Glucose Metabolism Derangements in Pediatric Age

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Edited by

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TYPE 1 DIABETES

SECTION 1 CHAPTER 1

EPIDEMIOLOGY AND PATHOGENESIS OF TYPE 1 DIABETES MELLITUS IN CHILDREN

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Key messages

- **Type 1 diabetes mellitus** (T1DM) is characterized by progressive destruction of insulin secreting β cells, leading to absolute insulin deficiency
- **Lifelong** treatment with insulin and intensive glucose management is necessary
- **The incidence** of T1DM is still rising in most parts of the world
- **Genetic susceptibility** in combination with environmental factors leads to an immune-mediated process and β cell destruction
- Diabetes pathogenesis is **heterogeneous**
- Prevention is not (yet) possible

Introduction

Type 1 diabetes mellitus (T1DM) is one of the most frequent chronic diseases in pediatric age. Current estimates of T1DM suggest that 1,110,100 young people live with T1DM (1). Each year around 128,900 new cases are diagnosed and, in most regions, the incidence of diabetes in the pediatric population is still rising. T1DM is characterized by progressive destruction of pancreatic insulin secreting β cells, leading to absolute insulin deficiency. This requires lifelong insulin treatment and intensive disease management. Without insulin, T1DM is lethal and without continuous intensive management of the disease, the risk of acute and chronic comorbidities is high (2). It is assumed that the health

expenses of diabetics are on average twice as much as those of non-diabetics, which adds a financial component to the burden of illness. Much progress has been made over the past 30 years, in particular in terms of treatment and understanding of the disease process. Yet, the cause of T1DM remains an enigma and prevention is not—yet—possible. In this chapter, a summary of T1DM epidemiology and the pathogenesis will be provided.

Epidemiology

Epidemiology is defined as the discipline that studies the distribution of health-related determinants states or events in specific populations and the use of these data to control health problems (3). The incidence rate represents the number of new cases of a disease over a period of time in relation to the population at risk for the disease. (3). The incidence rate represents the number of new cases of a disease within a time period in relation to the population at risk of the disease. Prevalence refers to the proportion of persons in a population with a disease (or other characteristic). When comparing reported incidence data of a disease—such as T1DM—it is important to consider the methodology which has been used to obtain the incidence data. The reliability of the numerator and denominator is a key element. For the numerator, a clear definition of the disease is required and all cases with the disease must be included.

For T1DM the criteria are well defined:

- Fasting glucose plasma value ≥ 7 mmol/l
- Classical symptoms and plasma glucose ≥ 11.1 mmol/l, or HbA1c (in NGSP certified lab) ≥ 6.5% (48 mmol/mol)
- At least one diabetes specific autoantibody
- Exclusion of monogenic diabetes, type 2 diabetes, or other forms of secondary diabetes

A person with T1DM will only survive when treated with insulin. In regions where children die before diagnosis, the numerator will be lower, leading to an underestimation of the incidence rate. When providing or analyzing incidence rates of T1DM, it is important to keep in mind where the data have been collected. A reported incidence rate can reflect local (for example hospital recruitment area), regional or national data. The data collection may or may not be exhaustive for that given population. Longitudinally collected data in a registry, for example in a hospital registry, can provide relevant information, when the data collection has

been consistent and within a well-defined recruitment area. Changes over time ('temporal trend') and geographical differences can be detected with registry data, provided that the registry includes mergeable data, a standardized dataset, rules for data collection, an inclusion principle (including long term outcome/clinical benchmarking for longitudinal studies), observations associated over time, and knowledge of outcome (4).

Although registries as surveillance systems have the advantage of providing fast (and continuous) information on temporal changes in the incidence of a disease, a disadvantage is the cost of maintaining them. This may be prohibitive. An alternative method of continuous surveillance is the capture-mark-recapture method, as suggested by LaPorte (5). This methodology was used (and is still used) to study the incidence rates of T1DM in Europe (EURODIAB substudy 2). It requires the inclusion of two independent data sources for the identification of newly diagnosed children with T1DM, to optimize data quality and comparability. The outcome of the EURODIAB substudy 2 confirmed a North-South gradient in Europe (2009–2013 incidence rates varied between 7.7/105 in Macedonia and 60.9/105 in Finland), with the exception of Sardinia. Over the 25 years of incidence data collection (1989–2013), this European project has recently shown that the estimated annual increase in incidence rate is 3.4% with a regional range of 0.5% (Spain) to 6.6% (Poland) (6). Although the suspected increase in the incidence of type 2 diabetes mellitus (T2DM) in the USA amongst Native Americans prompted the SEARCH study (SEARCH for diabetes in youth) (7,8), this study found an annual increase in the incidence of T1DM in that continent of 1.8% per year between 2002 and 2012 compared to an increase of 4.8% in T2DM amongst 0- to 19-year-olds. Another USA study, reporting on persons with private health care insurance between 2001 and 2015 (Clinformatics Data Mart Database), reported a 1.9% increase in the incidence of T1DM amongst young people (9). Incidence rates varied across the USA (2.4% to 3.8%) and, interestingly, a decrease in the incidence rate in adults was found (-1.3% between 2001 and 2015). This data set only reflects the population with private health insurance, and not the population as a whole, which may influence the outcome.

The DiaMond study reported that one of the lowest T1DM incidence rates is observed in China. Using the capture-mark-recapture method, Weng et al. reported the incidence of T1DM between 2010 and 2013 based on 10% of the population living in 13 areas across China (133×106 persons) (10). The incidence of T1DM among those aged 0–14 years was 1.93/105.

Importantly, while still among the lowest global incidence rates in those aged 0–14 years, the incidence has increased since 1985 (1985–1994 = 0.51/105; 1988–1996 = 0.59/105) and is an important consideration for adjusted health care planning and expenditure.

For a global overview of all forms of diabetes and estimates of absolute numbers of patients, every two years the International Diabetes Federation provides the IDF ATLAS (1). In the most recent update (2019) the high incidence of T1DM in Scandinavian countries was again confirmed with 62.3/105 children in Finland, 43.2/105 Sweden, 33.6/105 in Norway and 27/105 in Denmark, but it also reported high incidence rates of T1DM in the Middle East (Kuwait 41.7/105, Saudi Arabia 31.4/105, Qatar 28.4/105). Clearly, the genetic susceptibility and environmental factors that contribute to the development of T1DM need to be re-evaluated and cannot be only attributed to a North-South gradient. Disease burden expressed in absolute numbers shows that the largest number of children aged 0–14 years with T1DM live in India (95,600), followed by the USA (94,200), Brazil (51,500) and China (28,700). Consistent with the reports above, a recent systematic review confirmed a global increase in T1DM prevalence and incidence (11). The pace of this global increase demands responses at national and international levels to ensure that health care systems are equipped to provide lifesaving treatment and the necessary guidance to meet T1DM treatment targets. The increase in T1DM incidence also suggests that environmental factors that are as yet unidentified have a role in the pathogenesis of this multifactorial condition. Although much has been learned over the last decades, we are still faced with many gaps in our understanding. Continued surveillance of the incidence rates remains essential, as it may help to fill in some of these gaps.

Pathogenesis of type 1 diabetes: heterogeneity

Over the last four decades, more data on type 1 diabetes and its pathogenesis have been collected, confirming the heterogeneity of the disease pathway (12). So far, a genetic susceptibility, in combination with one or multiple environmental factor(s) seems to lead to the immune-mediated process with the subsequent progressive destruction of the pancreatic β cells. The temporal changes in incidence and the geographical variations confirm that environmental factors play an important role.

Figure 1. The pathogenesis of type 1 diabetes. Adapted from the Natural history of type 1 diabetes (NEJM, G Eisenbarth 1986).

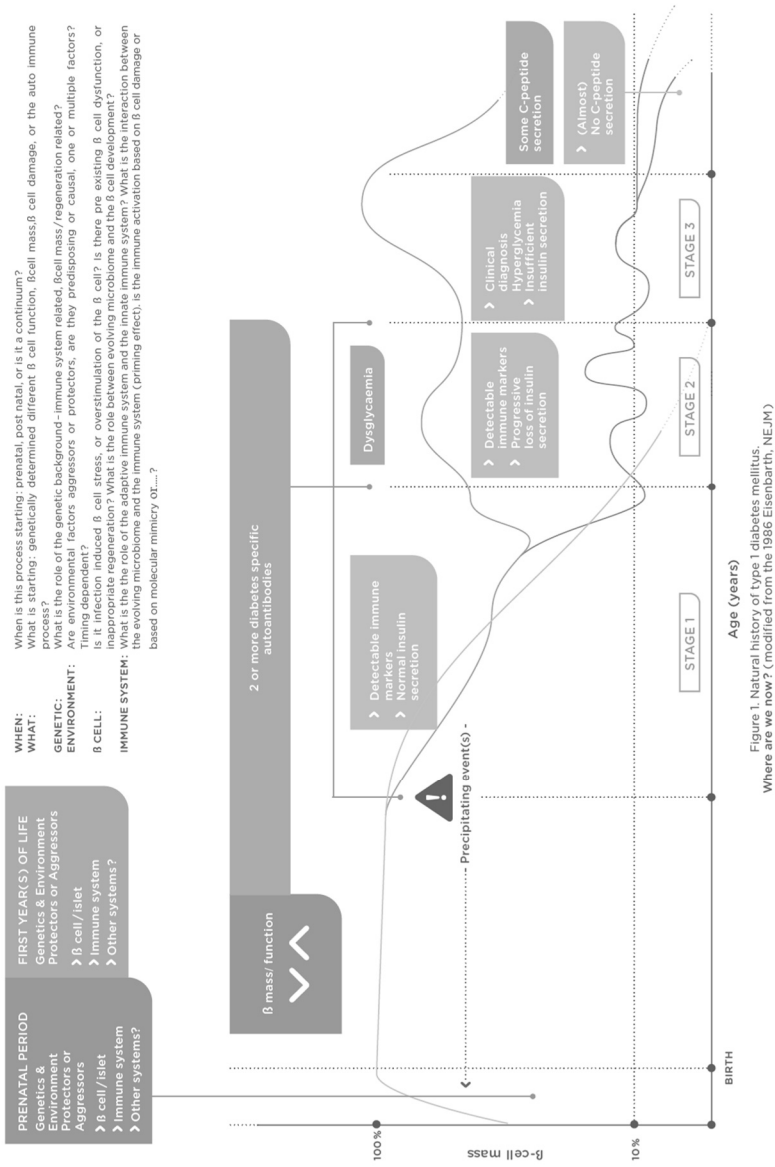

Figure 1. Natural history of type 1 diabetes mellitus.
Where are we now? (modified from the 1986 Eisenbarth, NEJM)

Although the endpoint is β cell destruction and insulin deficiency, many options, as listed in figure 1, are possible, confirming the complexity and heterogeneity of the disease. In the next paragraphs the key players, β cells, genetic predisposition, immune system and environmental factors are discussed.

β cells

Pancreatic cells, including β cells, develop from the endoderm through a complex interplay of signaling pathways (13). Throughout this development, a fine balance exists between proliferation and differentiation into the different islet cells. At birth, all populations of endocrine cells are formed and, shortly after birth, functional mature endocrine cells are grouped into islet structures. In the postnatal phase, β cells and their surrounding islet cells mature and become the key players in glucose homeostasis. The endocrine part of the pancreas is only a small part of the organ (<5%) compared to the exocrine pancreas, which excretes enzymes in the gut to support the digestion of food carbohydrates, lipids, and proteins. In humans, the expansion of β cells continues throughout the first years of life, reaching a stable mass at around the age of 5 years. Understanding the complex regulation of the expansion and maturation of β cells, ultimately determining β cell mass and function, may be essential to understand their fate in health or disease. Rodent data suggest that the maturation and development of glucose responsiveness of the β cells are determined by selective changes in micro-RNA profiles, occurring around the time of weaning (14). The micro-RNA molecules (miRNAs) are short non- coding RNAs, which support the regulation of gene expression post-transcriptionally. As such, they play a key role in a wide range of biological processes such as cell growth, proliferation, differentiation, development, and apoptosis and not only β cell function but also the regulation of the diverse immune cells. Their expression is influenced by environmental factors such as starvation, infections, etc., and this may point to a potential role in the pathogenesis of diabetes.

Shortly after the discovery of the islets and their role in diabetes, research into the transplantation of islets was initiated. One of the important lessons learned from the isolation and transplantation of islets and/or β cells was the detrimental impact of many environmental factors on the function of islets and β cells. Islets of Langerhans are part of a complex system, interacting continuously with neighboring cells and beyond. This interaction determines the function and viability of the cells within islets

(15). Loss of this interaction leads to changes in islet morphology and integrity, ultimately resulting in β cell apoptosis. The destruction of insulin secreting β cells is central in T1DM. Understanding their characteristics alone or in combination with the adjacent islet cells is essential when analyzing potential pathways leading to T1DM.

Immune-mediated process

Over 50 years ago, W. Gepts demonstrated the presence of "insulitis" in 15/22 pancreata of deceased patients with recent onset T1DM under 40 years of age, suggesting the presence of an immune reaction in association with insulin secreting islet cells. After this observation, diabetes specific autoantibodies were identified and considered to be involved in β cell death. Bottazzo was one of the first scientists to discuss whether β cell death was "homicide" or "suicide." In support of "homicide," he suggested that an environmental factor might stimulate the release of autoantigens by the β cell. These "self-antigens" would then be scavenged by macrophages and presented through their human leukocyte antigen (HLA) class II molecules (HLA-DR) to T helper cells. B lymphocytes would be activated by these T helper cells to secrete specific antibodies and activate cytotoxic T cells, ultimately leading to β cell death. In contrast, "suicide" would involve genetic or other predisposing characteristics of the β cell itself leading to its destruction. In the endocrine and the exocrine pancreatic tissue of newly onset patients' islet specific CD4+ and CD8+ T cells have been isolated with a predominance of CD8+ T cells. Major histocompatibility complexes (MHC) on antigen presenting cells bind the antigen peptides and present them to T cells by stimulating the activation of CD4+ and CD8+ T cell populations, necessary for disease induction. This implicates cytotoxic T cells (CTLs) in β cell destruction. Activated B lymphocytes, secreting disease specific antibodies, are detected as well. The process initiating this/these activation(s) remains uncertain. Potentially different pathways, such as infection, toxins, β cell stress due to high demand or even molecular mimicry should be considered. The immune system is trying to maintain a fundamental balance between host and environment. During evolution, the immune system has learned to cope with all kind of pathogens present in its vicinity. Through the innate immune system, a fast reaction can be mounted to clear the system of the potential pathogen. Different immune cells such as monocytes/macrophages, neutrophils, dendritic cells (DCs), natural killer (NK) cells and humoral components are part of this fast-acting innate immune system. The immune cells express different pattern recognition receptors (PRRs) that can detect

danger via recognizing specific pathogen-associated molecular patterns (PAMPs). The humoral components include the circulating complement system proteins/components, and cytokines and chemokines secreted by innate immune cells along with various antimicrobial peptides. Toll-like receptors (TLRs) are part of these PRRs, and TLR mediated recognition of pathogens by innate immune cells plays a very important role in the induction of the pro-inflammatory immune response required to clear the system of the presumed pathogen or altered self-antigens. However, under special circumstances, this a-specific response can be uncontrolled or exaggerated leading to the development of severe inflammation and cell death (16). Not only can this first a-specific response of the innate immune system contribute to the process leading to β cell death, but the adaptive immune system may also play a role. Through the adaptive immune system, specific T and B cells can be selected out of a large repertoire and they can be activated after exposure to detected antigens, whether the antigens are altered self or microorganism related. Many environmental factors such as microorganisms and viral infections have been discussed in relation to T1DM, but during periods of stress or increased demand for insulin new hybrid peptides may be secreted by the stressed β cell (17,18). The secretion of these hybrid molecules may lead to this activation of the autoreactive T cells and initiate loss of self-tolerance and autoimmune β cell destruction. This contributes to the heterogeneity of the disease.

Nowadays, the emergence of cellular and humoral autoimmunity of islet cells is the distinguishing feature of the disease process. The number of diabetes specific autoantibodies has increased to at least five, including the ICA, (directed against cytoplasmic proteins in the beta cell), antibodies to glutamic acid decarboxylase (GAD- 65), insulin autoantibodies (IAA), IA-2A, protein tyrosine phosphatase as well as the antibody against Zinc Transporter 8 (ZnT8). In people with at least two autoantibodies, symptomatic disease develops within five years in 44% of those people; within ten years in 70%. Over a lifetime, 100% conversion to overt disease is expected. Based on these observations a new definition for T1DM has been proposed distinguishing three stages of the disease, not limited to the clinical onset (as mentioned in figure 1) (19):

- Stage 1: the presence of β cell autoimmunity as evidenced by the presence of two or more islet autoantibodies with normoglycemia and in absence of any symptoms,
- Stage 2: the presence of β cell autoimmunity with dysglycemia and no symptoms,
- Stage 3: onset of symptomatic disease.

Although this may help to identify persons at risk at an earlier stage, one should keep in mind that not all persons will develop the disease within the next five to ten years.

Both the innate immune system and the adaptive immune system are involved in this complex interplay leading to β cell death. The early detection of autoantibodies and careful follow-up of people with potential early stages of T1DM may help to better understand the ongoing process and subsequently facilitate the development of new drugs for the appropriate population to prevent further β cell destruction and overt disease.

Genetic predisposition

T1DM is a polygenic disease. Susceptibility and resistance to develop T1DM are first of all associated with genetic polymorphisms in the major histocompatibility complex within the HLA classes. The potential role of HLA variants in the susceptibility and resistance to infectious diseases is well described as they bind and present processed peptides derived from phagocytosis to the CD4+ T cells, triggering the specific adaptive immune response. The HLA haplotypes linked to the highest risk are the heterozygous HLA DR4-DQ8 and HLA DR3-DQ2. Differences between ethnicities in high risk and protective variants are observed. The protective variants may act through the inability to present the relevant antigens to the T helper cells. It is important to note the observation that the relationship between HLA class II genotypes and T1DM is mainly based on the development of islet cell autoantibodies or seroconversion. The time between detection of the autoantibodies and progression to clinical disease is not affected by these polymorphisms. Recent observations suggest a shift in genetic markers in newly diagnosed patients to less frequent HLA subtypes. More than fifty non-HLA genes are associated with type 1 diabetes as well. Some of these are involved in the immune reaction (INS, PTPN22 IL2RA, CTLA4, IFIH1, UBASH3A) whereas others contribute to the regulation of life/death or function of the β cells (ERBB3, PTPN2, CTSH, BACH2) (12). This suggests that β cell death may be the effect of very different processes, confirming the heterogeneity.

The environment

The incidence of T1DM continues to increase. This supports the implication of fast changing factors such as environmental factors as a

cause. Different observations support the importance of the environment. An interesting example is the huge increase in incidence in Poland over a short time span after the transition to Western Europe. Many changes in lifestyle occurred simultaneously. This has led to new hypotheses, for example the hygiene hypothesis which associates improved hygiene with an increase in diabetes incidence (in animal models a germ-free environment may increase the risk of developing diabetes) (20, 21). It may be linked to changes in the ongoing interaction (from birth onwards) between our microbiome and immune system. It may also reflect changes in nutrition, lifestyle, infections, etc. Another example is the change in incidence observed in migrating populations. When people migrate from a country of low incidence to a country with a high incidence, there tends to be an increase in T1DM incidence. Diabetes incidence shows a seasonal variation and a North-South gradient. Seasonal variation has been associated with viral infections—an increase in the number of new cases in association with viral infections has supported a viral cause of diabetes. Mumps, rubella and enteroviruses and more (recently even SARS-CoV2 virus infection) have been linked to the onset of the disease. However, only in a limited number of cases has the virus been detected in the pancreatic tissue of the newly diagnosed patient. Furthermore, the presence of a virus is not enough proof that it has caused the disease. It could be a bystander or accelerator of an ongoing process. Modes of delivery and infant feeding have been associated with the risk of diabetes. Children who have been vaginally delivered and/or breastfed show a reduced risk of developing diabetes. The exclusion of cow milk proteins appeared to have a positive impact in some populations, although this was not confirmed in the global TRIGR study (22). This may suggest a specific genetic background. One may also consider a role for the colonization and succession of the infant's microbiome and the interaction between the microbiome and the immune system. In zebrafish a conserved bacterial protein induces pancreatic β cell expansion, suggesting a role of the microbiome on the developing β cell mass (23). Weaning in rodents has demonstrated an effect on the β cell function (glucose responsiveness). Both observations suggest a role for interaction at the gut level early in life (14). Whether these factors play a role in the human remains to be investigated. Many more interesting and relevant observations have been reported, linking T1DM to climate, vitamin D, viral or other microorganism infections, lifestyle and dietary habits (20, 24). The timing and duration of exposure to these factors may determine their effect. Genetic predisposition or previous priming by earlier exposures can influence the outcome. These risk factors and more information on

when/how/in whom need to be collected to improve our understanding of the environmental factors and the disease process. T1DM is a heterogeneous disease with a single outcome: β cell destruction. Carefully designed studies are needed, with "out of the box thinking" to move forward and obtain a more complete picture of this complex disease.

Conclusion

The incidence of T1DM is increasing globally. This needs to be addressed at national and international levels to ensure that appropriate care can be provided. The pace of the increase suggests that environmental factors play a key role in this immune-mediated disease. In a person with a genetic predisposition, exposure to one or more environmental factor(s) can lead to immune-mediated β cell destruction, necessitating lifelong insulin treatment. Despite huge progress in our understanding of T1DM, many gaps in our knowledge persist and further research to understand the pathogenesis of this chronic disease is needed.

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References

1. IDF Atlas 2019. https://diabetesatlas.org/en/resources/
2. ISPAD Clinical Practice Consensus Guidelines 2018. Pediatric Diabetes 2018; 19 (Suppl. 27).
3. Last JM. Dictionary of epidemiology. 4th ed. New York: Oxford University Press; 2001. p. 61
4. Drolet KB and Johnson. Journal of Biomedical Informatics 2008. 41: 1009–1020.
5. LaPorte et al. Capture Recapture and multi record systems estimation. History and theoretical development. Am J Epidemiol 1995. 142: 1047-58.
6. Patterson et al. Trends and cyclical variation in the incidence of childhood type 1 diabetes in 26 European centres in the 25 year period

1989–2013: a multicentre prospective registration study. Diabetologia 2019. 62: 408-417.
7. Dabelea et al. Incidence of diabetes in youth in the United States. JAMA 2007. 297:2716–2724.
8. Hamman et al. The SEARCH for Diabetes in Youth Study: Rationale, Findings, and Future Directions. Diabetes Care 2014.. 37(12): 3336–3344. DOI: 10.2337/dc14-0574
9. Rogers et al. Fluctuations in the incidence of type 1 diabetes in the United States from 2001 to 2015: a longitudinal study. BMC Medicine 2017. 15:199. DOI 10.1186/s12916-017-0958-6
10. Weng et al. Incidence of Type 1 diabetes in China 2010-2013. BMJ 2018. 360: 5295. DOI: 10.1136/bmj.j5295
11. Mobasseri et al. Prevalence and incidence of type 1 diabetes in the world in systematic review and meta analysis. Health Promotion Perspectives 2020. 10(2) 98–115.
12. Ilonen J, Lempainen J, Veijola R. The heterogeneous pathogenesis of type 1 diabetes. Nature Reviews 2019. 15: 635–650. DOI:10.1038/s41574-019-0254
13. Jorgensen et al An Illustrated Review of Early Pancreas Development in the Mouse. Endocrine Reviews 2007. 28(6):685–705. doi: 10.1210/er.2007-0016
14. Jacovetti et al. Postnatal b-cell maturation is associated with islet-specific microRNA changes induced by nutrient shifts at weaning. Nature Communications 2015. DOI: 10.1038/ncomms9084
15. Smink AM and de Vos P. Therapeutic Strategies for Modulating the Extracellular Matrix to Improve Pancreatic Islet Function and Survival After Transplantation Current Diabetes Reports 2018. 18: 39. DOI:10.1007/s11892-018-1014-4
16. Gao et al. Inhibition of Toll-Like Receptor Signaling as a Promising Therapy for Inflammatory Diseases: A Journey from Molecular to Nano Therapeutics. Front. Physiol 2017. 8:508. DOI:10.3389/fphys.2017.00508
17. Rewers M, Ludvigsson J. Environmental risk factors for type 1 diabetes. Lancet 2016. 387: 2340–2348. DOI:10.1016/S0140-6736(16)30507-4
18. Arribas-Layton et al. Hybrid Insulin Peptides Are Recognized by Human T Cells in the Context of DRB1*04:01. Diabetes 2020. 69:1492–1502. DOI:10.2337/db19-0620
19. Insel et al. Staging Presymptomatic Type 1 Diabetes: A Scientific Statement of JDRF, the Endocrine Society, and the American Diabetes Association. Diabetes Care 2015. 38:1964–1974.

20. Norris et al Type 1 diabetes: early life origins and changing epidemiology. Lancet- Diabetes –Endocrinol.2020. 8: (3) 226–238.
21. Wen et al. Innate immunity and intestinal microbiota in the development of Type 1 diabetes. Nature. (2008); 455(7216): 1109–1113. DOI:10.1038/nature07336
22. Knip et al. Effect of Hydrolyzed Infant Formula vs Conventional Formula on Risk of Type 1 Diabetes: The TRIGR Randomized Clinical Trial. JAMA 2018.319(1):38-48. DOI:10.1001/jama.2017.19826.
23. Hill et al. A conserved bacterial protein induces pancreatic beta cell expansion during zebrafish development. eLife 2016;5:e20145. DOI:10.7554/eLife.20145
24. Chen et al. Climates on incidence of childhood type 1 diabetes mellitus in 72 countries. Scientific Reports 2017. 7: 12810. DOI:10.1038/s41598-017-12954-8

SECTION 1 CHAPTER 2

DIABETIC KETOACIDOSIS: PROPER MANAGEMENT TO AVOID MISTAKES

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Diabetic ketoacidosis (DKA) is the most serious complication that can occur at the time of clinical onset of type 1 diabetes in children. The frequency of DKA is highly variable between countries, ranging from 80% to 12.8% (1), and despite the new progresses in diabetes management, no reduction through time has been reported. DKA is associated with increased morbidity and mortality (2), unsatisfactory long-term metabolic control (3), anomalies in brain imaging, low cognitive scores even after only one moderate or severe DKA episode (4), and high health care costs for DKA (5). This evidence should help as a call to promote early detection of diabetes in order to prevent DKA in children and adolescents worldwide (6). DKA is also a major problem in children and adolescents with established type 1 diabetes, with significant morbidity, mortality (7), and associated costs to patients, families, and health care systems. This chapter summarizes clinical and laboratory investigations and proper management to avoid errors that occur both at diagnosis of diabetes and in children and adolescents with established diabetes.

DKA definition and diagnostic criteria

Diabetic ketoacidosis (DKA) is combined with the absolute or relative insulin deficiency and increased levels of counter-regulatory hormones. This condition induces hypercatabolism (increased glycogenolysis and gluconeogenesis), reduced peripheral use of glucose, increased lipolysis and ketogenesis with hyperglycemia and consequent osmotic diuresis and dehydration, loss of electrolytes, hyperosmolarity, ketonemia and metabolic acidosis. The DKA clinical presentation is caratterized by serious dehydration (due to the imbalance between polyuria and polydipsia), tachycardia, tachypnea, Kussmaul breathing, acetone breath, nausea, vomiting, abdominal pain, blurred vision, confusion, drowsiness, progressive reduction of the level of consciousness and coma (2).

The biochemical criteria that define DKA are (2):

- Hyperglycemia (blood glucose > 11 mmol/L [>200 mg / dL])
- Venous pH <7.3 or serum bicarbonate <15 mmol/L
- Ketonemia (blood ß-hydroxybuyrate ≥3 mmol/L) or moderate or large ketonuria (8)

Summary of recommended procedures to manage DKA

Clinical and Biochemical assessments

- Confirmation of diagnosis of DKA (medical history, clinical examination, hyperglycemia, glycosuria, ketonuria)
- Evaluation of patient's weight, level of dehydration and level of consciousness (Glasgow coma scale)
- Biochemical monitoring (azotemia, EGA, glycemia, serum creatinine, electrolytes, osmolarity, CBC, glycosylated hemoglobin and, if available, blood beta hydroxybutyrate)
- ECG monitoring

Recommended procedures for treatment

Table 1 summarizes the main points for DKA management. Children with DKA should be managed by a specialized pediatric team properly trained for its management, composed of at least one senior pediatric diabetologist and supported by specialized nursery staff and other healthcare professionals involved in diabetes education, such as dietitians and

psychologists (2). The restoration of the circulating volume and the replacement of metabolic balance are the main goals of therapy.

Table 1. Summary of recommendations for DKA management

Hints for DKA management
• Manage the patient with severe DKA only if you have an expertise in treatment • Start with rehydration • Be careful not to overload liquids and do not use dilutions lower than hemiphysiological • Do not give insulin bolus • Do not be in a hurry to rebalance • Beware of blood sugar falling too fast • Monitor for signs of ketoacidosis complications and treat them right away • Vomiting in a patient with diabetes should first suggest a DKA onset before gastroenteritis

Rehydration

The initial use of rehydration reduces the dehydration-induced insulin resistance, decreases glycemia, avoiding too rapid falls both in glycemia and in plasma osmolarity, increases glucose renal excretion and dilutes counter-regulatory hormones (2). The addition of 5% glucose solution is suggested if blood glucose values fall to 250–300 mg/dL, 10% glucose solution is indicated if blood glucose falls rapidly (>90 mg/dL/h).

Insulin treatment

An intravenous infusion of regular insulin is recommended one hour after rehydration at a dosage from 0.1 to 0.025 U/kg/h, with wide variability in individual response (2). The blood glucose fall should not exceed 70–100 mg/dL/h. The solution with regular insulin (1 UI/cc or 0.5 UI/cc) must be replaced every 24 hours. As oral feeding is restarted and DKA is solved, subcutaneous insulin therapy should be started.

Potassium

The reintegration of potassium is necessary regardless of its blood concentration and should be initiated with insulin therapy, because children

with DKA have a total body potassium impairment on the order of 3-6 mmol/kg (2). If hyperkalemia is present, potassium supplementation should be delayed until diuresis resumes. Depending on potassium levels and the degree of ketoacidosis, a dose of 20 or 40 mEq/L of potassium replacement is indicated. The maximum dose should not be more than 0.5 mEq/kg/h (2).

Sodium bicarbonate

Bicarbonate supplementation should be reserved for cases of resistant and persistent acidosis (pH <7.0 and bicarbonates <5 mEq/L), because acidosis corrects spontaneously with rehydration alone and/or initiation of insulin therapy (2).

Complications of DKA

Cerebral edema is the most frequent and disabling complication of DKA, which in 0.6–5% of cases is associated with an unfavorable neurological outcome, while mortality ranges from 21 to 24% (10). The hyperglycemic hyperosmolar state is another serious complication of DKA (10); it is characterized by a very high concentration of glucose in the blood and hyperosmolarity without significant ketosis. Hypokalemia, hypocalcemia, hypomagnesemia, severe hypophosphatemia especially in the hyperglycemia hyperosmolar state, hypochloremic alkalosis, thrombosis, rhabdomyolysis and hypoglycemia are other life-threatening complications of DKA.

Cerebral edema, practical hints on the diagnosis and treatment

Early diagnosis, careful clinical monitoring and appropriate treatment are essential to prevent adverse outcomes. Signs and symptoms include the onset or worsening of headache following the start of the treatment, focal neurological deficits, reduction in O2 saturation; in addition, the Cushing triad may occur (bradycardia, rising blood pressure and Cheyne-Stokes breathing) (2). Bedside evaluation allows clinicians to define a diagnosis according to diagnostic criteria, major criteria and minor criteria (Table 1). The diagnosis of ketoacidosis can have a sensitivity of 92% and a false positivity rate of 4% in the case of presence two major criteria or one major and two minor criteria (13). The administration of cerebral edema is summarized in Table 2.

Table 2. Criteria for clinical diagnosis of cerebral oedema

Diagnostic criteria	Major criteria	Minor 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)	• Altered mentation, confusion, fluctuating level of consciousness • Sustained heart rate deceleration (decrease more than 20 beats per minute) not attributable to improved intravascular volume or sleep state • Age-inappropriate incontinence	• Vomiting • Headache • Lethargy or not easily arousable • Diastolic BP >90 mm Hg • Age <5 years

DKA at the clinical diagnosis of diabetes

The frequency of DKA at the diagnosis of type 1 diabetes shows a huge variation among regions (7) with differences ranging from 80% in the United Arab Emirates and Romania to 12.8% in Sweden, Canada and the Slovak Republic. A recent population-based study (7) reporting results of temporal trends across thirteen countries of three continents highlighted a high prevalence of children presenting with DKA at diagnosis and a slight increasing trend in the prevalence of DKA at diagnosis of type 1 diabetes during 2006–2016. The main risk factors associated with DKA at type 1 diabetes onset (1,7,9) are age under five years, lower socioeconomic status, ethnic minority status, and living in a country with a lower prevalence of type 1 diabetes.

DKA in children with established diabetes

Most cases of DKA occur in patients already diagnosed with diabetes (7). Around half of hospitalizations could be avoided by better adherence to self-

medication and improved outpatient treatment (7). Insulin omission and incorrect management of the insulin pump are the major causes of DKA in children with diabetes (2). The incidence of DKA in patients with diabetes shows a large variation ranging from 1.4 to 15 episodes per 100 patients (7). The main risk factors include peripubertal and adolescent age, high HbA1c, previous DKA episodes, female gender, high insulin dose, issues in family and school, eating disorders, psychiatric disorders, alcohol abuse, limited access to medical services, and gastroenteritis with many episodes of vomiting. Since almost all episodes of DKA are due to voluntary or non-voluntary omissions of insulin injections, the main causes of omission should be considered for the prevention of DKA:

- Incorrect insulin administration;
- Difficulties in taking their insulin injection in pump users when hyperglycemia and hyperketonemia occur;
- Pump technical issues due to bubbles in the cannula, tunnelling, pump blockage;
- Psychological causes of insulin omission (for example eating disorders in adolescents, the expression of unpleasant home situations, refusal or depression caused by the chronic disease);
- Difficulties in diabetes management while treating infections or other diseases.

Diabetes education is the cornerstone of DKA prevention. Intensifying structured diabetes education appears to be a way to prevent the recurrence of episodes, as it is effective in improving metabolic control (18). Educational training for patients and their families should be age-appropriate, guaranteed by quality and always available for children's needs (18).

How to avoid false steps during DKA management

DKA management requires specific consecutive steps to promote a rapid diagnosis and proper approach to treatment to avoid complications. The responsibility of treatment has to be shared with a senior pediatric diabetologist in order to prevent false steps. The most common mistakes in DKA management can be summarized as followed:

1. The underestimation of the symptoms of diabetes and DKA onset, which may lead to a delayed diagnosis.
2. The lack of communication of suspected DKA to a senior pediatric diabetologist. Children and adolescents with DKA diagnosis should

be sent to a pediatric intensive care unit or an expert center for diabetes and DKA treatment (2).

3. The treatment of the child with DKA without defining the DKA severity level (by diagnostic exams and laboratory data, pH level), which is fundamental in order to assess the risk of developing cerebral oedema in a short time (2).
4. Inaccurate or delayed treatment and a lack of monitoring. These are the basis of the unfavorable events, which lead to increased mortality, morbidity and management costs (find further indications in Table 3).
5. The omission of screening for DKA risk factors in children and adolescents with diabetes. This screening is important to prevent further DKA episodes (7,16): critical situations should be recognized and identified during ambulatory periodical visits in order to correct them as soon as possible and to support the child with diabetes and their family.
6. Discharging the patient, once recovered from DKA, without knowing the cause of insulin omission in children with established diabetes (psychological issues, problems with pumps, incorrect insulin administration).
7. Disregard of a focused education or re-education about diabetes management, after DKA recovery hospitalization (18). Intensification of structured diabetes education seems to be a way to prevent the recurrence of episodes, as it is effective in improving metabolic control (18).

Ultimately, understanding possible errors increases the level of accuracy in managing DKA and decreases the risk of complications.

Table 3. Recommended procedures and treatment of cerebral oedema

Management of Cerebral oedema
• Fluid restriction • Mannitol: 0.5–1 g / Kg i.v. infusion (20 min), it can be repeated if necessary, after 30 minutes • Hypertonic saline solution (3%) 2.5–5 mL/kg in 30 minutes (alternatively, if there was no response to mannitol) • Keep the patient in a semi-sitting position • Evaluate intubation and ventilation

References

1. Usher-Smith, J. A., et al. "Variation between countries in the frequency of diabetic ketoacidosis at first presentation of type 1 diabetes in children: a systematic review." *Diabetologia* 55.11 (2012): 2878-2894.
2. Wolfsdorf JI, Glaser N, Agus M, et al. ISPAD Clinical Practice Consensus Guidelines 2018: Diabetic ketoacidosis and the hyperglycemic hyperosmolar state. *Pediatr Diabetes*. 2018;19 Suppl 27:155-177. doi:10.1111/pedi.12701
3. Duca LM, Wang B, Rewers M, Rewers A (2017) Diabetic Ketoacidosis at Diagnosis of Type 1 Diabetes Predicts Poor Long-term Glycemic Control. Diabetes Care 40:1249-1255.
4. Aye T, Mazaika PK, Mauras N, Marzelli MJ et al (2019) Impact of Early Diabetic Ketoacidosis on the Developing Brain. Diabetes Care 42:443-449
5. Shrestha SS, Zhang P, Barker L, Imperatore G (2010) Medical expenditures associated with diabetes acute complications in privately insured U.S. youth. Diabetes Care 33:2617-2622. doi: 10.2337/dc10-1406
6. 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 May;146(5):688-92. doi: 10.1016/j.jpeds.2004.12.041.
7. Maahs DM, Hermann JM, Holman N, et al. Rates of diabetic ketoacidosis: international comparison with 49,859 pediatric patients with type 1 diabetes from England, Wales, the U.S., Austria, and Germany. Diabetes Care. 2015;38(10):1876-1882.
8. Sheikh-Ali M, Karon BS, Basu A, et al. Can serum beta-hydroxybutyrate be used to diagnose diabetic ketoacidosis? Diabetes Care. 2008;31(4):643-647
9. Cherubini V, Grimsmann JM, Åkesson K, et al. Temporal trends in diabetic ketoacidosis at diagnosis of paediatric type 1 diabetes between 2006 and 2016: results from 13 countries in three continents [published online ahead of print, 2020 May 8]. *Diabetologia*. 2020; 10.1007/s00125-020-05152-1. doi:10.1007/s00125-020-05152-1
10. Watts, Wendy, and Julie A. Edge. "How can cerebral edema during treatment of diabetic ketoacidosis be avoided?" *Pediatric diabetes* 15.4 (2014): 271-276.
11. Zeitler P, Haqq A, Rosenbloom A, Glaser N. Hyperglycemic hyperosmolar syndrome in children: pathophysiological considerations and suggested guidelines for treatment. J Pediatr. 2011;158(1):9-14,