus due to complete glucokinase deficiency. N Engl J Med 2001: 344: 1588–1592.
84. Bennett CL, Christie J, Ramsdell F et al. The immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome (IPEX) is caused by mutations of FOXP3. Nat Genet 2001: 27: 20–21.
85. Verbsky JW, Chatila TA. Immune dysregulation, polyendocrinopathy, enteropathy, X-linked (IPEX) and IPEX-related disorders: an evolving web of heritable autoimmune diseases. Curr Opin Pediatr 2013: 25: 708–714.
86. Bindl L, Torgerson T, Perroni L et al. Successful use of the new immune-suppressor sirolimus in IPEX (immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome). J Pediatr 2005: 147: 256–259.
87. Yong PL, Russo P, Sullivan KE. Use of sirolimus in IPEX and IPEX-like children. J Clin Immunol 2008: 28: 581–587.
88. Rao A, Kamani N, Filipovich A et al. Successful bone marrow transplantation for IPEX syndrome after reduced-intensity conditioning. Blood 2007: 109: 383–385.
89. Weedon MN, Cebola I, Patch AM et al. Recessive mutations in a distal PTF1A enhancer cause isolated pancreatic agenesis. Nat Genet 2014: 46: 61–64.
90. Lango Allen H, Flanagan SE, Shaw-Smith C et al. GATA6 haploinsufficiency causes pancreatic agenesis in humans. Nat Genet 2012: 44: 20–22.
91. Shields BM, Hicks S, Shepherd MH, Colclough K, Hattersley AT, Ellard S. Maturity-onset diabetes of the young (MODY): how many cases are we missing? Diabetologia 2010: 53: 2504–2508.
92. Stanik J, Dusatkova P, Cinek O et al. De novo mutations of GCK, HNF1A and HNF4A may be more frequent in MODY than previously assumed. Diabetologia 2014: 57: 480–484.
93. Raeder H, Johansson S, Holm PI et al. Mutations in the CEL VNTR cause a syndrome of diabetes and pancreatic exocrine dysfunction. Nat Genet 2006: 38: 54–62.
94. Lorini R, Alibrandi A, Vitali L et al. Risk of type 1 diabetes development in children with incidental hyperglycemia: a multicenter Italian study. Diabetes Care 2001: 24: 1210–1216.
95. Feigerlova E, Pruhova S, Dittertova L et al. Aetiological heterogeneity of asymptomatic hyperglycaemia in children and adolescents. Eur J Pediatr 2006: 165: 446–452.
96. Lorini R, Klersy C, d'Annunzio G et al. Maturity-onset diabetes of the young in children with incidental hyperglycemia: a multicenter Italian study of 172 families. Diabetes Care 2009: 32: 1864–1866.
97. Prisco F, Iafusco D, Franzese A, Sulli N, Barbetti F. MODY 2 presenting as neonatal hyperglycaemia: a need to reshape the definition of "neonatal diabetes"? Diabetologia 2000: 43: 1331–1332.
98. Steele AM, Wensley KJ, Ellard S et al. Use of HbA1c in the identification of patients with hyperglycaemia caused by a glucokinase mutation: observational case control studies. PLoS One 2013: 8: e65326.
99. Stride A, Vaxillaire M, Tuomi T et al. The genetic abnormality in the beta cell determines the response to an oral glucose load. Diabetologia 2002: 45: 427–435.
100. Steele AM, Shields BM, Wensley KJ, Colclough K, Ellard S, Hattersley AT. Prevalence of vascular complications among patients with glucokinase mutations and prolonged, mild hyperglycemia. JAMA 2014: 311: 279–286.
101. Velho G, Blanché H, Vaxillaire M et al. Identification of 14 new glucokinase mutations and description of the clinical profile of 42 MODY-2 families. Diabetologia 1997: 40: 217–224.
102. Stride A, Shields B, Gill-Carey O et al. Cross-sectional and longitudinal studies suggest pharmacological treatment used in patients with glucokinase mutations does not alter glycaemia. Diabetologia 2014: 57: 54–56.

103. Fendler W, Malachowska B, Baranowska-Jazwiecka A et al. Population-based estimates for double diabetes amongst people with glucokinase monogenic diabetes, GCK-MODY. Diabet Med 2014: 31: 881–883.
104. Pearson ER, Pruhova S, Tack CJ et al. Molecular genetics and phenotypic characteristics of MODY caused by hepatocyte nuclear factor 4alpha mutations in a large European collection. Diabetologia 2005: 48: 878–885.
105. Ostoft SH, Bagger JI, Hansen T et al. Incretin effect and glucagon responses to oral and intravenous glucose in patients with maturity onset diabetes of the young - type 2 and type 3. Diabetes 2014: Mar 27. [Epub ahead of print].
106. Isomaa B, Henricsson M, Lehto M et al. Chronic diabetic complications in patients with MODY3 diabetes. Diabetologia 1998: 41: 467–473.
107. Steele AM, Shields BM, Shepherd M, Ellard S, Hattersley AT, Pearson ER. Increased all-cause and cardiovascular mortality in monogenic diabetes as a result of mutations in the HNF1A gene. Diabet Med 2010: 27: 157–161.
108. Bellanne-Chantelot C, Carette C, Riveline JP et al. The type and the position of HNF1A mutation modulate age at diagnosis of diabetes in patients with maturity-onset diabetes of the young (MODY)-3. Diabetes 2008: 57: 503–508.
109. Harries LW, Ellard S, Stride A, Morgan NG, Hattersley AT. Isomers of the TCF1 gene encoding hepatocyte nuclear factor-1 alpha show differential expression in the pancreas and define the relationship between mutation position and clinical phenotype in monogenic diabetes. Hum Mol Genet 2006: 15: 2216–2224.
110. Stride A, Ellard S, Clark P et al. Beta-cell dysfunction, insulin sensitivity, and glycosuria precede diabetes in hepatocyte nuclear factor-1alpha mutation carriers. Diabetes Care 2005: 28: 1751–1756.
111. Hamilton AJ, Bingham C, McDonald TJ et al. The HNF4A R76W mutation causes atypical dominant Fanconi syndrome in addition to a beta cell phenotype. J Med Genet 2014: 51: 165–169.
112. Pearson ER, Boj SF, Steele AM et al. Macrosomia and hyperinsulinaemic hypoglycaemia in patients with heterozygous mutations in the HNF4A gene. PLoS Med 2007: 4: e118.
113. Flanagan SE, Kapoor RR, Mali G et al. Diazoxide-responsive hyperinsulinemic hypoglycemia caused by HNF4A gene mutations. Eur J Endocrinol 2010: 162: 987–992.
114. Kapoor RR, Locke J, Colclough K et al. Persistent hyperinsulinemic hypoglycemia and maturity-onset diabetes of the young due to heterozygous HNF4A mutations. Diabetes 2008: 57: 1659–1663.
115. Stanescu DE, Hughes N, Kaplan B, Stanley CA, De Leon DD. Novel presentations of congenital hyperinsulinism due to mutations in the MODY genes: HNF1A and HNF4A. J Clin Endocrinol Metab 2012: 97: E2026–E2030.
116. Pearson ER, Starkey BJ, Powell RJ, Gribble FM, Clark PM, Hattersley AT. Genetic cause of hyperglycaemia and response to treatment in diabetes. Lancet 2003: 362: 1275–1281.
117. Byrne MM, Sturis J, Menzel S et al. Altered insulin secretory responses to glucose in diabetic and nondiabetic subjects with mutations in the diabetes susceptibility gene MODY3 on chromosome 12. Diabetes 1996: 45: 1503–1510.
118. Fajans SS, Brown MB. Administration of sulfonylureas can increase glucose-induced insulin secretion for decades in patients with maturity-onset diabetes of the young. Diabetes Care 1993: 16: 1254–1261.
119. Shepherd M, Shields B, Ellard S, Rubio-Cabezas O, Hattersley AT. A genetic diagnosis of HNF1A diabetes alters treatment and improves glycaemic control in the majority of insulin-treated patients. Diabet Med 2009: 26: 437–441.
120. Becker M, Galler A, Raile K. Meglitinide analogues in adolescent patients with HNF1A-MODY (MODY 3). Pediatrics 2014: 133: e775–e779.
121. Tuomi T, Honkanen EH, Isomaa B, Sarelin L, Groop LC. Improved prandial glucose control with lower risk of hypoglycemia with nateglinide than with glibenclamide in patients with maturity-onset diabetes of the young type 3. Diabetes Care 2006: 29: 189–194.
122. Ostoft SH, Bagger JI, Hansen T et al. Glucose-lowering effects and low risk of hypoglycemia in patients with maturity-onset diabetes of the young when treated with a GLP-1 receptor agonist: a double-blind, randomized, crossover trial. Diabetes Care 2014: 37: 1797–1805.
123. Schmidt F, Kapellen TM, Wiegand S et al. Diabetes mellitus in children and adolescents with genetic syndromes. Exp Clin Endocrinol Diabetes 2012: 120: 579–585.
124. Farmer A, Ayme S, de Heredia ML et al. EURO-WABB: an EU rare diseases registry for Wolfram syndrome, Alstrom syndrome and Bardet-Biedl syndrome. BMC Pediatr 2013: 13: 130.
125. Domenech E, Gomez-Zaera M, Nunes V. Wolfram/DIDMOAD syndrome, a heterogenic and molecularly complex neurodegenerative disease. Pediatr Endocrinol Rev 2006: 3: 249–257.
126. Barrett TG, Bundey SE, Macleod AF. Neurodegeneration and diabetes: UK nationwide study of Wolfram (DIDMOAD) syndrome. Lancet 1995: 346: 1458–1463.
127. Marshall SL, Edidin D, Sharma V, Ogle G, Arena VC, Orchard T. Current clinical status, glucose control, and complication rates of children and youth with type 1 diabetes in Rwanda. Pediatr Diabetes 2013: 14: 217–226.
128. de Heredia ML, Cleries R, Nunes V. Genotypic classification of patients with Wolfram syndrome: insights into the natural history of the disease and correlation with phenotype. Genet Med 2013: 15: 497–506.
129. Zmyslowska A, Borowiec M, Fichna P et al. Delayed recognition of Wolfram syndrome frequently misdiagnosed as type 1 diabetes with early chronic complications. Exp Clin Endocrinol Diabetes 2014: 122: 35–38.
130. Inoue H, Tanizawa Y, Wasson J et al. A gene encoding a transmembrane protein is mutated in patients with diabetes mellitus and optic atrophy (Wolfram syndrome). Nat Genet 1998: 20: 143–148.

131. Khanim F, Kirk J, Latif F, Barrett TG. WFS1/wolframin mutations, Wolfram syndrome, and associated diseases. Hum Mutat 2001: 17: 357–367.
132. Amr S, Heisey C, Zhang M et al. A homozygous mutation in a novel zinc-finger protein, ERIS, is responsible for Wolfram syndrome 2. Am J Hum Genet 2007: 81: 673–683.
133. Bingham C, Hattersley AT. Renal cysts and diabetes syndrome resulting from mutations in hepatocyte nuclear factor-1beta. Nephrol Dial Transplant 2004: 19: 2703–2708.
134. Ulinski T, Lescure S, Beaufils S et al. Renal phenotypes related to hepatocyte nuclear factor-1beta (TCF2) mutations in a pediatric cohort. J Am Soc Nephrol 2006: 17: 497–503.
135. Edghill EL, Bingham C, Ellard S, Hattersley AT. Mutations in hepatocyte nuclear factor-1beta and their related phenotypes. J Med Genet 2006: 43: 84–90.
136. Raile K, Klopocki E, Holder M et al. Expanded clinical spectrum in hepatocyte nuclear factor 1b-maturity-onset diabetes of the young. J Clin Endocrinol Metab 2009: 94: 2658–2664.
137. Edghill EL, Bingham C, Slingerland AS et al. Hepatocyte nuclear factor-1 beta mutations cause neonatal diabetes and intrauterine growth retardation: support for a critical role of HNF-1beta in human pancreatic development. Diabet Med 2006: 23: 1301–1306.
138. Bellanné-Chantelot C, Chauveau D, Gautier JF et al. Clinical spectrum associated with hepatocyte nuclear factor-1beta mutations. Ann Intern Med 2004: 140: 510–517.
139. Pearson ER, Badman MK, Lockwood CR et al. Contrasting diabetes phenotypes associated with hepatocyte nuclear factor-1alpha and -1beta mutations. Diabetes Care 2004: 27: 1102–1107.
140. Tjora E, Wathle G, Erchinger F et al. Exocrine pancreatic function in hepatocyte nuclear factor 1beta-maturity-onset diabetes of the young (HNF1B-MODY) is only moderately reduced: compensatory hypersecretion from a hypoplastic pancreas. Diabet Med 2013: 30: 946–955.
141. Haldorsen IS, Vesterhus M, Raeder H et al. Lack of pancreatic body and tail in HNF1B mutation carriers. Diabet Med 2008: 25: 782–787.
142. Maassen JA, T Hart LM, Van Essen E et al. Mitochondrial diabetes: molecular mechanisms and clinical presentation. Diabetes 2004: 53 (Suppl. 1): S103–S109.
143. Guillausseau PJ, Dubois-Laforgue D, Massin P et al. Heterogeneity of diabetes phenotype in patients with 3243 bp mutation of mitochondrial DNA (maternally inherited diabetes and deafness or MIDD). Diabetes Metab 2004: 30: 181–186.
144. Laloi-Michelin M, Meas T, Ambonville C et al. The clinical variability of maternally inherited diabetes and deafness is associated with the degree of heteroplasmy in blood leukocytes. J Clin Endocrinol Metab 2009: 94: 3025–3030.
145. Goto Y, Nonaka I, Horai S. A mutation in the tRNA(Leu)(UUR) gene associated with the MELAS subgroup of mitochondrial encephalomyopathies. Nature 1990: 348: 651–653.
146. Lalau JD. Lactic acidosis induced by metformin: incidence, management and prevention. Drug Saf 2010: 33: 727–740.
147. Laloi-Michelin M, Virally M, Jardel C et al. Kearns Sayre syndrome: an unusual form of mitochondrial diabetes. Diabetes Metab 2006: 32: 182–186.
148. Superti-Furga A, Schoenle E, Tuchschmid P et al. Pearson bone marrow-pancreas syndrome with insulin-dependent diabetes, progressive renal tubulopathy, organic aciduria and elevated fetal haemoglobin caused by deletion and duplication of mitochondrial DNA. Eur J Pediatr 1993: 152: 44–50.
149. Raeder H, Haldorsen IS, Ersland L et al. Pancreatic lipomatosis is a structural marker in nondiabetic children with mutations in carboxyl-ester lipase. Diabetes 2007: 56: 444–449.
150. Raeder H, McAllister FE, Tjora E et al. Carboxyl-ester lipase maturity-onset diabetes of the young is associated with development of pancreatic cysts and upregulated MAPK signaling in secretin-stimulated duodenal fluid. Diabetes 2014: 63: 259–269.
151. Moran A, Pillay K, Becker D, Acerini CL. Management of cystic fibrosis related diabetes in children and adolescents. Pediatr Diabetes 2014: 15: 65–76.
152. Rebours V, Boutron-Ruault MC, Schnee M et al. The natural history of hereditary pancreatitis: a national series. Gut 2009: 58: 97–103.
153. Semple RK, Savage DB, Cochran EK, Gorden P, O'Rahilly S. Genetic syndromes of severe insulin resistance. Endocr Rev 2011: 32: 498–514.
154. Parker VE, Semple RK. Genetics in endocrinology: genetic forms of severe insulin resistance: what endocrinologists should know. Eur J Endocrinol 2013: 169: R71–R80.
155. Musso C, Cochran E, Moran SA et al. Clinical course of genetic diseases of the insulin receptor (type A and Rabson-Mendenhall syndromes): a 30-year prospective. Medicine (Baltimore) 2004: 83: 209–222.
156. Regan FM, Williams RM, McDonald A et al. Treatment with recombinant human insulin-like growth factor (rhIGF)-I/rhIGF binding protein-3 complex improves metabolic control in subjects with severe insulin resistance. J Clin Endocrinol Metab 2010: 95: 2113–2122.
157. Garg A. Acquired and inherited lipodystrophies. N Engl J Med 2004: 350: 1220–1234.
158. Agarwal AK, Simha V, Oral EA et al. Phenotypic and genetic heterogeneity in congenital generalized lipodystrophy. J Clin Endocrinol Metab 2003: 88: 4840–4847.
159. Weedon MN, Ellard S, Prindle MJ et al. An in-frame deletion at the polymerase active site of POLD1 causes a multisystem disorder with lipodystrophy. Nat Genet 2013: 45: 947–950.
160. Chudasama KK, Winnay J, Johansson S et al. SHORT syndrome with partial lipodystrophy due to impaired phosphatidylinositol 3 kinase signaling. Am J Hum Genet 2013: 93: 150–157.
161. Owen KR, Donohoe M, Ellard S, Hattersley AT. Response to treatment with rosiglitazone in familial partial lipodystrophy due to a mutation in the LMNA gene. Diabet Med 2003: 20: 823–827.

162. Beltrand J, Beregszaszi M, Chevenne D et al. Metabolic correction induced by leptin replacement treatment in young children with Berardinelli-Seip congenital lipoatrophy. Pediatrics 2007: 120: e291–e296.
163. Simha V, Subramanyam L, Szczepaniak L et al. Comparison of efficacy and safety of leptin replacement therapy in moderately and severely hypoleptinemic patients with familial partial lipodystrophy of the Dunnigan variety. J Clin Endocrinol Metab 2012: 97: 785–792.
164. Alstrom CH, Hallgren B, Nilsson LB, Asander H. Retinal degeneration combined with obesity, diabetes mellitus and neurogenous deafness: a specific syndrome (not hitherto described) distinct from the Laurence-Moon-Bardet-Biedl syndrome: a clinical, endocrinological and genetic examination based on a large pedigree. Acta Psychiatr Neurol Scand Suppl 1959: 129: 1–35.
165. Hearn T, Renforth GL, Spalluto C et al. Mutation of ALMS1, a large gene with a tandem repeat encoding 47 amino acids, causes Alstrom syndrome. Nat Genet 2002: 31: 79–83.
166. Mokashi A, Cummings EA. Presentation and course of diabetes in children and adolescents with Alstrom syndrome. Pediatr Diabetes 2011: 12 (3 Pt 2): 270–275.
167. Paisey RB, Geberhiwot T, Waterson M et al. Modification of severe insulin resistant diabetes in response to lifestyle changes in Alstrom syndrome. Eur J Med Genet 2014: 57: 71–75.
168. Tobin JL, Beales PL. Bardet-Biedl syndrome: beyond the cilium. Pediatr Nephrol 2007: 22: 926–936.
169. Scheidecker S, Etard C, Pierce NW et al. Exome sequencing of Bardet-Biedl syndrome patient identifies a null mutation in the BBSome subunit BBIP1 (BBS18). J Med Genet 2014: 51: 132–136.
170. Guo DF, Rahmouni K. Molecular basis of the obesity associated with Bardet-Biedl syndrome. Trends Endocrinol Metab 2011: 22: 286–293.
171. Abu-Safieh L, Al-Anazi S, Al-Abdi L et al. In search of triallelism in Bardet-Biedl syndrome. Eur J Hum Genet 2012: 20: 420–427.
172. Katsanis N, Ansley SJ, Badano JL et al. Triallelic inheritance in Bardet-Biedl syndrome, a Mendelian recessive disorder. Science 2001: 293: 2256–2259.
173. Stoffers DA, Zinkin NT, Stanojevic V, Clarke WL, Habener JF. Pancreatic agenesis attributable to a single nucleotide deletion in the human IPF1 gene coding sequence. Nat Genet 1997: 15: 106–110.
174. Sellick GS, Barker KT, Stolte-Dijkstra I et al. Mutations in PTF1A cause pancreatic and cerebellar agenesis. Nat Genet 2004: 36: 1301–1305.
175. Smith SB, Qu HQ, Taleb N et al. Rfx6 directs islet formation and insulin production in mice and humans. Nature 2010: 463: 775–780.
176. D'Amato E, Giacopelli F, Giannattasio A et al. Genetic investigation in an Italian child with an unusual association of atrial septal defect, attributable to a new familial GATA4 gene mutation, and neonatal diabetes due to pancreatic agenesis. Diabet Med 2010: 27: 1195–1200.
177. Senee V, Chelala C, Duchatelet S et al. Mutations in GLIS3 are responsible for a rare syndrome with neonatal diabetes mellitus and congenital hypothyroidism. Nat Genet 2006: 38: 682–687.
178. Rubio-Cabezas O, Jensen JN, Hodgson MI et al. Permanent neonatal diabetes and enteric anendocrinosis associated with biallelic mutations in NEUROG3. Diabetes 2011: 60: 1349–1353.
179. Rubio-Cabezas O, Minton JA, Kantor I, Williams D, Ellard S, Hattersley AT. Homozygous mutations in NEUROD1 are responsible for a novel syndrome of permanent neonatal diabetes and neurological abnormalities. Diabetes 2010: 59: 2326–2331.
180. Solomon BD, Pineda-Alvarez DE, Balog JZ et al. Compound heterozygosity for mutations in PAX6 in a patient with complex brain anomaly, neonatal diabetes mellitus, and microophthalmia. Am J Med Genet A 2009: 149A: 2543–2546.
181. Bonnefond A, Vaillant E, Philippe J et al. Transcription factor gene MNX1 is a novel cause of permanent neonatal diabetes in a consanguineous family. Diabetes Metab 2013: 39: 276–280.
182. Flanagan SE, De Franco E, Lango Allen H et al. Analysis of transcription factors key for mouse pancreatic development establishes NKX2-2 and MNX1 mutations as causes of neonatal diabetes in man. Cell Metab 2014: 19: 146–154.
183. Yoo HW, Shin YL, Seo EJ, Kim GH. Identification of a novel mutation in the GLUT2 gene in a patient with Fanconi-Bickel syndrome presenting with neonatal diabetes mellitus and galactosaemia. Eur J Pediatr 2002: 161: 351–353.
184. Mandel H, Berant M, Hazani A, Naveh Y. Thiamine-dependent beriberi in the "thiamine-responsive anemia syndrome". N Engl J Med 1984: 311: 836–838.
185. Abdel-Salam GM, Schaffer AE, Zaki MS et al. A homozygous IER3IP1 mutation causes microcephaly with simplified gyral pattern, epilepsy, and permanent neonatal diabetes syndrome (MEDS). Am J Med Genet A 2012: 158A: 2788–2796.
186. Wildin RS, Ramsdell F, Peake J et al. X-linked neonatal diabetes mellitus, enteropathy and endocrinopathy syndrome is the human equivalent of mouse scurfy. Nat Genet 2001: 27: 18–20.
187. Yamagata K, Furuta H, Oda N et al. Mutations in the hepatocyte nuclear factor-4alpha gene in maturity-onset diabetes of the young (MODY1). Nature 1996: 384: 458–460.
188. Vionnet N, Stoffel M, Takeda J et al. Nonsense mutation in the glucokinase gene causes early-onset non-insulin-dependent diabetes mellitus. Nature 1992: 356: 721–722.
189. Yamagata K, Oda N, Kaisaki PJ et al. Mutations in the hepatocyte nuclear factor-1alpha gene in maturity-onset diabetes of the young (MODY3). Nature 1996: 384: 455–458.
190. Horikawa Y, Iwasaki N, Hara M et al. Mutation in hepatocyte nuclear factor-1 beta gene (TCF2) associated with MODY. Nat Genet 1997: 17: 384–385.

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ISPAD Clinical Practice Consensus Guidelines 2014 Compendium

Diabetic ketoacidosis and hyperglycemic hyperosmolar state

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This article is a chapter in the *ISPAD Clinical Practice Consensus Guidelines 2014 Compendium*. The complete set of guidelines can be found for free download at www.ispad.org. The evidence grading system used in the ISPAD Guidelines is the same as that used by the American Diabetes Association. See page 3 (the Introduction in *Pediatric Diabetes* 2014; 15 (Suppl. 20): 1-3).

Executive summary and Recommendations

The **biochemical criteria** for the diagnosis of diabetic ketoacidosis (DKA) are:

- Hyperglycemia [blood glucose (BG) >11 mmol/L (≈200 mg/dL)]
- Venous pH < 7.3 or bicarbonate <15 mmol/L
- Ketonemia and ketonuria.

The **clinical signs of DKA** include:

- Dehydration (which may be difficult to detect)
- Tachycardia
- Tachypnea (which may be mistaken for pneumonia or asthma)
- Deep, sighing (Kussmaul) respiration; breath has the smell of acetone (variously described as the odor of nail polish remover or rotten fruit)
- Nausea, vomiting (which may be mistaken for gastroenteritis)
- Abdominal pain that may mimic an acute abdominal condition
- Confusion, drowsiness, progressive reduction in level of consciousness and, eventually, loss of consciousness.

Risk factors for DKA in newly diagnosed cases include younger age (<2 yr), delayed diagnosis, lower socioeconomic status, and countries with low prevalence of type 1 diabetes mellitus.

Risk factors for DKA in patients with known diabetes include insulin omission, poor metabolic control, previous episodes of DKA, gastroenteritis with persistent vomiting and inability to maintain hydration, psychiatric (including eating) disorders, challenging social and family circumstances, peripubertal and adolescent girls, limited access to medical services, failures in insulin pump therapy.

The following recommendations are based on currently available evidence and are intended only as a general guide to DKA management. Because there is considerable individual variability in presentation of DKA (ranging from mild with only minimal dehydration to severe with profound dehydration), some patients may require specific treatment that, in the judgment of the treating physician, may be within or, occasionally, outside the range of options presented here. Clinical judgment should always be used to determine optimal treatment of the individual patient, and timely adjustments to treatment (insulin dose, electrolyte composition and rate of infusion of rehydration fluids) should be based on ongoing, careful clinical and biochemical monitoring of the patient's response.

Emergency assessment should follow the general guidelines for Pediatric Advanced Life Support (PALS) and includes: immediate measurement of BG, blood or urine ketones, serum electrolytes, blood gases and full blood count; assessment of severity of dehydration and level of consciousness (E). A second peripheral IV catheter should be inserted (E).

Management should be in centers experienced in the treatment of DKA in children and adolescents and where vital signs, neurological status and laboratory results can be monitored frequently (E). Where geographic constraints require that management be initiated in a center with less experience and with fewer resources, there should be arrangements in place for telephone or videoconference support from a physician with expertise in DKA (E).

Meticulous monitoring of the clinical and biochemical response to treatment is necessary so that timely adjustments in treatment can be made when indicated by the patient's clinical or laboratory data (E).

Goals of therapy are to correct dehydration, correct acidosis and reverse ketosis, slowly correct hyperosmolality and restore BG to near normal, monitor for complications of DKA and its treatment, and identify and treat any precipitating event.

Fluid replacement should begin before starting insulin therapy. Expand volume, as required, to restore peripheral circulation (E). Calculate the subsequent rate of fluid administration, including the provision of maintenance fluid requirements, aiming to replace the estimated fluid deficit evenly over 48 h. The rate of fluid administration should seldom exceed 1.5–2 times the usual daily maintenance requirement (C).

Insulin therapy: begin with 0.05–0.1 U/kg/h 1–2 h AFTER starting fluid replacement therapy (C, B).

Potassium: If the patient is hyperkalemic, *defer* potassium replacement therapy until urine output is documented. Otherwise, begin with 40 mmol potassium/L in the infusate or 20 mmol potassium/L in the patient receiving fluid at a rate >10 mL/kg/h (E).

Bicarbonate administration is not recommended except for treatment of life-threatening hyperkalemia (B).

Warning signs and symptoms of cerebral edema include: headache (variable severity) and slowing of heart rate, change in neurological status (restlessness, irritability, increased drowsiness, incontinence), specific neurological signs (e.g., cranial nerve palsies), rising blood pressure and decreased oxygen saturation.

In patients with multiple risk factors for cerebral edema, have mannitol or hypertonic saline at the bedside and the dose to be given calculated beforehand (E). If neurologic status deteriorates acutely, hyperosmolar therapy should be given immediately (C).

Prevention: Management of an episode of DKA is not complete until an attempt has been made to identify and treat the cause. Recurrent DKA without a preceding febrile or vomiting illness is almost always the result of psychosocial problems and failure to take insulin (E).

The criteria for **hyperglycemic hyperosmolar state (HHS) include:**

- Plasma glucose concentration >33.3 mmol/L (600 mg/dL)
- Venous pH > 7.25; arterial pH > 7.30
- Serum bicarbonate >15 mmol/L
- Small ketonuria, absent to mild ketonemia
- Effective serum osmolality >320 mOsm/kg
- Altered consciousness (e.g., obtundation, combativeness) or seizures.

In HHS, the goals of initial fluid therapy are to expand the intra- and extravascular volume, restore normal renal perfusion and promote a gradual decline in serum sodium concentration and osmolality.

In HHS, insulin administration should begin at a dose of 0.025 to 0.05 U/kg/h once plasma glucose is no longer declining at a rate of at least 3 mmol/L (50 mg/dL) per hour with fluid alone (C).

Diabetic ketoacidosis (DKA) results from deficiency of circulating insulin and increased levels of the counterregulatory hormones: catecholamines, glucagon,

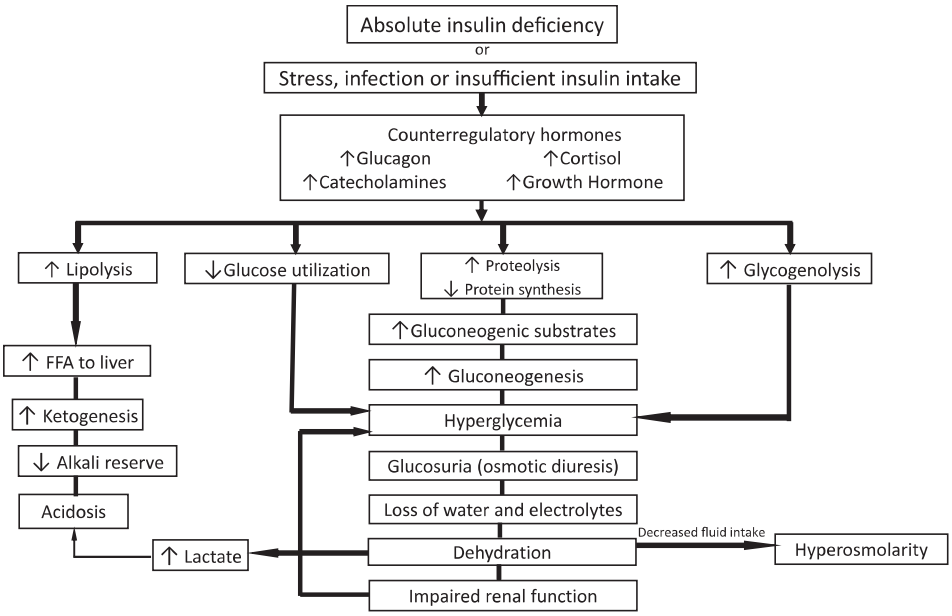

Fig. 1. Pathophysiology of diabetic ketoacidosis. Reprinted with permission from Wolfsdorf et al. (232).

cortisol and growth hormone (1, 2). Severe insulin deficiency occurs in previously undiagnosed type 1 diabetes mellitus and when patients on treatment deliberately or inadvertently do not take insulin, especially the long-acting component of a basal-bolus regimen. Patients who use an insulin pump can rapidly develop DKA when insulin delivery fails for any reason (3). Relative insulin deficiency occurs when the concentrations of counterregulatory hormones markedly increase in response to stress in conditions such as sepsis, trauma, or gastrointestinal illness with diarrhea and vomiting, which overwhelm homeostatic mechanisms and lead to metabolic decompensation despite the patient taking the usual recommended dose of insulin.

The combination of absolute or relative insulin deficiency and high counterregulatory hormone concentrations results in an accelerated catabolic state with increased glucose production by the liver and kidney (via glycogenolysis and gluconeogenesis), and simultaneously impaired peripheral glucose utilization, which combine to result in hyperglycemia and hyperosmolality; insulin deficiency and high counterregulatory hormones also increase lipolysis and ketogenesis and cause ketonemia and metabolic acidosis. Hyperglycemia that exceeds the usual renal threshold of approximately 10 mmol/L (180 mg/dL) (the range in normal and diabetic individuals varies) together with hyperketonemia cause osmotic diuresis, dehydration, and obligatory loss of electrolytes, often aggravated by vomiting associated with severe ketosis. These changes stimulate further stress hormone production, which induces more severe insulin resistance and worsening hyperglycemia and hyperketonemia. If this cycle is not interrupted by exogenous insulin as well as fluid and electrolyte therapy, fatal dehydration and metabolic acidosis will ensue. Lactic acidosis from hypoperfusion or sepsis contributes to the acidosis (4) (Fig. 1).

DKA is characterized by severe depletion of water and electrolytes from both the intra- and extracellular fluid (ECF) compartments; the range of losses is shown in Table 1. Despite their dehydration, patients generally continue to maintain normal or even have high blood pressure (5), possibly due to elevated plasma catecholamine concentrations, increased release of antidiuretic (ADH) in response to hyperosmolality, which increases blood pressure via V2 receptors, or other factors (5). Considerable urine output persists because of glucosuria until extreme volume depletion leads to a critical decrease in renal blood flow and glomerular filtration. At presentation, the specific deficits in an individual patient vary depending upon the duration and severity of illness, the extent to which the patient was able to maintain intake of fluid and electrolytes, and the content of food and fluids consumed before coming to medical attention. Consumption of fluids with a high-carbohydrate content (juices or sugar containing soft drinks) may exacerbate the hyperglycemia (6). Rapid emptying of stomach contents containing an abundant quantity of sugar, which occurs as gastroparesis is relieved with therapy, accounts for the rise in plasma glucose concentration observed in some patients after onset of therapy despite ongoing large loss of glucose in the urine (7).

Table 1. Losses of fluids and electrolytes in diabetic ketoacidosis and maintenance requirements in normal children

Average (range) losses per kg			24-h maintenance requirements
Water	70 mL (30–100)	≤10 kg*	100 mL/kg/24 h
		11–20 kg	1000 mL + 50 mL/kg/24 h for each kg from 11–20
		>20 kg	1500 mL + 20 mL/kg/24 h for each kg >20
Sodium	6 mmol (5–13)		2–4 mmol†
Potassium	5 mmol (3–6)		2–3 mmol
Chloride	4 mmol (3–9)		2–3 mmol
Phosphate	(0.5–2.5) mmol		1–2 mmol

Data are from measurements in only a few children and adolescents (8–12). In any individual patient, actual losses may be less or greater than the ranges shown in Table 1.
Three methods for determining maintenance water requirements in children are commonly used: *the Holliday-Segar formula (13) (shown in Table 1), a simplified Holliday-Segar formula (Simplified method based on Holliday-Segar: <10 kg 4 mL/kg/h; 11–20 kg 40 + 2 mL/kg/h for each kg between 11 and 20; >20 kg 60 + 1 mL/kg/h for each kg >20), and a formula based on body surface area for children more than 10 kg (1500 mL/m^2/24 h) (14).
†Maintenance electrolyte requirements in children are per 100 mL of maintenance IV fluid (14, 15).

Clinical manifestations of DKA

- Dehydration
- Tachypnea; deep, sighing (Kussmaul) respiration
- Nausea, vomiting, and abdominal pain that may mimic an acute abdominal condition
- Confusion, drowsiness, progressive obtundation and loss of consciousness

Table 2 shows the volume of maintenance and replacement fluid volumes (based on body weight and an assumption of 10% dehydration) according to Darrrow (16).

Definition of diabetic ketoacidosis (DKA)

The **biochemical criteria** for the diagnosis of DKA are (17):

- Hyperglycemia [BG >11 mmol/L (≈200 mg/dL)]
- Venous pH < 7.3 or bicarbonate <15 mmol/L
- Ketonemia* and ketonuria.

*Although not universally available, blood β-hydroxybutyrate (BOHB) concentration should be measured whenever possible; a level ≥3 mmol/L is indicative of DKA (18).

Urine ketones are typically ≥2+ ('moderate or large') positive. Partially treated children and children who have consumed little or no carbohydrate may rarely have only modestly elevated BG concentrations, referred to as 'euglycemic ketoacidosis' (19, 20).

Type 2 diabetes mellitus in the pediatric age range is increasing in frequency. The worldwide incidence and prevalence of type 2 diabetes in children and adolescents vary substantially among countries, age categories and ethnic groups, which can be explained by variations in population characteristics and methodological dissimilarities between studies (21). At some centers in the USA, type 2 diabetes now accounts for up to one half of newly diagnosed diabetes in children aged 10–21 yr (22). The SEARCH for Diabetes in Youth Study in the USA found that nearly 10% of youth with type 2 diabetes presented with DKA (23); however, overall, 5–25% of patients with type 2 diabetes have DKA at the time of diagnosis (24).

The **severity of DKA** is categorized by the degree of acidosis (25):

- Mild: venous pH < 7.3 or bicarbonate <15 mmol/L
- Moderate: pH < 7.2, bicarbonate <10 mmol/L
- Severe: pH < 7.1, bicarbonate <5 mmol/L.

HHS, formerly referred to as hyperosmolar non-ketotic coma, may occur in young patients with type 2 diabetes (26–28), in type 1 diabetes subjects (29) and in infants, especially those with 6q24-related transient neonatal diabetes mellitus (30). **The criteria for HHS** include (31, 32):

- Plasma glucose concentration >33.3 mmol/L (600 mg/dL)
- Arterial pH > 7.30; venous pH > 7.25
- Serum bicarbonate >15 mmol/L
- Small ketonuria, absent to small ketonemia[1]
- Effective serum osmolality >320 mOsm/kg
- Obtundation, combativeness, or seizures (in approximately 50%).

It is important to recognize that the overlap between the characteristic features of HHS and DKA may occur, and some patients with HHS, especially when there is severe dehydration, have mild or moderate acidosis that is mainly due

[1]Nitroprusside reaction method.

Table 2. An alternative example of fluid volumes for the **subsequent phase of rehydration**

Body weight, kg	Maintenance	DKA: give maintenance + 5% of body weight/24 h	
	mL/24 h	mL/24 h	mL/h
4	325	530	22
5	405	650	27
6	485	790	33
7	570	920	38
8	640	1040	43
9	710	1160	48
10	780	1280	53
11	840	1390	58
12	890	1490	62
13	940	1590	66
14	990	1690	70
15	1030	1780	74
16	1070	1870	78
17	1120	1970	82
18	1150	2050	85
19	1190	2140	89
20	1230	2230	93
22	1300	2400	100
24	1360	2560	107
26	1430	2730	114
28	1490	2890	120
30	1560	3060	128
32	1620	3220	134
34	1680	3360	140
36	1730	3460	144
38	1790	3580	149
40	1850	3700	154
45	1980	3960	165
50	2100	4200	175
55	2210	4420	184
60	2320	4640	193
65	2410	4820	201
70	2500	5000	208
75	2590	5180	216
80	2690	5380	224

DKA, diabetic ketoacidosis.
After initial resuscitation, and assuming 10% dehydration, the total amount of fluid should be given over 48 h. Table 2 shows volumes for maintenance and rehydration per 24 h and per hour. Fluids given orally (when patient has improved) should be subtracted from the amount in the table. Table 2 is based on maintenance volumes according to Darrow (16). For body weights >32 kg, the volumes have been adjusted so as not to exceed twice the maintenance rate of fluid administration. Example: A 6-yr-old boy weighing 20 kg will receive 10 mL/kg (or 200 mL) in the first 1-2 h and thereafter 93 mL/h or a total volume of 2230 mL/24 h for 48 h.

to hypoperfusion/lactic acidosis. Conversely, some children with type 1 diabetes may have features of HHS (severe hyperglycemia) especially if high carbohydrate containing beverages have been used to quench thirst and replace urinary losses before diagnosis (6). Therapy must be appropriately modified to address the pathophysiology and particular biochemical disturbances of the individual patient (see below). See page 16 regarding specific therapy of HHS.

Frequency of DKA

At disease onset

There is wide geographic variation in the frequency of DKA at onset of diabetes; rates inversely correlate with the regional incidence of type 1 diabetes. Frequencies range from approximately 15–70% in Europe and North America (23, 33–38). DKA at diagnosis is more common in younger children (<2 yr of age), often the consequence of diagnostic error or delayed treatment (39–41), those from ethnic minority groups, and in children whose families do not have ready access to medical care for social or economic reasons (20, 23, 37, 39, 42, 43).

In children with established diabetes

The risk of DKA in established type 1 diabetes is 1–10% per patient per year (3, 44–48):

Risk is increased in (47):

- Children who omit insulin (46).
- Children with poor metabolic control or previous episodes of DKA.
- Gastroenteritis with persistent vomiting and inability to maintain hydration.
- Children with psychiatric disorders, including those with eating disorders.
- Children with difficult or unstable family circumstances (e.g., parental abuse).
- Peripubertal and adolescent girls.
- Children with limited access to medical services.
- Insulin pump therapy (as only rapid- or short-acting insulin is used in pumps, interruption of insulin delivery for any reason rapidly leads to insulin deficiency) (3, 49).

In recurrent DKA, insulin omission or failure to follow sick day or pump failure management guidelines accounts for almost all episodes.

Management of DKA (Figure 2)

Emergency assessment

Acute management should follow the general guidelines for PALS (50, 51), with particular attention to the following aspects for the child who presents in DKA.

- Immediately measure BG and blood BOHB (or urine ketone) concentrations with bedside meters. Perform a clinical evaluation to identify a possible infection.
  - Measurement of blood BOHB concentration with a point-of-care meter, if available, is useful to

confirm ketoacidosis (≥3 mmol/L in children) (18) and to monitor the response to treatment (52–58).

- **Weigh** the patient. If body surface area is used for fluid therapy calculations, measure height or length to determine surface area. The current weight should be used for calculations and not the weight from a previous office visit or hospital record.
- **Assess severity of dehydration**.
  - Estimation of the degree of dehydration is imprecise and generally shows only fair to moderate agreement among examiners (59–61). It should be based on a combination of physical signs. The three most useful individual signs for predicting 5% dehydration in young children aged 1 month to 5 yr are:
    - Prolonged capillary refill time (normal capillary refill is ≤1.5–2 s)
    - Abnormal skin turgor ('tenting' or inelastic skin)
    - Abnormal respiratory pattern (hyperpnea) (62).
  - Other useful signs in assessing degree of dehydration include: dry mucus membranes, sunken eyes, absent tears, weak pulses, and cool extremities. More signs of dehydration tend to be associated with more severe dehydration (62).
  - ≥10% dehydration is suggested by the presence of weak or impalpable peripheral pulses, hypotension, and oliguria.
- **Assess level of consciousness** [Glasgow coma scale (GCS) – see Table 3] (63).
- Obtain a **blood sample for laboratory measurement** of:
  - Serum or plasma glucose
  - Electrolytes (including bicarbonate)
  - Blood urea nitrogen, creatinine
  - Serum osmolality
  - Venous pH, pCO_2
  - Hemoglobin, hematocrit and complete blood count. Note that an increased white blood cell count in response to stress is characteristic of DKA and is not indicative of infection (64)
  - Albumin, calcium, phosphorus, magnesium concentrations (if possible).
- Although not essential for management of DKA *per se*, hemoglobin A1c (HbA1c) may be useful in the evaluation and management of specific patients as it provides information about the duration of hyperglycemia.
- Perform a **urinalysis** for ketones.
- Obtain appropriate **specimens for culture** (blood, urine, and throat), only if there is evidence of infection (e.g., fever).
- If laboratory measurement of serum potassium is delayed, perform an **electrocardiogram** (ECG) for baseline evaluation of potassium status (65, 66).

Additional measures

For the pediatric patient who presents with a hyperglycemic crisis, the following aspects of emergency care warrant particular attention:

- **Secure the airway** and empty the stomach by continuous nasogastric suction to prevent pulmonary aspiration in the unconscious or severely obtunded patient.

Table 3. Glasgow coma scale or score (GCS)

Best eye response	Best verbal response	Best verbal response (non-verbal children)	Best motor response
1. No eye opening	1. No verbal response	1. No response	1. No motor response
2. Eyes open to pain	2. No words, only incomprehensible sounds; moaning	2. Inconsolable, irritable, restless, cries	2. Extension to pain (decerebrate posture)
3. Eyes open to verbal command	3. Words, but incoherent*	3. Inconsistently consolable and moans; makes vocal sounds	3. Flexion to pain (decorticate posture)
4. Eyes open spontaneously	4. Confused, disoriented conversation†	4. Consolable when crying and interacts inappropriately	4. Withdrawal from pain
	5. Oriented, normal conversation	5. Smiles, oriented to sound, follows objects and interacts	5. Localizes pain
			6. Obeys commands

The GCS consists of three parameters and is scored between 3 and 15; 3 being the worst and 15 the best (63). One of the components of the GCS is the best verbal response, which cannot be assessed in non-verbal young children. A modification of the GCS was created for children too young to talk.
*Inappropriate words, random or exclamatory articulated speech, but no sustained conversational exchange.
†Attention can be held; patient responds to questions coherently, but there is some disorientation and confusion.

  - Intubation should be avoided if possible; a sudden increase of pCO_2 during or following intubation may cause cerebrospinal fluid (CSF) pH to decrease and contribute to worsening of cerebral edema (67).

- If there is a history of recent large consumption of glucose-containing fluids, consider emptying the stomach even in the patient who is not obtunded.

  - When large quantities of fruit juice or sweetened soft drinks have been ingested, the stomach may contain a large volume of water with little sodium. Gastric emptying early in the course of therapy leads to absorption of glucose and electrolyte-free water from the intestinal tract (7, 68).

- Give **oxygen** to patients with severe circulatory impairment or shock.
- A **cardiac monitor** should be used for continuous electrocardiographic monitoring to assess T waves for evidence of hyper- or hypokalemia (65, 66).
- A second **peripheral intravenous (IV) catheter** should be placed for convenient and painless repetitive blood sampling. An **arterial catheter** may, rarely, be necessary in some critically ill patients managed in an intensive care unit.

  - Unless absolutely necessary, avoid placing a central venous catheter because of the high risk of thrombosis, especially in the very young; if a central catheter has been inserted, remove it as soon as the patient's clinical status permits (69, 70).
  - Insulin should preferably not be given through a central line unless it is the only available option because its infusion may be interrupted when other fluids are given through the same line.

- **Give antibiotics** to **febrile patients** after obtaining appropriate cultures of body fluids.
- Catheterization of the bladder usually is not necessary, but if the child is unconscious or unable to void on demand (e.g., infants and very ill young children) the bladder should be catheterized.

Where should the child with DKA be managed?

The child should receive care in a unit that has:

- Experienced nursing staff trained in monitoring and management of DKA in children and adolescents.
- Written guidelines for DKA management in children.
- Access to a laboratory that can provide frequent and timely measurements of biochemical variables.

Whenever possible, a specialist/consultant pediatrician with training and expertise in the management of DKA should direct inpatient management. Where geographic constraints require that management be initiated in a center with less experience and with fewer resources, there should be arrangements in place for telephone or videoconference support from a physician with expertise in DKA.

Children with severe DKA (long duration of symptoms, compromised circulation, or depressed level of consciousness) or those who are at increased risk of cerebral edema (e.g., <5 yr of age, severe acidosis, low pCO_2, high blood urea nitrogen) should be considered for immediate treatment in an intensive care unit (pediatric if available) or in a unit that has equivalent resources and supervision, such as a children's ward specializing in diabetes care (17, 71).

In a child with **established diabetes**, whose parents have been trained in sick day management, hyperglycemia and ketosis without vomiting or severe dehydration can be managed at home or in an outpatient health care facility (e.g., emergency ward), provided an experienced diabetes team supervises the care (25, 72, 73).

Clinical and biochemical monitoring

Successful management of DKA and HHS requires **meticulous monitoring** of the patient's clinical and biochemical response to treatment so that timely adjustments in treatment can be made when indicated by the patient's clinical or laboratory data.

There should be documentation on a **flow chart** of hour-by-hour clinical observations, IV and oral medications, fluids, and laboratory results. Monitoring should include the following:

- Hourly (or more frequently as indicated) **vital signs** (heart rate, respiratory rate, blood pressure).
- Hourly (or more frequently as indicated) **neurological observations** (GCS; Table 3) for warning signs and symptoms of cerebral edema (see below).

  - Headache
  - Inappropriate slowing of heart rate
  - Recurrence of vomiting
  - Change in neurological status (restlessness, irritability, increased drowsiness, incontinence) or specific neurologic signs (e.g., cranial nerve palsies, abnormal pupillary responses)
  - Rising blood pressure
  - Decreased oxygen saturation
  - Rapidly increasing serum sodium concentration suggesting loss of urinary free water as a manifestation of diabetes insipidus (from

interruption of blood flow to the pituitary gland due to cerebral herniation).

- Amount of administered insulin.
- Hourly (or more frequently as indicated) accurate **fluid input** (including all oral fluid) **and output**.
- **Capillary blood glucose** concentration should be measured hourly (but must be cross-checked against laboratory venous glucose, as capillary methods may be inaccurate in the presence of poor peripheral circulation and acidosis).
- **Laboratory tests**: serum electrolytes, glucose, blood urea nitrogen, calcium, magnesium, phosphorus, hematocrit, and blood gases should be repeated 2–4 h, or more frequently, as clinically indicated, in more severe cases.
- Blood BOHB concentrations, if available, every 2 h (53–57).
  - Near-patient (also referred to as point-of-care) BOHB measurements correlate well with a reference method up to 3 mmol/L, but are not accurate above 5 mmol/L (55, 74).
- Lipids and triglycerides can be grossly elevated causing the blood sample to show a visible rim of lipids (75).
- If the laboratory cannot provide timely results, a portable biochemical analyzer that measures serum electrolytes and blood gases on fingerstick blood samples at the bedside is a useful adjunct to laboratory-based determinations. BG and blood or urine ketone concentrations can be measured with a bedside meter while awaiting results from the laboratory.
- **Calculations**:
  - Anion gap $= Na - (Cl + HCO_3)$: normal is 12 ± 2 mmol/L.
    - In DKA, the anion gap is typically 20–30 mmol/L; an anion gap >35 mmol/L suggests concomitant lactic acidosis.
  - Corrected sodium = measured Na + 2 [(plasma glucose − 5.6)/5.6] mmol/L or measured Na + 2 [(plasma glucose − 100)/100] mg/dL.
  - Effective osmolality (mOsm/kg) $= 2 \times$ (plasma Na) + plasma glucose mmol/L (76).

Goals of therapy

- Correct dehydration
- Correct acidosis and reverse ketosis
- Restore BG to near normal
- Monitor for complications of DKA and its treatment
- Identify and treat any precipitating event

Fluids and salt

Patients with DKA have a deficit in ECF volume that usually is in the range of 5–10% (8, 9). Shock with hemodynamic compromise is rare in pediatric DKA. Clinical estimates of the volume deficit are subjective and inaccurate (59–61); therefore, in moderate DKA use 5–7% and in severe DKA 7–10% dehydration. The effective osmolality (formula above) is frequently in the range of 300–350 mmol/kg. Increased serum urea nitrogen and hematocrit or hemoglobin concentration or, alternatively, plasma albumin or total protein concentration if anemia is suspected (77) are useful markers of the degree of ECF contraction (73, 78, 79), and should be determined frequently during fluid resuscitation and deficit replacement (80). The serum sodium concentration is an unreliable measure of the degree of ECF contraction for two reasons: (i) glucose, largely restricted to the extracellular space, causes osmotic movement of water into the extracellular space thereby causing dilutional hyponatremia (81, 82) and (ii) the low sodium content of the elevated lipid fraction of the serum in DKA. The latter is not a concern with most modern methods for measuring sodium. It is useful to calculate the corrected sodium (using the above formula), which represents the expected sodium concentration in the absence of hyperglycemia, and monitor its changes throughout the course of therapy. As the plasma glucose concentration decreases after administering fluid and insulin, the measured serum sodium concentration should increase and the glucose-corrected sodium concentration (formula above) should slowly decrease. It is important to appreciate that the increase in measured serum sodium concentration does not indicate a worsening of the hypertonic state. A failure of measured serum sodium levels to rise or a further decline in serum sodium levels with therapy is thought to be a potentially ominous sign of impending cerebral edema (83–85). Too rapid and ongoing rise in serum sodium concentration may also indicate possible cerebral edema as a result of loss of free water in the urine from diabetes insipidus.

The objectives of fluid and electrolyte replacement therapy are:

- Restoration of circulating volume
- Replacement of sodium and the ECF and intracellular fluid deficit of water
- Improved glomerular filtration with enhanced clearance of glucose and ketones from the blood.

Principles of water and salt replacement

Despite much effort to identify the cause of cerebral edema its pathogenesis is incompletely understood. There continues to be controversy concerning the

association between the rate of fluid or sodium administration used in the treatment of DKA and the development of cerebral edema (86–88). No treatment strategy can be definitively recommended as being superior to another based on current evidence (87). The principles described below were developed after a comprehensive review of the literature and were accepted and endorsed by a panel of expert physicians representing the Lawson Wilkins Pediatric Endocrine Society (LWPES), the European Society for Paediatric Endocrinology (ESPE), and the International Society for Pediatric and Adolescent Diabetes (ISPAD) (17, 89).

- Water and salt deficits must be replaced.
- IV or oral fluids that may have been given in another facility before assessment should be factored into calculation of deficit and repair.

- **Resuscitation fluids** For patients who are severely volume depleted but not in shock, volume ex pansion (resuscitation) should begin immediately with 0.9% saline to restore the peripheral circulation. The volume administered typically is 10–20 mL/kg over 1–2 h, and may need to be repeated until tissue perfusion is adequate.
  - In the rare patient with DKA in shock, rapidly restore circulatory volume with isotonic saline in 20 mL/kg boluses infused as quickly as possible through a large bore cannula with reassessment after each bolus.
  - Use crystalloid not colloid. There are no data to support the use of colloid in preference to crystalloid in the treatment of DKA.

- **Deficit replacement fluids**
  Subsequent fluid management (deficit replacement) should be with an isotonic solution (0.9% saline, Ringer's lactate or Plasmalyte) for at least 4–6 h (78, 83, 90–93).
  - Patients with mild DKA usually do not have impaired peripheral circulation and, therefore, do not require a fluid bolus. Fluid therapy should begin with deficit replacement plus maintenance fluid requirements.
    - All children will experience a decrease in vascular volume when plasma glucose concentrations fall during treatment. It is, therefore, essential to ensure that they receive sufficient fluid and salt to maintain adequate tissue perfusion.
  - Deficit replacement after 4–6 h should be with a solution that has a tonicity $\geq$0.45% saline with added potassium chloride, potassium phosphate, or potassium acetate (see below under potassium replacement) (78, 83, 90, 94–96). The decision to change from an isotonic to a hypotonic solution will depend on the patient's hydration status, serum sodium concentration, and osmolality.
  - In addition to providing the usual daily maintenance fluid requirement, replace the estimated fluid deficit at an even rate over 48 h (17, 78, 97). Except for severely ill individuals, oral intake typically begins within 24 h (97). Although rehydration was planned to occur over 48 h, in a study of 635 episodes of DKA the mean time to correction of DKA and complete restoration of the circulation was 11.6 ± 6.2 h. At this point, any remaining deficits were replenished by oral intake once DKA resolved and patients were transitioned to subcutaneous (SC) insulin (97).
  - As the severity of dehydration may be difficult to determine and frequently is under- or overestimated (59–61), infuse fluid each day at a rate that seldom exceeds 1.5–2 times the usual daily maintenance requirement based on age, weight, or body surface area (17). See Table 2 for examples of calculations.
  - Satisfactory outcomes have been reported using an alternative simplified method: after an initial fluid bolus of 20 mL/kg of normal saline, 0.675% saline (3/4 normal saline, 115.5 mmol sodium) is infused at 2–2.5 times the usual maintenance rate of fluid administration regardless of the degree of dehydration, and decreased to 1–1.5 times the maintenance rate after 24 h, or earlier if acidosis resolved, until urine ketones are negative (95, 98).

- Clinical assessment of hydration status and calculated effective osmolality are valuable guides to fluid and electrolyte therapy. The aim is gradually to reduce serum effective osmolality to normal (80, 97, 99). There should be a concomitant increase in serum sodium concentration as the serum glucose concentration decreases (sodium should rise by 0.5 mmol/L for each 1 mmol/L decrease in glucose concentration).
- Urinary losses should not routinely be added to the calculation of replacement fluid, but this may be necessary in rare circumstances.
- The sodium content of the fluid should be increased if measured serum sodium concentration is low and does not rise appropriately as the plasma glucose concentration falls (83, 93, 99, 100).
- The use of large amounts of chloride-rich fluids (combined with preferential renal excretion of ketones over chloride) may be associated with the rapid development of hyperchloremia (101–103) (defined as a ratio of chloride:sodium [Cl^-:Na^+]

>0.79 (104)) and hyperchloremic metabolic acidosis (96, 102, 105–107).

- The acidifying effect of chloride can mask recognition of resolution of ketoacidosis when total base deficit is used to monitor biochemical improvement (103).
- When hyperchloremia develops, a persisting base deficit or low bicarbonate concentration can be erroneously interpreted as being due to ongoing ketosis.
- To prevent this misinterpretation, measurement of bedside BOHB levels will prevent any confusion and can demonstrate that ketoacidosis has resolved. Hyperchloremic acidosis resolves spontaneously.
- Although the anion gap is useful to track resolution of ketosis, it has two limitations in this setting: it is unable to differentiate a mixed metabolic acidosis (hyperchloremic and ketotic), and the degree of hyperchloremic acidosis is not quantifiable.

  - Normally the difference between the serum sodium and chloride concentrations is 30–35 mmol/L. To partition the chloride component of the base deficit, the following formula has been proposed to enable clinicians to track resolution of ketoacidosis at the bedside: Chloride-induced base deficit = (plasma sodium − plasma chloride − 32) (103).
  - The chloride load can be reduced by not giving potassium as potassium chloride and by using fluids such as Ringer's lactate or Plasmalyte in which a portion of the chloride is replaced by lactate or acetate, respectively (108).

Insulin therapy

DKA is caused by a decrease in effective circulating insulin associated with increases in counterregulatory hormone concentrations. Although rehydration alone frequently causes a marked decrease in BG concentration (109, 110), insulin therapy is essential to restore normal cellular metabolism and to normalize BG concentration and suppress lipolysis and ketogenesis (111).

There is evidence that '**low dose**' IV insulin administration is safe and effective (97, 98, 112).

- Start insulin infusion 1–2 h after starting fluid replacement therapy; i.e., after the patient has received initial volume expansion (88).
- Correction of insulin deficiency.

  - Dose: 0.05–0.1 unit/kg/h [e.g., one method is to dilute 50 units regular (soluble) insulin in 50 mL normal saline, 1 unit = 1 mL] (113–120)
  - Route of administration IV
  - An IV bolus should *not* be used at the start of therapy; it is unnecessary (119, 121), may increase the risk of cerebral edema (88, 99, 122), and can exacerbate hypokalemia.

- The dose of insulin should usually remain at 0.05–0.1 unit/kg/h at least until resolution of DKA (pH > 7.30, bicarbonate >15 mmol/L, BOHB <1 mmol/L, or closure of the anion gap), which invariably takes longer than normalization of BG concentrations (123).
- If the patient shows marked sensitivity to insulin (e.g., some young children with DKA, patients with HHS, and some older children with established diabetes), the dose may be decreased provided that metabolic acidosis continues to resolve. For example, if a young child is receiving 0.05 unit/kg/h, it may be necessary to reduce the insulin dose to 0.03 unit/kg/h to prevent hypoglycemia.
- Uncontrolled retrospective and observational studies have reported comparable efficacy and safety using 0.05 unit/kg/h (124, 125), and some pediatric centers routinely use this dose for treatment of DKA. There are no comparative randomized controlled trial data, however, and no evidence that the higher dose is harmful.
- Insulin has an aldosterone-like effect leading to increased urinary potassium excretion (126–130). High doses administered intravenously for a prolonged period of time may contribute to a decrease in serum potassium concentration due to increased urinary potassium excretion despite potassium administration.

  - Time on IV insulin infusion and dose of insulin should be minimized to avoid severe hypokalemia (131).

- During initial volume expansion, the plasma glucose concentration falls steeply (109). Thereafter, and after commencing insulin therapy, the plasma glucose concentration typically decreases at a rate of 2–5 mmol/L/h, depending on the timing and amount of glucose administration (113–116, 118, 119, 132).
- To prevent an unduly rapid decrease in plasma glucose concentration and hypoglycemia, 5% glucose should be added to the IV fluid (e.g., 5% glucose added to 0.9 or 0.45% saline) when the plasma glucose falls to approximately 14–17 mmol/L (250–300 mg/dL), or sooner if the rate of fall is precipitous.

  - It may be necessary to use 10% or even 12.5% dextrose to prevent hypoglycemia while continuing to infuse insulin to correct the metabolic acidosis.

- If BG falls very rapidly (>5 mmol/L/h) after initial fluid expansion, consider adding glucose even before plasma glucose has decreased to 17 mmol/L (300 mg/dL).
- If biochemical parameters of DKA (pH, anion gap, BOHB concentration) do not improve, reassess the patient, review insulin therapy, and consider other possible causes of impaired response to insulin; e.g., infection, errors in insulin preparation.
- In circumstances where continuous IV administration is not possible and in patients with uncomplicated DKA, hourly or 2-hourly SC or intramuscular (IM) administration of a short- or rapid-acting insulin analog (insulin lispro or insulin aspart) is safe and may be as effective as IV regular insulin infusion (132–136), but should not be used in patients whose peripheral circulation is impaired.
    - Initial dose SC: 0.3 unit/kg, followed 1 h later by SC insulin lispro or aspart at 0.1 unit/kg every hour, or 0.15–0.20 units/kg every 2 h.
    - If BG falls to <14 mmol/L (250 mg/dL) before DKA has resolved, reduce SC insulin lispro or aspart to 0.05 unit/kg per hour to keep BG ≈ 11 mmol/L (200 mg/dL) until resolution of DKA.

Potassium replacement

Children with DKA suffer total body potassium deficits in the order of 3–6 mmol/kg (8–12). The major loss of potassium is from the intracellular pool. Intracellular potassium is depleted because of transcellular shifts of this ion caused by hypertonicity (increased plasma osmolality causes solvent drag in which water and potassium are drawn out of cells) and glycogenolysis and proteolysis secondary to insulin deficiency cause potassium efflux from cells. Potassium is lost from the body due to vomiting and as a consequence of osmotic diuresis. Volume depletion causes secondary hyperaldosteronism, which promotes urinary potassium excretion. Thus, total body depletion of potassium occurs, but at presentation serum potassium levels may be normal, increased or decreased (137). Renal dysfunction, by enhancing hyperglycemia and reducing potassium excretion, contributes to hyperkalemia (137). Administration of insulin and the correction of acidosis drive potassium back into the cells, decreasing serum levels (138). The serum potassium concentration may decrease abruptly, predisposing the patient to cardiac arrhythmias.

Replacement therapy is required regardless of the serum potassium concentration, except if renal failure is present (139, 140).

- If the patient is hypokalemic, start potassium replacement *at the time of* initial volume expansion and before starting insulin therapy. Otherwise, start replacing potassium *after* initial volume expansion and concurrent with starting insulin therapy. If the patient is hyperkalemic, *defer* potassium replacement therapy until urine output is documented.
- If immediate serum potassium measurements are unavailable, an ECG may help to determine whether the child has hyper- or hypokalemia (65, 66). Prolongation of the PR interval, T-wave flattening and inversion, ST depression, prominent U waves, and apparent long QT interval (due to fusion of the T and U waves) indicates hypokalemia. Tall, peaked, and symmetrical T waves and shortening of the QT interval are the signs of hyperkalemia.
- The starting potassium concentration in the infusate should be 40 mmol/L. Subsequent potassium replacement therapy should be based on serum potassium measurements.
    - If potassium is given with the initial rapid volume expansion, a concentration of 20 mmol/L should be used.
- Potassium phosphate may be used together with potassium chloride or acetate; e.g., 20 mmol/L potassium chloride and 20 mmol/L potassium phosphate or 20 mmol/L potassium phosphate and 20 mmol/L potassium acetate. Administration of potassium entirely as potassium chloride contributes to the risk of hyperchloremic metabolic acidosis, whereas administration entirely as potassium phosphate can result in hypocalcemia.
- Potassium replacement should continue throughout IV fluid therapy.
- The maximum recommended rate of IV potassium replacement is usually 0.5 mmol/kg/h.
- If hypokalemia persists despite a maximum rate of potassium replacement, then the rate of insulin infusion can be reduced.

Phosphate

Depletion of intracellular phosphate occurs in DKA and phosphate is lost as a result of osmotic diuresis (8–10). Plasma phosphate levels fall after starting treatment and this is exacerbated by insulin, which promotes entry of phosphate into cells (141–143). Total body phosphate depletion has been associated with a variety of metabolic disturbances (144–146). Clinically significant hypophosphatemia may occur if IV therapy without food intake is prolonged beyond 24 h (8–10).

- Prospective studies involving relatively small numbers of subjects and with limited statistical power

have not shown clinical benefit from phosphate replacement (147–152).

- Severe hypophosphatemia combined with phosphate depletion (i.e., when not solely due to intracellular phosphate translocation) is uncommon, but can have severe consequences. Manifestations depend on the severity and chronicity of the phosphate depletion; patients usually do not have symptoms until plasma phosphate is <1 mg/dL (0.32 mmol/L).
- Severe hypophosphatemia can occur during the treatment of DKA; however, symptoms are uncommon because the hypophosphatemia is usually acute and typically there is no antecedent chronic phosphate deficiency.
- Clinical manifestations of hypophosphatemia are largely due to intracellular phosphate depletion. Decreased intracellular ATP levels impair cellular functions that depend on energy-rich phosphate compounds, and a decrease in 2,3-diphosphoglycerate (DPG) levels increases the affinity of hemoglobin for oxygen and reduces oxygen release in tissues (152). Many organ systems can be affected (145, 153). Manifestations include:
    - Metabolic encephalopathy (irritability, paresthesias, confusion, seizures, coma); impaired myocardial contractility and respiratory failure due to weakness of the diaphragm; muscle dysfunction with proximal myopathy, dysphagia, and ileus; rare hematologic effects include hemolysis, decreased phagocytosis and granulocyte chemotaxis, defective clot retraction and thrombocytopenia. Acute hypophosphatemia in a patient with preexisting severe phosphate depletion can lead to rhabdomyolysis (145, 154, 155).
- Severe hypophosphatemia associated with any of the above symptoms should be treated (156, 157).
- Administration of phosphate may induce hypocalcemia (158, 159).
- Potassium phosphate salts may be safely used as an alternative to or combined with potassium chloride or acetate, provided that careful monitoring of serum calcium is performed to avoid hypocalcemia (158, 159).

Acidosis

Severe acidosis is reversible by fluid and insulin replacement; insulin stops further ketoacid production and allows ketoacids to be metabolized, which generates bicarbonate. Treatment of hypovolemia improves tissue perfusion and renal function, thereby increasing the excretion of organic acids.

Controlled trials have shown no clinical benefit from bicarbonate administration (160–163). Bicarbonate therapy may cause paradoxical CNS acidosis (164, 165) and rapid correction of acidosis with bicarbonate causes hypokalemia (164, 166, 167). Bicarbonate administration may be beneficial in the rare patient with life-threatening hyperkalemia (168).

- If bicarbonate is considered necessary, cautiously give 1–2 mmol/kg over 60 min.

Complications of therapy

- Inadequate rehydration
- Hypoglycemia
- Hypokalemia
- Hyperchloremic acidosis
- Cerebral edema

Introduction of oral fluids and transition to SC Insulin Injections

- Oral fluids should be introduced only when substantial clinical improvement has occurred (mild acidosis/ketosis may still be present).
    - Persistent ketonuria (measurement of urine ketones with test strips is based on the nitroprusside reaction, which measures acetoacetate and acetone) characteristically occurs for several hours after serum BOHB levels have returned to normal (53, 57).
    - Absence of ketonuria should *not* be used as an endpoint for determining resolution of DKA.
- When oral fluid is tolerated, IV fluid should be reduced accordingly so that the sum of IV and oral fluids does not exceed the calculated IV rate (i.e., not in excess of 1.5–2 times maintenance fluid rate). This fluid restriction should be applied for 48 h from admission (72 h if there is severe hyperosmolality at onset of treatment).
- When ketoacidosis has resolved, oral intake is tolerated, and the change to SC insulin is planned, the most convenient time to change to SC insulin is just before a mealtime.
- To prevent rebound hyperglycemia, the first SC injection should be given 15–30 min (with rapid-acting insulin) or 1–2 h (with regular insulin) before stopping the insulin infusion to allow sufficient time for the insulin to be absorbed. With intermediate- or long-acting insulin, the overlap should be longer and the rate of IV insulin infusion gradually lowered. For example, for patients on a basal-bolus insulin regimen, the first dose of basal insulin may be administered in the evening and the insulin infusion is stopped the next morning.

- The dose and type of SC insulin should be according to local preferences and circumstances.
- After transitioning to SC insulin, frequent BG monitoring is required to avoid marked hyperglycemia and hypoglycemia.

Morbidity and mortality

In population studies, the mortality rate from DKA in children is 0.15–0.30% (169–171) and may be decreasing (171). Cerebral injury is the major cause of mortality and morbidity (170, 172). Cerebral edema accounts for 60–90% of all DKA deaths (85, 173). From 10–25% of survivors of cerebral edema have significant residual morbidity (85, 173, 174). Children without overt neurological symptoms during DKA treatment may have subtle evidence of brain injury, particularly memory deficits, after recovery from DKA (175).

Other rare causes of morbidity and mortality include:

- Hypokalemia*
- Hypocalcemia, hypomagnesemia
- Severe hypophosphatemia*
- Hypoglycemia
- Other central nervous system complications include dural sinus thrombosis, basilar artery thrombosis, intracranial hemorrhage, and cerebral infarction (176–178)
- Venous thrombosis (69, 70)*
- Pulmonary embolism*
- Sepsis
- Rhinocerebral or pulmonary mucormycosis (179)
- Aspiration pneumonia*
- Pulmonary edema*
- Adult respiratory distress syndrome (ARDS)
- Pneumothorax, pneumomediastinum, and SC emphysema (180)
- Rhabdomyolysis*
- Ischemic bowel necrosis
- Acute renal failure*
- Acute pancreatitis (181)*

*These complications, often with fatality, have been frequent in HHS [see (32)]. The pathophysiology and management of HHS are discussed below.

Cerebral edema

The incidence of clinically overt cerebral edema in national population studies is 0.5–0.9% and the mortality rate is 21–24% (85, 173, 174). Mental status abnormalities (GCS scores <14), however, occur in approximately 15% of children treated for DKA and are associated with evidence of cerebral edema on neuroimaging (182, 183). The complication is rarely seen after adolescence. Neuroimaging studies have led to the appreciation that cerebral edema is not a rare phenomenon in children with DKA, but occurs frequently with varying severity (182, 184, 185). Clinically overt cerebral edema likely represents the most severe manifestation of a common phenomenon (186).

The cause of cerebral edema is controversial. Some have explained the pathogenesis as the result of rapid fluid administration with abrupt changes in serum osmolality (100, 187–190). More recent investigations, however, have found that dehydration and cerebral hypoperfusion may be associated with DKA-related cerebral injury (85, 191–193), which have led to the formulation of an alternative hypothesis; namely, that factors intrinsic to DKA may be the cause of brain injury, which could be worsened during treatment (194, 195). It is noteworthy that the degree of edema that develops during DKA correlates with the degree of dehydration and hyperventilation at presentation, but not with factors related to initial osmolality or osmotic changes during treatment (183). Disruption of the blood–brain-barrier has been found in cases of fatal cerebral edema associated with DKA (196, 197), which further supports the view that cerebral edema is not simply caused by a reduction in serum osmolality.

Demographic factors that have been associated with an increased risk of cerebral edema include:

- Younger age (198)
- New onset diabetes (170, 198)
- Longer duration of symptoms (199)

These risk associations may reflect the greater likelihood of severe DKA.

Epidemiological studies have identified several potential risk factors at diagnosis or during treatment of DKA. These include:

- Greater hypocapnia at presentation after adjusting for degree of acidosis (85, 183, 200).
- Increased serum urea nitrogen at presentation (85, 183).
- More severe acidosis at presentation (88, 201, 202).
- Bicarbonate treatment for correction of acidosis (85, 203).
- A marked early decrease in serum effective osmolality (99, 202).
- An attenuated rise in serum sodium concentration or an early fall in glucose-corrected sodium during therapy (83–85, 202).
- Greater volumes of fluid given in the first 4 h (88, 200, 202).
- Administration of insulin in the first hour of fluid treatment (88).

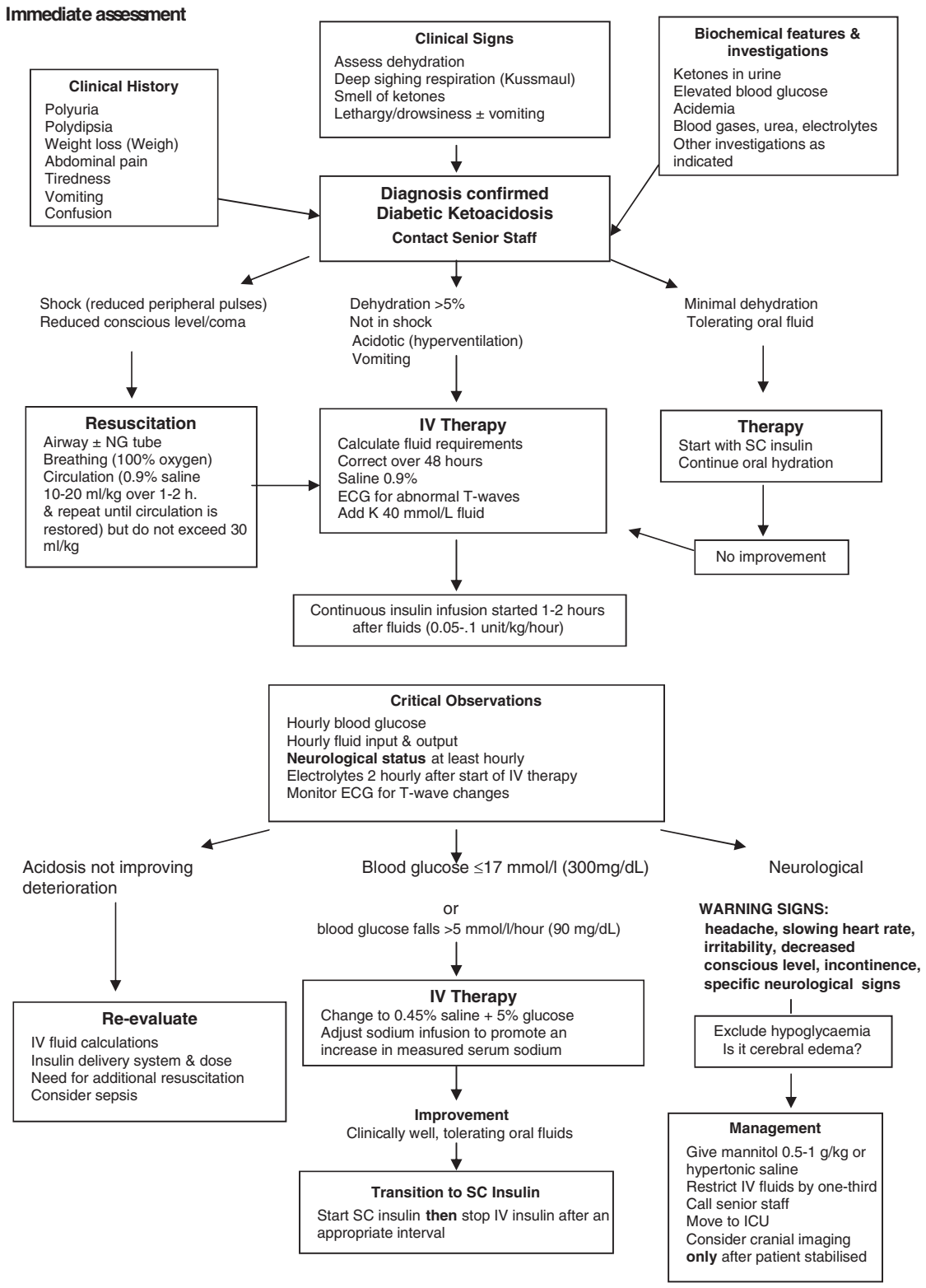

Fig. 2. Algorithm for the management of diabetic ketoacidosis. Adapted from Dunger et al. (233). NG, nasogastric; SC, subcutaneous.

Signs and symptoms of cerebral edema include:

Headache and slowing of heart rate
Change in neurological status (restlessness, irritability, increased drowsiness, and incontinence)
Specific neurological signs (e.g., cranial nerve palsies, papilledema)
Rising blood pressure
Decreased O_2 saturation

Clinically significant cerebral edema usually develops within the first 12 h after treatment has started, but can occur before treatment has begun (85, 174, 204–207) or, rarely, may develop as late as 24–48 h after the start of treatment (85, 198, 208). Symptoms and signs are variable. Although mild to moderate headache at presentation may not be unusual (Glaser personal communication), development of a severe headache after treatment is always concerning. A method of clinical diagnosis based on bedside evaluation of neurological state is shown below (209). One diagnostic criterion, two major criteria, or one major and two minor criteria have a sensitivity of 92% and a false positive rate of only 4%. Signs that occur before treatment should not be considered in the diagnosis of cerebral edema.

Diagnostic criteria

- Abnormal motor or verbal response to pain
- Decorticate or decerebrate posture
- Cranial nerve palsy (especially III, IV, and VI)
- Abnormal neurogenic respiratory pattern (e.g., grunting, tachypnea, Cheyne–Stokes respiration, apneusis)

Major criteria

- Altered mentation/fluctuating level of consciousness
- Sustained heart rate deceleration (decrease more than 20 beats/min) not attributable to improved intravascular volume or sleep state
- Age-inappropriate incontinence

Minor criteria

- Vomiting
- Headache
- Lethargy or not easily arousable
- Diastolic blood pressure >90 mmHg
- Age <5 yr

A chart with the reference ranges for blood pressure and heart rate, which vary depending on height, weight, and gender, should be readily available, either in the patient's chart or at the bedside.

The appearance of diabetes insipidus, manifested by increased urine output with a concomitant marked increase in the serum sodium concentration, reflecting loss of free water in the urine, is a sign of cerebral herniation causing interruption of blood flow to the pituitary gland.

Treatment of cerebral edema

- Initiate treatment as soon as the condition is suspected.
- Reduce the rate of fluid administration by one-third.
- Give mannitol, 0.5–1 g/kg IV over 10–15 min, and repeat if there is no initial response in 30 min to 2 h (210–212).
- Hypertonic saline (3%), suggested dose 2.5–5 mL/kg over 10–15 min, may be used as an alternative to mannitol, especially if there is no initial response to mannitol (213, 214).
    - A recent 11-yr retrospective cohort study showed that hypertonic saline has replaced mannitol as the most commonly used hyperosmolar agent in many US institutions. Although further investigation is needed, the data suggest that hypertonic saline may not have benefits over mannitol and may be associated with a higher mortality rate (171).
- Hyperosmolar agents should be readily available at the bedside.
- Elevate the head of the bed to 30°.
- Intubation may be necessary for the patient with impending respiratory failure.
- *After* treatment for cerebral edema has been started, cranial imaging may be considered as with any critically ill patient with encephalopathy or acute focal neurologic deficit. The primary concern is whether the patient has a lesion requiring emergency neurosurgery (e.g., intracranial hemorrhage) or a lesion that may necessitate anticoagulation (e.g., cerebrovascular thrombosis) (177, 215–217).

Hyperglycemic hyperosmolar state

This syndrome is characterized by extreme elevations in serum glucose concentrations and hyperosmolality without significant ketosis (32). Although the incidence of HHS is increasing (27, 28, 218), it is considerably less frequent in children than DKA.

Unlike the usual symptoms of DKA (hyperventilation, vomiting and abdominal pain), which typically bring children to medical attention, the gradually increasing polyuria and polydipsia of HHS may go unrecognized resulting in profound dehydration and

electrolyte losses. In adults, fluid losses in HHS have been estimated to be twice those of DKA; furthermore, obesity and hyperosmolality can make the clinical assessment of dehydration challenging. Despite severe volume depletion and electrolyte losses, hypertonicity preserves intravascular volume, and signs of dehydration may be less evident.

During therapy, decreasing serum osmolality (from enhanced glucosuria and insulin-mediated glucose uptake) results in the movement of water out of the intravascular space resulting in decreased intravascular volume, and osmotic diuresis may continue for hours in patients with extremely increased plasma glucose concentrations. Early in the course of treatment, urinary fluid losses may be considerable. As intravascular volume may decrease rapidly during treatment in patients with HHS, more aggressive replacement of intravascular volume (as compared to treatment of children with DKA) is required to avoid vascular collapse.

Treatment of HHS

There are no prospective data to guide treatment of children and adolescents with HHS. The following recommendations are based on extensive experience in adults and an appreciation of the pathophysiological differences between HHS and DKA (32); see Fig. 3. Patients should be admitted to an intensive care unit or comparable setting where expert medical, nursing, and laboratory services are available.

Fluid therapy

The goal of initial fluid therapy is to expand the intra- and extravascular volume and restore normal renal perfusion. The rate of fluid replacement should be more rapid than is recommended for DKA.

- The initial bolus should be ≥20 mL/kg of isotonic saline (0.9% NaCl) and a fluid deficit of approximately 12–15% of body weight should be assumed. Additional fluid boluses should be given, if necessary, to restore peripheral perfusion.
- Thereafter, 0.45–0.75% NaCl should be administered to replace the deficit over 24–48 h.
- The goal is to promote a gradual decline in serum sodium concentration and osmolality.
- As isotonic fluids are more effective in maintaining circulatory volume, isotonic saline should be restarted if perfusion and hemodynamic status appear inadequate as serum osmolality declines.
- Serum sodium concentrations should be measured frequently and the sodium concentration in fluids adjusted to promote a gradual decline in corrected serum sodium concentration. Mortality has been associated with failure of the corrected serum sodium concentration to decline with treatment, which may be an indication for hemodialysis. Hemodialysis has resulted in 80% survival in contrast to 20% with peritoneal dialysis (28).
  - Although there are no data to indicate an optimal rate of decline in serum sodium, 0.5 mmol/L per hour has been recommended for hypernatremic dehydration (219). With adequate rehydration alone (i.e., before commencing insulin therapy), serum glucose concentrations should decrease by 75–100 mg/dL (4.1–5.5 mmol/L) per hour (220, 221).
  - A more rapid rate of decline in serum glucose concentration is typical during the first several hours of treatment when an expanded vascular volume leads to improved renal perfusion. If there is a continued rapid fall in serum glucose (>90 mg/dL, 5 mmol/L per hour) after the first few hours, consider adding 2.5 or 5% glucose to the rehydration fluid. Failure of the expected decrease of plasma glucose concentration should prompt reassessment and evaluation of renal function.
  - Unlike treatment of DKA, replacement of urinary losses is recommended (120). The typical urine sodium concentration during an osmotic diuresis approximates 0.45% saline; however, when there is concern about the adequacy of circulatory volume, urinary losses may be replaced with a fluid containing a higher sodium concentration.

Insulin therapy

Whereas tissue hypoperfusion in HHS commonly causes lactic acidosis, ketosis is usually minimal. Early insulin administration is unnecessary in HHS. Fluid administration alone causes a marked decline in serum glucose concentration as a result of dilution, improved renal perfusion leading to glucosuria, and increased tissue glucose uptake with improved circulation. The osmotic pressure that glucose exerts within the vascular space contributes to the maintenance of blood volume. A rapid fall in serum glucose concentration and osmolality after insulin administration may lead to circulatory compromise and thrombosis unless fluid replacement is adequate. Patients with HHS also have extreme potassium deficits; a rapid insulin-induced shift of potassium to the intracellular space can trigger an arrhythmia.

- Insulin administration should be initiated when serum glucose concentration is no longer declining at a rate of at least 50 mg/dL (3 mmol/L) per hour with fluid administration alone.

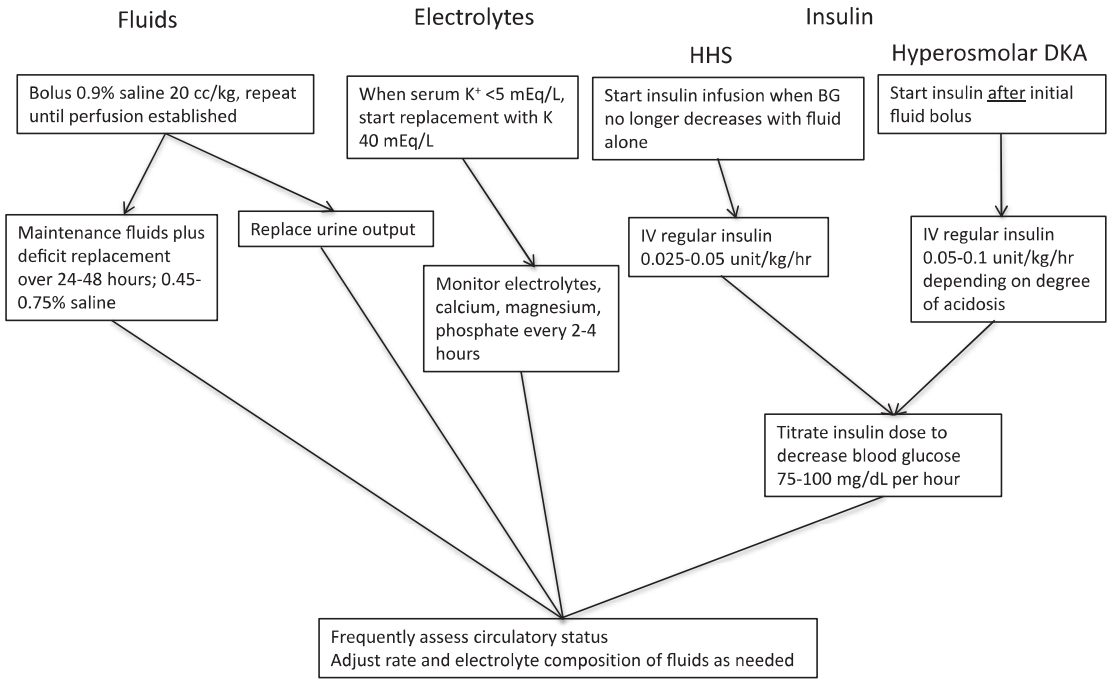

Fig. 3. Treatment of hyperglycemic hyperosmolar state (HHS). Adapted from Zeitler et al. (32).

- In patients with more severe ketosis and acidosis, however, insulin administration should be initiated earlier.
- Continuous administration of 0.025–0.05 units/kg/h can be used initially, with the dosage titrated to achieve a decrease in serum glucose concentration of 50–75 mg/dL (3–4 mmol/L) per hour.
    - Insulin boluses are not recommended.

Electrolytes

In general, deficits of potassium, phosphate, and magnesium are greater in HHS than DKA.

- Potassium replacement (40 mmol/L of replacement fluid) should begin as soon as serum potassium concentration is within the normal range and adequate renal function has been established.
    - Higher rates of potassium administration may be necessary after starting an insulin infusion.
    - Serum potassium concentrations should be monitored every 2–3 h along with ECG monitoring.
    - Hourly potassium measurements may be necessary if the patient has hypokalemia.
- Bicarbonate therapy is contraindicated; it increases the risk of hypokalemia and may adversely affect tissue oxygen delivery.
- Severe hypophosphatemia may lead to rhabdomyolysis, hemolytic uremia, muscle weakness, and paralysis. Although administration of phosphate is associated with a risk of hypocalcemia, an IV solution that contains a 50:50 mixture of potassium phosphate and another suitable potassium salt (potassium chloride or potassium acetate) generally permits adequate phosphate replacement while avoiding clinically significant hypocalcemia.
    - Serum phosphate concentrations should be measured every 3–4 h.
- Patients with HHS frequently have large magnesium deficits, but there are no data to determine whether the replacement of magnesium is beneficial.
    - Replacement of magnesium should be considered in the occasional patient who experiences severe hypomagnesemia and hypocalcemia during therapy. The recommended dose is 25–50 mg/kg per dose for 3–4 doses given every 4–6 h with a maximum infusion rate of 150 mg/min and 2 g/h.

Complications

- Venous thrombosis associated with the use of central venous catheters is a common hazard in HHS (69). Prophylactic use of low-dose heparin has been

suggested in adults but there are no data to indicate benefit from this practice. Heparin treatment should be reserved for children who require central venous catheters for physiologic monitoring or venous access and are immobile for more than 24–48 h (32). The central venous catheter should not be used for insulin administration because the large dead space may cause erratic insulin delivery.

- Rhabdomyolysis may occur in children with HHS resulting in acute kidney failure, severe hyperkalemia, hypocalcemia, and muscle swelling causing compartment syndrome (222). The classic symptom triad of rhabdomyolysis includes myalgia, weakness, and dark urine; monitoring creatine kinase concentrations every 2–3 h is recommended for early detection.
- For unknown reasons, several children with HHS have had clinical manifestations consistent with malignant hyperthermia, which is associated with a high mortality rate (26, 223–225). Patients who have a fever associated with a rise in creatine kinase concentrations may be treated with dantrolene, which reduces release of calcium from the sarcoplasmic reticulum and stabilizes calcium metabolism within muscle cells. Nonetheless, of the three reported patients with HHS reported to have been treated with dantrolene only one survived (223, 225).
- Altered mental status is common in adults whose serum osmolality exceeds 330 mOsm/kg; however, cerebral edema is rare (28). Among 96 cases of HHS reported in the literature as of 2010, including 32 deaths, there was only one instance of cerebral edema (Rosenbloom, personal communication). A decline in mental status after hyperosmolality has improved with treatment is unusual and should be promptly investigated.

Mixed HHS and DKA

Treatment must take into account potential complications of both DKA and HHS. Mental status must be closely monitored and frequent reassessment of circulatory status and fluid balance is necessary to guide therapy. To maintain an adequate circulatory volume, the rate of fluid and electrolyte administration usually exceeds that required for the typical case of DKA. Insulin is necessary to resolve ketosis and arrest hepatic gluconeogenesis; however, insulin infusion should be deferred until after the patient has received an initial fluid bolus and the circulation has been stabilized. Serum potassium and phosphate concentrations should be carefully monitored as described above for HHS.

Prevention of recurrent DKA

Management of an episode of DKA is not complete until its cause has been identified and an attempt made to treat it.

- Insulin omission, either inadvertently or deliberately, is the cause in most cases.
- The most common cause of DKA in insulin pump users is failure to take extra insulin with a pen or syringe when hyperglycemia and hyperketonemia or ketonuria occur.
- Home measurement of blood BOHB concentrations, when compared to urine ketone testing, decreases diabetes-related hospital visits (both emergency department visits and hospitalizations) by the early identification and treatment of ketosis (226). Blood BOHB measurements may be especially valuable to prevent DKA in patients who use a pump because interrupted insulin delivery rapidly leads to ketosis.
    - There may be dissociation between urine ketone (sodium nitroprusside only measures acetoacetate and acetone) and serum BOHB concentrations, which may be increased to levels consistent with DKA at a time when a urine ketone test is negative or shows only trace or small ketonuria (227).
- There usually is an important psychosocial reason for insulin omission.
    - An attempt to lose weight in an adolescent girl with an eating disorder.
    - A means of escaping an intolerable or abusive home situation.
    - Depression or other reason for inability of the patient to manage the diabetes unassisted.
- A psychiatric social worker or clinical psychologist should be consulted to identify the psychosocial reason(s) contributing to development of DKA.
- An infection is rarely the cause of DKA when the patient/family is properly educated in diabetes management and is receiving appropriate follow-up care by a diabetes team with a 24-h telephone helpline (228–230).
- Insulin omission can be prevented by comprehensive programs that provide education, psychosocial evaluation, and treatment combined with adult supervision of the entire process of insulin administration (231).
    - Parents and patients should learn how to recognize and treat ketosis and impending DKA with additional rapid- or short-acting insulin and oral fluids.

- Families should have access to a 24-h telephone helpline for emergency advice and treatment (228).
- When a responsible adult administers insulin there may be as much as a 10-fold reduction in frequency of recurrent DKA (231).

Conflicts of interest

The authors have declared no conflicts of interest.

References

1. Foster DW, McGarry JD. The metabolic derangements and treatment of diabetic ketoacidosis. N Engl J Med 1983: 309: 159–169.
2. Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. Diabetes Care 2006: 29: 2739–2748.
3. Hanas R, Lindgren F, Lindblad B. A 2-year national population study of pediatric ketoacidosis in Sweden: predisposing conditions and insulin pump use. Pediatr Diabetes 2009: 10: 33–37.
4. Cox K, Cocchi MN, Salciccioli JD, Carney E, Howell M, Donnino MW. Prevalence and significance of lactic acidosis in diabetic ketoacidosis. J Crit Care 2012: 27: 132–137.
5. Deeter KH, Roberts JS, Bradford H et al. Hypertension despite dehydration during severe pediatric diabetic ketoacidosis. Pediatr Diabetes 2011: 12 (4 Pt 1): 295–301.
6. McDonnell CM, Pedreira CC, Vadamalayan B, Cameron FJ, Werther GA. Diabetic ketoacidosis, hyperosmolarity and hypernatremia: are high-carbohydrate drinks worsening initial presentation? Pediatr Diabetes 2005: 6: 90–94.
7. Carlotti AP, St George-Hyslop C, Guerguerian AM, Bohn D, Kamel KS, Halperin M. Occult risk factor for the development of cerebral edema in children with diabetic ketoacidosis: possible role for stomach emptying. Pediatr Diabetes 2009: 10: 522–533.
8. Atchley D, Loeb R, Richards D Jr, Benedict E, Driscoll M. On diabetic ketoacidosis: a detailed study of electrolyte balances following the withdrawal and reestablishment of insulin therapy. J Clin Invest 1933: 12: 297–326.
9. Nabarro J, Spencer A, Stowers J. Metabolic studies in severe diabetic ketosis. Q J Med 1952: 82: 225–248.
10. Butler A, Talbot N, Burnett C, Stanbury J, MacLachlan E. Metabolic studies in diabetic coma. Trans Assoc Am Physicians 1947: 60: 102–109.
11. Danowski T, Peters J, Rathbun J, Quashnock J, Greenman L. Studies in diabetic acidosis and coma, with particular emphasis on the retention of administered potassium. J Clin Invest 1949: 28: 1–9.
12. Darrow D, Pratt E. Retention of water and electrolyte during recovery in a patient with diabetic acidosis. J Pediatr 1952: 41: 688–696.
13. Holliday MA, Segar WE. The maintenance need for water in parenteral fluid therapy. Pediatrics 1957: 19: 823–832.
14. Friedman AL. Pediatric hydration therapy: historical review and a new approach. Kidney Int 2005: 67: 380–388.
15. Hendricks K, Duggan C (Eds). Manual of Pediatric Nutrition. 4th edn. Hamilton: BC Decker, 2005.
16. Darrow DC. The physiologic basis for estimating requirements for parenteral fluids. Pediatr Clin North Am 1959: 6: 29–41.
17. Dunger DB, Sperling MA, Acerini CL et al. ESPE/LWPES consensus statement on diabetic ketoacidosis in children and adolescents. Arch Dis Child 2004: 89: 188–194.
18. Sheikh-Ali M, Karon BS, Basu A et al. Can serum beta-hydroxybutyrate be used to diagnose diabetic ketoacidosis? Diabetes Care 2008: 31: 643–647.
19. Burge MR, Hardy KJ, Schade DS. Short-term fasting is a mechanism for the development of euglycemic ketoacidosis during periods of insulin deficiency. J Clin Endocrinol Metab 1993: 76: 1192–1198.
20. Pinkey JH, Bingley PJ, Sawtell PA, Dunger DB, Gale EA. Presentation and progress of childhood diabetes mellitus: a prospective population-based study. The Bart's-Oxford Study Group. Diabetologia 1994: 37: 70–74.
21. Fazeli Farsani S, van der Aa MP, van der Vorst MM, Knibbe CA, de Boer A. Global trends in the incidence and prevalence of type 2 diabetes in children and adolescents: a systematic review and evaluation of methodological approaches. Diabetologia 2013: 56: 1471–1488.
22. American Diabetes Association. Type 2 diabetes in children and adolescents. (Consensus statement). Diabetes Care 2000: 23: 381–389.
23. Rewers A, Klingensmith G, Davis C et al. Presence of diabetic ketoacidosis at diagnosis of diabetes mellitus in youth: the Search for Diabetes in Youth Study. Pediatrics 2008: 121: e1258–e1266.
24. Gungor N, Hannon T, Libman I, Bacha F, Arslanian S. Type 2 diabetes mellitus in youth: the complete picture to date. Pediatr Clin North Am 2005: 52: 1579–1609.
25. Chase HP, Garg SK, Jelley DH. Diabetic ketoacidosis in children and the role of outpatient management. Pediatr Rev 1990: 11: 297–304.
26. Morales AE, Rosenbloom AL. Death caused by hyperglycemic hyperosmolar state at the onset of type 2 diabetes. J Pediatr 2004: 144: 270–273.
27. Canarie MF, Bogue CW, Banasiak KJ, Weinzimer SA, Tamborlane WV. Decompensated hyperglycemic hyperosmolarity without significant ketoacidosis in the adolescent and young adult population. J Pediatr Endocrinol Metab 2007: 20: 1115–1124.
28. Rosenbloom AL. Hyperglycemic hyperosmolar state: an emerging pediatric problem. J Pediatr 2010: 156: 180–184.
29. Bagdure D, Rewers A, Campagna E, Sills MR. Epidemiology of hyperglycemic hyperosmolar syndrome in children hospitalized in USA. Pediatr Diabetes 2013: 14: 18–24.

30. Temple IK, Shield JP. 6q24 transient neonatal diabetes. Rev Endocr Metab Disord 2010: 11: 199–204.
31. Kitabchi AE, Nyenwe EA. Hyperglycemic crises in diabetes mellitus: diabetic ketoacidosis and hyperglycemic hyperosmolar state. Endocrinol Metab Clin North Am 2006: 35: 725–751.
32. Zeitler P, Haqq A, Rosenbloom A, Glaser N. Hyperglycemic hyperosmolar syndrome in children: pathophysiological considerations and suggested guidelines for treatment. J Pediatr 2011: 158: 9–14 14 e11–12.
33. Levy-Marchal C, Papoz L, de Beaufort C et al. Clinical and laboratory features of type 1 diabetic children at the time of diagnosis. Diabet Med 1992: 9: 279–284.
34. Komulainen J, Lounamaa R, Knip M, Kaprio EA, Akerblom HK. Ketoacidosis at the diagnosis of type 1 (insulin dependent) diabetes mellitus is related to poor residual beta cell function. Childhood Diabetes in Finland Study Group. Arch Dis Child 1996: 75: 410–415.
35. Levy-Marchal C, Patterson CC, Green A. Geographical variation of presentation at diagnosis of type I diabetes in children: the EURODIAB study. European and Dibetes. Diabetologia 2001: 44 (Suppl 3): B75–B80.
36. Hanas R, Lindgren F, Lindblad B. Diabetic ketoacidosis and cerebral oedema in Sweden--a 2-year paediatric population study. Diabet Med 2007: 24: 1080–1085.
37. Rodacki M, Pereira JR, Nabuco de Oliveira AM et al. Ethnicity and young age influence the frequency of diabetic ketoacidosis at the onset of type 1 diabetes. Diabetes Res Clin Pract 2007: 78: 259–262.
38. Usher-Smith JA, Thompson M, Ercole A, Walter FM. Variation between countries in the frequency of diabetic ketoacidosis at first presentation of type 1 diabetes in children: a systematic review. Diabetologia 2012: 55: 2878–2894.
39. Quinn M, Fleischman A, Rosner B, Nigrin DJ, Wolfsdorf JI. Characteristics at diagnosis of type 1 diabetes in children younger than 6 years. J Pediatr 2006: 148: 366–371.
40. Bui H, To T, Stein R, Fung K, Daneman D. Is diabetic ketoacidosis at disease onset a result of missed diagnosis? J Pediatr 2010: 156: 472–477.
41. Szypowska A, Skorka A. The risk factors of ketoacidosis in children with newly diagnosed type 1 diabetes mellitus. Pediatr Diabetes 2011: 12 (4 Pt 1): 302–306.
42. Komulainen J, Kulmala P, Savola K et al. Clinical, autoimmune, and genetic characteristics of very young children with type 1 diabetes. Childhood Diabetes in Finland (DiMe) Study Group. Diabetes Care 1999: 22: 1950–1955.
43. Usher-Smith JA, Thompson MJ, Sharp SJ, Walter FM. Factors associated with the presence of diabetic ketoacidosis at diagnosis of diabetes in children and young adults: a systematic review. BMJ 2011: 343: d4092.
44. Rosilio M, Cotton JB, Wieliczko MC et al. Factors associated with glycemic control. A cross-sectional nationwide study in 2,579 French children with type 1 diabetes. The French Pediatric Diabetes Group [see comments]. Diabetes Care 1998: 21: 1146–1153.
45. Smith CP, Firth D, Bennett S, Howard C, Chisholm P. Ketoacidosis occurring in newly diagnosed and established diabetic children. Acta Paediatr 1998: 87: 537–541.
46. Morris AD, Boyle DI, McMahon AD, Greene SA, MacDonald TM, Newton RW. Adherence to insulin treatment, glycaemic control, and ketoacidosis in insulin-dependent diabetes mellitus. The DARTS/MEMO Collaboration. Diabetes Audit and Research in Tayside Scotland. Medicines Monitoring Unit. Lancet 1997: 350: 1505–1510.
47. Rewers A, Chase HP, Mackenzie T et al. Predictors of acute complications in children with type 1 diabetes. JAMA 2002: 287: 2511–2518.
48. Cengiz E, Xing D, Wong JC et al. Severe hypoglycemia and diabetic ketoacidosis among youth with type 1 diabetes in the T1D Exchange clinic registry. Pediatr Diabetes 2013: 14: 447–454.
49. Cope JU, Morrison AE, Samuels-Reid J. Adolescent use of insulin and patient-controlled analgesia pump technology: a 10-year Food and Drug Administration retrospective study of adverse events. Pediatrics 2008: 121: e1133–e1138.
50. Kleinman ME, Chameides L, Schexnayder SM et al. Pediatric advanced life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Pediatrics 2010: 126: e1361–e1399.
51. Kleinman ME, de Caen AR, Chameides L et al. Pediatric basic and advanced life support: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science with Treatment Recommendations. Pediatrics 2010: 126: e1261–e1318.
52. Wiggam MI, O'Kane MJ, Harper R et al. Treatment of diabetic ketoacidosis using normalization of blood 3- hydroxybutyrate concentration as the endpoint of emergency management. A randomized controlled study. Diabetes Care 1997: 20: 1347–1352.
53. Vanelli M, Chiari G, Capuano C, Iovane B, Bernardini A, Giacalone T. The direct measurement of 3-beta-hydroxy butyrate enhances the management of diabetic ketoacidosis in children and reduces time and costs of treatment. Diabetes Nutr Metab 2003: 16 (5–6): 312–316.
54. Ham MR, Okada P, White PC. Bedside ketone determination in diabetic children with hyperglycemia and ketosis in the acute care setting. Pediatr Diabetes 2004: 5: 39–43.
55. Rewers A, McFann K, Chase HP. Bedside monitoring of blood beta-hydroxybutyrate levels in the management of diabetic ketoacidosis in children. Diabetes Technol Ther 2006: 8: 671–676.
56. Prisco F, Picardi A, Iafusco D et al. Blood ketone bodies in patients with recent-onset type 1 diabetes (a multicenter study). Pediatr Diabetes 2006: 7: 223–228.
57. Noyes KJ, Crofton P, Bath LE et al. Hydroxybutyrate near-patient testing to evaluate a new end-point for intravenous insulin therapy in the treatment of diabetic ketoacidosis in children. Pediatr Diabetes 2007: 8: 150–156.

58. Klocker AA, Phelan H, Twigg SM, Craig ME. Blood beta-hydroxybutyrate vs. urine acetoacetate testing for the prevention and management of ketoacidosis in Type 1 diabetes: a systematic review. Diabet Med 2013: 30: 818–824.
59. Koves IH, Neutze J, Donath S et al. The accuracy of clinical assessment of dehydration during diabetic ketoacidosis in childhood. Diabetes Care 2004: 27: 2485–2487.
60. Sottosanti M, Morrison GC, Singh RN et al. Dehydration in children with diabetic ketoacidosis: a prospective study. Arch Dis Child 2012: 97: 96–100.
61. Ugale J, Mata A, Meert KL, Sarnaik AP. Measured degree of dehydration in children and adolescents with type 1 diabetic ketoacidosis. Pediatr Crit Care Med 2012: 13: e103–e107.
62. Steiner MJ, DeWalt DA, Byerley JS. Is this child dehydrated? JAMA 2004: 291: 2746–2754.
63. Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale Lancet 1974: 2: 81–84.
64. Flood RG, Chiang VW. Rate and prediction of infection in children with diabetic ketoacidosis. Am J Emerg Med 2001: 19: 270–273.
65. Malone JI, Brodsky SJ. The value of electrocardiogram monitoring in diabetic ketoacidosis. Diabetes Care 1980: 3: 543–547.
66. Soler NG, Bennett MA, Fitzgerald MG, Malins JM. Electrocardiogram as a guide to potassium replacement in diabetic ketoacidosis. Diabetes 1974: 23: 610–615.
67. Tasker RC, Lutman D, Peters MJ. Hyperventilation in severe diabetic ketoacidosis. Pediatr Crit Care Med 2005: 6: 405–411.
68. Davids MR, Edoute Y, Stock S, Halperin ML. Severe degree of hyperglycaemia: insights from integrative physiology. QJM 2002: 95: 113–124.
69. Gutierrez JA, Bagatell R, Samson MP, Theodorou AA, Berg RA. Femoral central venous catheter-associated deep venous thrombosis in children with diabetic ketoacidosis. Crit Care Med 2003: 31: 80–83.
70. Worly JM, Fortenberry JD, Hansen I, Chambliss CR, Stockwell J. Deep venous thrombosis in children with diabetic ketoacidosis and femoral central venous catheters. Pediatrics 2004: 113 (1 Pt 1): e57–e60.
71. Monroe KW, King W, Atchison JA. Use of PRISM scores in triage of pediatric patients with diabetic ketoacidosis. Am J Manag Care 1997: 3: 253–258.
72. Bonadio WA, Gutzeit MF, Losek JD, Smith DS. Outpatient management of diabetic ketoacidosis. Am J Dis Child 1988: 142: 448–450.
73. Linares MY, Schunk JE, Lindsay R. Laboratory presentation in diabetic ketoacidosis and duration of therapy. Pediatr Emerg Care 1996: 12: 347–351.
74. Yu HY, Agus M, Kellogg MD. Clinical utility of Abbott Precision Xceed Pro(R) ketone meter in diabetic patients. Pediatr Diabetes 2011: 12: 649–655.
75. Lutfi R, Huang J, Wong HR. Plasmapheresis to treat hypertriglyceridemia in a child with diabetic ketoacidosis and pancreatitis. Pediatrics 2012: 129: e195–e198.
76. Halperin ML, Goldstein MB. Fluid, electrolyte, and acid–base physiology. 3rd edn. Philadelphia: Saunders, 1999.
77. Love AH, Phillips RA. Measurement of dehydration in cholera. J Infect Dis 1969: 119: 39–42.
78. Harris GD, Fiordalisi I. Physiologic management of diabetic ketoacidemia. A 5-year prospective pediatric experience in 231 episodes. Arch Pediatr Adolesc Med 1994: 148: 1046–1052.
79. Napolova O, Urbach S, Davids MR, Halperin ML. Assessing the degree of extracellular fluid volume contraction in a patient with a severe degree of hyperglycaemia. Nephrol Dial Transplant 2003: 18: 2674–2677.
80. Halperin ML, Maccari C, Kamel KS, Carlotti AP, Bohn D. Strategies to diminish the danger of cerebral edema in a pediatric patient presenting with diabetic ketoacidosis. Pediatr Diabetes 2006: 7: 191–195.
81. Katz MA. Hyperglycemia-induced hyponatremia – calculation of expected serum sodium depression. N Engl J Med 1973: 289: 843–844.
82. Hillier TA, Abbott RD, Barrett EJ. Hyponatremia: evaluating the correction factor for hyperglycemia. Am J Med 1999: 106: 399–403.
83. Harris GD, Fiordalisi I, Harris WL, Mosovich LL, Finberg L. Minimizing the risk of brain herniation during treatment of diabetic ketoacidemia: a retrospective and prospective study. J Pediatr 1990: 117: 22–31.
84. Hale PM, Rezvani I, Braunstein AW, Lipman TH, Martinez N, Garibaldi L. Factors predicting cerebral edema in young children with diabetic ketoacidosis and new onset type I diabetes. Acta Paediatr 1997: 86: 626–631.
85. Glaser N, Barnett P, McCaslin I et al. Risk factors for cerebral edema in children with diabetic ketoacidosis. The Pediatric Emergency Medicine Collaborative Research Committee of the American Academy of Pediatrics. N Engl J Med 2001: 344: 264–269.
86. Brown TB. Cerebral oedema in childhood diabetic ketoacidosis: is treatment a factor? Emerg Med J 2004: 21: 141–144.
87. Glaser NS, Ghetti S, Casper TC, Dean JM, Kuppermann N. Pediatric diabetic ketoacidosis, fluid therapy, and cerebral injury: the design of a factorial randomized controlled trial. Pediatr Diabetes 2013: 14: 435–446.
88. Edge JA, Jakes RW, Roy Y et al. The UK case–control study of cerebral oedema complicating diabetic ketoacidosis in children. Diabetologia 2006: 49: 2002–2009.
89. Dunger DB, Sperling MA, Acerini CL et al. European Society for Paediatric Endocrinology/Lawson Wilkins Pediatric Endocrine Society consensus statement on diabetic ketoacidosis in children and adolescents. Pediatrics 2004: 113: e133–e140.
90. Adrogue HJ, Barrero J, Eknoyan G. Salutary effects of modest fluid replacement in the treatment of adults with diabetic ketoacidosis. Use in patients without extreme volume deficit. JAMA 1989: 262: 2108–2113.
91. Mel JM, Werther GA. Incidence and outcome of diabetic cerebral oedema in childhood: are there predictors? J Paediatr Child Health 1995: 31: 17–20.

92. Wagner A, Risse A, Brill HL et al. Therapy of severe diabetic ketoacidosis. Zero-mortality under very-low-dose insulin application. Diabetes Care 1999: 22: 674–677.
93. Toledo JD, Modesto V, Peinador M et al. Sodium concentration in rehydration fluids for children with ketoacidotic diabetes: effect on serum sodium concentration. J Pediatr 2009: 154: 895–900.
94. Rother KI, Schwenk WF 2nd. Effect of rehydration fluid with 75 mmol/L of sodium on serum sodium concentration and serum osmolality in young patients with diabetic ketoacidosis. Mayo Clin Proc 1994: 69: 1149–1153.
95. Felner EI, White PC. Improving management of diabetic ketoacidosis in children. Pediatrics 2001: 108: 735–740.
96. Basnet S, Venepalli PK, Andoh J, Verhulst S, Koirala J. Effect of normal saline and half normal saline on serum electrolytes during recovery phase of diabetic ketoacidosis. J Intensive Care Med 2014: 29: 38–42.
97. Fiordalisi I, Novotny WE, Holbert D, Finberg L, Harris GD. An 18-yr prospective study of pediatric diabetic ketoacidosis: an approach to minimizing the risk of brain herniation during treatment. Pediatr Diabetes 2007: 8: 142–149.
98. White PC, Dickson BA. Low morbidity and mortality in children with diabetic ketoacidosis treated with isotonic fluids. J Pediatr 2013: 163: 761–766.
99. Hoorn EJ, Carlotti AP, Costa LA et al. Preventing a drop in effective plasma osmolality to minimize the likelihood of cerebral edema during treatment of children with diabetic ketoacidosis. J Pediatr 2007: 150: 467–473.
100. Duck SC, Wyatt DT. Factors associated with brain herniation in the treatment of diabetic ketoacidosis. J Pediatr 1988: 113: 10–14.
101. Adrogue HJ, Wilson H, Boyd AE 3rd, Suki WN, Eknoyan G. Plasma acid–base patterns in diabetic ketoacidosis. N Engl J Med 1982: 307: 1603–1610.
102. Adrogue HJ, Eknoyan G, Suki WK. Diabetic ketoacidosis: role of the kidney in the acid–base homeostasis re-evaluated. Kidney Int 1984: 25: 591–598.
103. Taylor D, Durward A, Tibby SM et al. The influence of hyperchloraemia on acid base interpretation in diabetic ketoacidosis. Intensive Care Med 2006: 32: 295–301.
104. Durward A, Skellett S, Mayer A, Taylor D, Tibby SM, Murdoch IA. The value of the chloride: sodium ratio in differentiating the aetiology of metabolic acidosis. Intensive Care Med 2001: 27: 828–835.
105. Oh MS, Carroll HJ, Goldstein DA, Fein IA. Hyperchloremic acidosis during the recovery phase of diabetic ketosis. Ann Intern Med 1978: 89: 925–927.
106. Oh MS, Banerji MA, Carroll HJ. The mechanism of hyperchloremic acidosis during the recovery phase of diabetic ketoacidosis. Diabetes 1981: 30: 310–313.
107. Oh MS, Carroll HJ, Uribarri J. Mechanism of normochloremic and hyperchloremic acidosis in diabetic ketoacidosis. Nephron 1990: 54: 1–6.
108. Chua HR, Venkatesh B, Stachowski E et al. Plasma-Lyte 148 vs 0.9% saline for fluid resuscitation in diabetic ketoacidosis. J Crit Care 2012: 27: 138–145.
109. Waldhausl W, Kleinberger G, Korn A, Dudczak R, Bratusch-Marrain P, Nowotny P. Severe hyperglycemia: effects of rehydration on endocrine derangements and blood glucose concentration. Diabetes 1979: 28: 577–584.
110. Owen OE, Licht JH, Sapir DG. Renal function and effects of partial rehydration during diabetic ketoacidosis. Diabetes 1981: 30: 510–518.
111. Luzi L, Barrett EJ, Groop LC, Ferrannini E, DeFronzo RA. Metabolic effects of low-dose insulin therapy on glucose metabolism in diabetic ketoacidosis. Diabetes 1988: 37: 1470–1477.
112. Kitabchi AE. Low-dose insulin therapy in diabetic ketoacidosis: fact or fiction? Diabetes Metab Rev 1989: 5: 337–363.
113. Martin MM, Martin AA. Continuous low-dose infusion of insulin in the treatment of diabetic ketoacidosis in children. J Pediatr 1976: 89: 560–564.
114. Edwards GA, Kohaut EC, Wehring B, Hill LL. Effectiveness of low-dose continuous intravenous insulin infusion in diabetic ketoacidosis. A prospective comparative study. J Pediatr 1977: 91: 701–705.
115. Drop SL, Duval-Arnould JM, Gober AE, Hersh JH, McEnery PT, Knowles HC. Low-dose intravenous insulin infusion versus subcutaneous insulin injection: a controlled comparative study of diabetic ketoacidosis. Pediatrics 1977: 59: 733–738.
116. Lightner ES, Kappy MS, Revsin B. Low-dose intravenous insulin infusion in patients with diabetic ketoacidosis: biochemical effects in children. Pediatrics 1977: 60: 681–688.
117. Perkin RM, Marks JF. Low-dose continuous intravenous insulin infusion in childhood diabetic ketoacidosis. Clin Pediatr (Phila) 1979: 18: 540, 545–540, 548.
118. Kappy MS, Lightner ES. Low-dose intravenous insulin in the treatment of diabetic ketoacidosis. Am J Dis Child 1979: 133: 523–525.
119. Burghen GA, Etteldorf JN, Fisher JN, Kitabchi AQ. Comparison of high-dose and low-dose insulin by continuous intravenous infusion in the treatment of diabetic ketoacidosis in children. Diabetes Care 1980: 3: 15–20.
120. Kitabchi AE, Umpierrez GE, Fisher JN, Murphy MB, Stentz FB. Thirty years of personal experience in hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state. J Clin Endocrinol Metab 2008: 93: 1541–1552.
121. Lindsay R, Bolte RG. The use of an insulin bolus in low-dose insulin infusion for pediatric diabetic ketoacidosis. Pediatr Emerg Care 1989: 5: 77–79.
122. Van der Meulen JA, Klip A, Grinstein S. Possible mechanism for cerebral oedema in diabetic ketoacidosis. Lancet 1987: 2: 306–308.
123. Soler NG, FitzGerald MG, Wright AD, Malins JM. Comparative study of different insulin regimens in management of diabetic ketoacidosis. Lancet 1975: 2: 1221–1224.
124. Puttha R, Cooke D, Subbarayan A et al. Low dose (0.05 units/kg/h) is comparable with standard dose (0.1 units/kg/h) intravenous insulin infusion for the initial treatment of diabetic ketoacidosis in children with type 1 diabetes-an observational study. Pediatr Diabetes 2010: 11: 12–17.

125. Al Hanshi S, Shann F. Insulin infused at 0.05 versus 0.1 units/kg/hr in children admitted to intensive care with diabetic ketoacidosis. Pediatr Crit Care Med 2011: 12: 137–140.
126. Wang J, Barbry P, Maiyar AC et al. SGK integrates insulin and mineralocorticoid regulation of epithelial sodium transport. Am J Physiol Renal Physiol 2001: 280: F303–F313.
127. Tallini NY, Stoner LC. Amiloride-sensitive sodium current in everted Ambystoma initial collecting tubule: short-term insulin effects. Am J Physiol Cell Physiol 2002: 283: C1171–C1181.
128. McCormick JA, Bhalla V, Pao AC, Pearce D. SGK1: a rapid aldosterone-induced regulator of renal sodium reabsorption. Physiology 2005: 20: 134–139.
129. Tiwari S, Nordquist L, Halagappa VK, Ecelbarger CA. Trafficking of ENaC subunits in response to acute insulin in mouse kidney. Am J Physiol Renal Physiol 2007: 293: F178–F185.
130. Frindt G, Palmer LG. Effects of insulin on Na and K transporters in the rat CCD. Am J Physiol Renal Physiol 2012: 302: F1227–F1233.
131. Carlotti AP, St George-Hyslop C, Bohn D, Halperin ML. Hypokalemia during treatment of diabetic ketoacidosis: clinical evidence for an aldosterone-like action of insulin. J Pediatr 2013: 163: 207–212 e201.
132. Fisher JN, Shahshahani MN, Kitabchi AE. Diabetic ketoacidosis: low-dose insulin therapy by various routes. N Engl J Med 1977: 297: 238–241.
133. Sacks HS, Shahshahani M, Kitabchi AE, Fisher JN, Young RT. Similar responsiveness of diabetic ketoacidosis to low-dose insulin by intramuscular injection and albumin-free infusion. Ann Intern Med 1979: 90: 36–42.
134. Umpierrez GE, Latif K, Stoever J et al. Efficacy of subcutaneous insulin lispro versus continuous intravenous regular insulin for the treatment of patients with diabetic ketoacidosis. Am J Med 2004: 117: 291–296.
135. Umpierrez GE, Cuervo R, Karabell A, Latif K, Freire AX, Kitabchi AE. Treatment of diabetic ketoacidosis with subcutaneous insulin aspart. Diabetes Care 2004: 27: 1873–1878.
136. Della Manna T, Steinmetz L, Campos PR et al. Subcutaneous use of a fast-acting insulin analog: an alternative treatment for pediatric patients with diabetic ketoacidosis. Diabetes Care 2005: 28: 1856–1861.
137. Adrogue HJ, Lederer ED, Suki WN, Eknoyan G. Determinants of plasma potassium levels in diabetic ketoacidosis. Medicine (Baltimore) 1986: 65: 163–172.
138. DeFronzo RA, Felig P, Ferrannini E, Wahren J. Effect of graded doses of insulin on splanchnic and peripheral potassium metabolism in man. Am J Physiol 1980: 238: E421–E427.
139. Tattersall RB. A paper which changed clinical practice (slowly). Jacob Holler on potassium deficiency in diabetic acidosis (1946). Diabet Med 1999: 16: 978–984.
140. Nabarro JD, Spencer AG, Stowers JM. Treatment of diabetic ketosis. Lancet 1952: 1: 983–989.
141. Guest G. Organic phosphates of the blood and mineral metabolism in diabetic acidosis. Am J Dis Child 1942: 64: 401–412.
142. Guest G, Rapoport S. Electrolytes of blood plasma and cells in diabetic acidosis and during recovery. Proc Am Diabetes Assoc 1947: 7: 95–115.
143. Riley MS, Schade DS, Eaton RP. Effects of insulin infusion on plasma phosphate in diabetic patients. Metabolism 1979: 28: 191–194.
144. Alberti KG, Emerson PM, Darley JH, Hockaday TD. 2,3-Diphosphoglycerate and tissue oxygenation in uncontrolled diabetes mellitus. Lancet 1972: 2: 391–395.
145. Knochel JP. The pathophysiology and clinical characteristics of severe hypophosphatemia. Arch Intern Med 1977: 137: 203–220.
146. O'Connor LR, Wheeler WS, Bethune JE. Effect of hypophosphatemia on myocardial performance in man. N Engl J Med 1977: 297: 901–903.
147. Gibby OM, Veale KE, Hayes TM, Jones JG, Wardrop CA. Oxygen availability from the blood and the effect of phosphate replacement on erythrocyte 2,3-diphosphoglycerate and haemoglobin-oxygen affinity in diabetic ketoacidosis. Diabetologia 1978: 15: 381–385.
148. Keller U, Berger W. Prevention of hypophosphatemia by phosphate infusion during treatment of diabetic ketoacidosis and hyperosmolar coma. Diabetes 1980: 29: 87–95.
149. Wilson HK, Keuer SP, Lea AS, Boyd AE 3rd, Eknoyan G. Phosphate therapy in diabetic ketoacidosis. Arch Intern Med 1982: 142: 517–520.
150. Becker DJ, Brown DR, Steranka BH, Drash AL. Phosphate replacement during treatment of diabetic ketosis. Effects on calcium and phosphorus homeostasis. Am J Dis Child 1983: 137: 241–246.
151. Fisher JN, Kitabchi AE. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. J Clin Endocrinol Metab 1983: 57: 177–180.
152. Clerbaux T, Reynaert M, Willems E, Frans A. Effect of phosphate on oxygen-hemoglobin affinity, diphosphoglycerate and blood gases during recovery from diabetic ketoacidosis. Intensive Care Med 1989: 15: 495–498.
153. Weisinger JR, Bellorin-Font E. Magnesium and phosphorus. Lancet 1998: 352: 391–396.
154. Singhal PC, Kumar A, Desroches L, Gibbons N, Mattana J. Prevalence and predictors of rhabdomyolysis in patients with hypophosphatemia. Am J Med 1992: 92: 458–464.
155. Kutlu AO, Kara C, Cetinkaya S. Rhabdomyolysis without detectable myoglobulinuria due to severe hypophosphatemia in diabetic ketoacidosis. Pediatr Emerg Care 2011: 27: 537–538.
156. Bohannon NJ. Large phosphate shifts with treatment for hyperglycemia. Arch Intern Med 1989: 149: 1423–1425.
157. de Oliveira Iglesias SB, Pons Leite H, de Carvalho WB. Hypophosphatemia-induced seizure in a child with diabetic ketoacidosis. Pediatr Emerg Care 2009: 25: 859–861.
158. Zipf WB, Bacon GE, Spencer ML, Kelch RP, Hopwood NJ, Hawker CD. Hypocalcemia,

hypomagnesemia, and transient hypoparathyroidism during therapy with potassium phosphate in diabetic ketoacidosis. Diabetes Care 1979: 2: 265–268.
159. Winter RJ, Harris CJ, Phillips LS, Green OC. Diabetic ketoacidosis. Induction of hypocalcemia and hypomagnesemia by phosphate therapy. Am J Med 1979: 67: 897–900.
160. Hale PJ, Crase J, Nattrass M. Metabolic effects of bicarbonate in the treatment of diabetic ketoacidosis. Br Med J (Clin Res Ed) 1984: 289: 1035–1038.
161. Morris LR, Murphy MB, Kitabchi AE. Bicarbonate therapy in severe diabetic ketoacidosis. Ann Intern Med 1986: 105: 836–840.
162. Okuda Y, Adrogue HJ, Field JB, Nohara H, Yamashita K. Counterproductive effects of sodium bicarbonate in diabetic ketoacidosis. J Clin Endocrinol Metab 1996: 81: 314–320.
163. Green SM, Rothrock SG, Ho JD et al. Failure of adjunctive bicarbonate to improve outcome in severe pediatric diabetic ketoacidosis. Ann Emerg Med 1998: 31: 41–48.
164. Assal JP, Aoki TT, Manzano FM, Kozak GP. Metabolic effects of sodium bicarbonate in management of diabetic ketoacidosis. Diabetes 1974: 23: 405–411.
165. Ohman JL Jr, Marliss EB, Aoki TT, Munichoodappa CS, Khanna VV, Kozak GP. The cerebrospinal fluid in diabetic ketoacidosis. N Engl J Med 1971: 284: 283–290.
166. Soler NG, Bennett MA, Dixon K, FitzGerald MG, Malins JM. Potassium balance during treatment of diabetic ketoacidosis with special reference to the use of bicarbonate. Lancet 1972: 2: 665–667.
167. Lever E, Jaspan JB. Sodium bicarbonate therapy in severe diabetic ketoacidosis. Am J Med 1983: 75: 263–268.
168. Narins RG, Cohen JJ. Bicarbonate therapy for organic acidosis: the case for its continued use. Ann Intern Med 1987: 106: 615–618.
169. Curtis JR, To T, Muirhead S, Cummings E, Daneman D. Recent trends in hospitalization for diabetic ketoacidosis in Ontario children. Diabetes Care 2002: 25: 1591–1596.
170. Edge JA, Ford-Adams ME, Dunger DB. Causes of death in children with insulin dependent diabetes 1990–96. Arch Dis Child 1999: 81: 318–323.
171. Decourcey DD, Steil GM, Wypij D, Agus MS. Increasing use of hypertonic saline over mannitol in the treatment of symptomatic cerebral edema in pediatric diabetic ketoacidosis: an 11-year retrospective analysis of mortality*. Pediatr Crit Care Med 2013: 14: 694–700.
172. Daneman D. Diabetes-related mortality. A pediatrician's view. Diabetes Care 2001: 24: 801–802.
173. Edge JA, Hawkins MM, Winter DL, Dunger DB. The risk and outcome of cerebral oedema developing during diabetic ketoacidosis. Arch Dis Child 2001: 85: 16–22.
174. Lawrence SE, Cummings EA, Gaboury I, Daneman D. Population-based study of incidence and risk factors for cerebral edema in pediatric diabetic ketoacidosis. J Pediatr 2005: 146: 688–692.
175. Ghetti S, Lee JK, Sims CE, Demaster DM, Glaser NS. Diabetic ketoacidosis and memory dysfunction in children with type 1 diabetes. J Pediatr 2010: 156: 109–114.
176. Cooper MR, Turner RA Jr, Hutaff L, Prichard R. Diabetic keto-acidosis complicated by disseminated intravascular coagulation. South Med J 1973: 66: 653–657.
177. Keane S, Gallagher A, Ackroyd S, McShane MA, Edge JA. Cerebral venous thrombosis during diabetic ketoacidosis. Arch Dis Child 2002: 86: 204–205.
178. Ho J, Mah JK, Hill MD, Pacaud D. Pediatric stroke associated with new onset type 1 diabetes mellitus: case reports and review of the literature. Pediatr Diabetes 2006: 7: 116–121.
179. Moye J, Rosenbloom AL, Silverstein J. Clinical predictors of mucormycosis in children with type 1 diabetes mellitus. J Pediatr Endocrinol Metab 2002: 15: 1001–1004.
180. Watson JP, Barnett AH. Pneumomediastinum in diabetic ketoacidosis. Diabet Med 1989: 6: 173–174.
181. Haddad NG, Croffie JM, Eugster EA. Pancreatic enzyme elevations in children with diabetic ketoacidosis. J Pediatr 2004: 145: 122–124.
182. Glaser NS, Wootton-Gorges SL, Buonocore MH et al. Frequency of sub-clinical cerebral edema in children with diabetic ketoacidosis. Pediatr Diabetes 2006: 7: 75–80.
183. Glaser NS, Marcin JP, Wootton-Gorges SL et al. Correlation of clinical and biochemical findings with diabetic ketoacidosis-related cerebral edema in children using magnetic resonance diffusion-weighted imaging. J Pediatr 2008: 153: 541–546.
184. Krane EJ, Rockoff MA, Wallman JK, Wolfsdorf JI. Subclinical brain swelling in children during treatment of diabetic ketoacidosis. N Engl J Med 1985: 312: 1147–1151.
185. Hoffman WH, Steinhart CM, el Gammal T, Steele S, Cuadrado AR, Morse PK. Cranial CT in children and adolescents with diabetic ketoacidosis. AJNR Am J Neuroradiol 1988: 9: 733–739.
186. Sperling MA. Cerebral edema in diabetic ketoacidosis: an underestimated complication? Pediatr Diabetes 2006: 7: 73–74.
187. Arieff AI, Kleeman CR. Studies on mechanisms of cerebral edema in diabetic comas. Effects of hyperglycemia and rapid lowering of plasma glucose in normal rabbits. J Clin Invest 1973: 52: 571–583.
188. Arieff AI, Kleeman CR. Cerebral edema in diabetic comas. II. Effects of hyperosmolality, hyperglycemia and insulin in diabetic rabbits. J Clin Endocrinol Metab 1974: 38: 1057–1067.
189. Prockop LD. Hyperglycemia, polyol accumulation, and increased intracranial pressure. Arch Neurol 1971: 25: 126–140.
190. Harris GD, Fiordalisi I, Finberg L. Safe management of diabetic ketoacidemia. J Pediatr 1988: 113: 65–67.
191. Glaser NS, Wootton-Gorges SL, Marcin JP et al. Mechanism of cerebral edema in children with diabetic ketoacidosis. J Pediatr 2004: 145: 164–171.
192. Glaser N, Yuen N, Anderson SE, Tancredi DJ, O'Donnell ME. Cerebral metabolic alterations in rats with diabetic ketoacidosis: effects of treatment with insulin and intravenous fluids and effects of bumetanide. Diabetes 2010: 59: 702–709.

193. Yuen N, Anderson SE, Glaser N, Tancredi DJ, O'Donnell ME. Cerebral blood flow and cerebral edema in rats with diabetic ketoacidosis. Diabetes 2008: 57: 2588–2594.
194. Rosenbloom AL, Schatz DA, Krischer JP et al. Therapeutic controversy: prevention and treatment of diabetes in children. J Clin Endocrinol Metab 2000: 85: 494–522.
195. Glaser N. Cerebral injury and cerebral edema in children with diabetic ketoacidosis: could cerebral ischemia and reperfusion injury be involved? Pediatr Diabetes 2009: 10: 534–541.
196. Hoffman WH, Stamatovic SM, Andjelkovic AV. Inflammatory mediators and blood brain barrier disruption in fatal brain edema of diabetic ketoacidosis. Brain Res 2009: 1254: 138–148.
197. Vavilala MS, Richards TL, Roberts JS et al. Change in blood–brain barrier permeability during pediatric diabetic ketoacidosis treatment*. Pediatr Crit Care Med 2010: 11: 332–338.
198. Rosenbloom AL. Intracerebral crises during treatment of diabetic ketoacidosis. Diabetes Care 1990: 13: 22–33.
199. Bello FA, Sotos JF. Cerebral oedema in diabetic ketoacidosis in children [letter]. Lancet 1990: 336: 64.
200. Mahoney CP, Vlcek BW, DelAguila M. Risk factors for developing brain herniation during diabetic ketoacidosis. Pediatr Neurol 1999: 21: 721–727.
201. Durr JA, Hoffman WH, Sklar AH, el Gammal T, Steinhart CM. Correlates of brain edema in uncontrolled IDDM. Diabetes 1992: 41: 627–632.
202. Durward A, Ferguson LP, Taylor D, Murdoch IA, Tibby SM. The temporal relationship between glucose-corrected serum sodium and neurological status in severe diabetic ketoacidosis. Arch Dis Child 2011: 96: 50–57.
203. Bureau MA, Begin R, Berthiaume Y, Shapcott D, Khoury K, Gagnon N. Cerebral hypoxia from bicarbonate infusion in diabetic acidosis. J Pediatr 1980: 96: 968–973.
204. Deeb L. Development of fatal cerebral edema during outpatient therapy for diabetic ketoacidosis. Pract Diabetes 1989: 6: 212–213.
205. Glasgow AM. Devastating cerebral edema in diabetic ketoacidosis before therapy [letter]. Diabetes Care 1991: 14: 77–78.
206. Couch RM, Acott PD, Wong GW. Early onset fatal cerebral edema in diabetic ketoacidosis. Diabetes Care 1991: 14: 78–79.
207. Fiordalisi I, Harris GD, Gilliland MG. Prehospital cardiac arrest in diabetic ketoacidemia: why brain swelling may lead to death before treatment. J Diabetes Complications 2002: 16: 214–219.
208. Edge JA. Cerebral oedema during treatment of diabetic ketoacidosis: are we any nearer finding a cause? Diabetes Metab Res Rev 2000: 16: 316–324.
209. Muir AB, Quisling RG, Yang MC, Rosenbloom AL. Cerebral edema in childhood diabetic ketoacidosis: natural history, radiographic findings, and early identification. Diabetes Care 2004: 27: 1541–1546.
210. Franklin B, Liu J, Ginsberg-Fellner F. Cerebral edema and ophthalmoplegia reversed by mannitol in a new case of insulin-dependent diabetes mellitus. Pediatrics 1982: 69: 87–90.
211. Shabbir N, Oberfield SE, Corrales R, Kairam R, Levine LS. Recovery from symptomatic brain swelling in diabetic ketoacidosis. Clin Pediatr (Phila) 1992: 31: 570–573.
212. Roberts MD, Slover RH, Chase HP. Diabetic ketoacidosis with intracerebral complications. Pediatr Diabetes 2001: 2: 109–114.
213. Curtis JR, Bohn D, Daneman D. Use of hypertonic saline in the treatment of cerebral edema in diabetic ketoacidosis (DKA). Pediatr Diabetes 2001: 2: 191–194.
214. Kamat P, Vats A, Gross M, Checchia PA. Use of hypertonic saline for the treatment of altered mental status associated with diabetic ketoacidosis. Pediatr Crit Care Med 2003: 4: 239–242.
215. Kanter RK, Oliphant M, Zimmerman JJ, Stuart MJ. Arterial thrombosis causing cerebral edema in association with diabetic ketoacidosis. Crit Care Med 1987: 15: 175–176.
216. Roe TF, Crawford TO, Huff KR, Costin G, Kaufman FR, Nelson MD Jr. Brain infarction in children with diabetic ketoacidosis. J Diabetes Complications 1996: 10: 100–108.
217. Rosenbloom AL. Fatal cerebral infarctions in diabetic ketoacidosis in a child with previously unknown heterozygosity for factor V Leiden deficiency. J Pediatr 2004: 145: 561–562.
218. Fourtner SH, Weinzimer SA, Levitt Katz LE. Hyperglycemic hyperosmolar non-ketotic syndrome in children with type 2 diabetes. Pediatr Diabetes 2005: 6: 129–135.
219. Kronan K, Normal ME. Renal and electrolyte emergencies. In: Fleisher GR, Ludwig S, eds. Textbook of Emergency Medicine. 4th edn. Philadelphia: Lippincott Williams and Wilkins, 2000.
220. Matz R. Management of the hyperosmolar hyperglycemic syndrome. Am Fam Physician 1999: 60: 1468–1476.
221. Delaney MF, Zisman A, Kettyle WM. Diabetic ketoacidosis and hyperglycemic hyperosmolar nonketotic syndrome. Endocrinol Metab Clin North Am 2000: 29: 683–705, V.
222. Mannix R, Tan ML, Wright R, Baskin M. Acute pediatric rhabdomyolysis: causes and rates of renal failure. Pediatrics 2006: 118: 2119–2125.
223. Hollander AS, Olney RC, Blackett PR, Marshall BA. Fatal malignant hyperthermia-like syndrome with rhabdomyolysis complicating the presentation of diabetes mellitus in adolescent males. Pediatrics 2003: 111 (6 Pt 1): 1447–1452.
224. Carcillo JA, Tasker RC. Fluid resuscitation of hypovolemic shock: acute medicine's great triumph for children. Intensive Care Med 2006: 32: 958–961.
225. Kilbane BJ, Mehta S, Backeljauw PF, Shanley TP, Crimmins NA. Approach to management of malignant hyperthermia-like syndrome in pediatric diabetes mellitus. Pediatr Crit Care Med 2006: 7: 169–173.
226. Laffel LM, Wentzell K, Loughlin C, Tovar A, Moltz K, Brink S. Sick day management using blood 3-hydroxybutyrate (3-OHB) compared with urine ketone monitoring reduces hospital visits in young people with T1DM: a randomized clinical trial. Diabet Med 2006: 23: 278–284.

227. Laffel L. Sick-day management in type 1 diabetes. Endocrinol Metab Clin North Am 2000: 29: 707–723.
228. Hoffman WH, O'Neill P, Khoury C, Bernstein SS. Service and education for the insulin-dependent child. Diabetes Care 1978: 1: 285–288.
229. Drozda DJ, Dawson VA, Long DJ, Freson LS, Sperling MA. Assessment of the effect of a comprehensive diabetes management program on hospital admission rates of children with diabetes mellitus. Diabetes Educ 1990: 16: 389–393.
230. Grey M, Boland EA, Davidson M, Li J, Tamborlane WV. Coping skills training for youth with diabetes mellitus has long-lasting effects on metabolic control and quality of life. J Pediatr 2000: 137: 107–113.
231. Golden MP, Herrold AJ, Orr DP. An approach to prevention of recurrent diabetic ketoacidosis in the pediatric population. J Pediatr 1985: 107: 195–200.
232. Wolfsdorf J, Glaser N, Sperling MA. Diabetic ketoacidosis in infants, children, and adolescents: a consensus statement from the American Diabetes Association. Diabetes Care 2006: 29: 1150–1159.
233. Dunger D, Menon RK, Sperling MA. Ketoacidosis. In: Hochberg Z, ed. Practical Algorithms in Pediatric Endocrinology. Basel: S. Karger AG, 1999: 104–105.