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Contents

Thrice Monthly Volume 10 Number 30 October 26, 2022

REVIEW

MINIREVIEWS

ORIGINAL ARTICLE

Retrospective Cohort Study

Retrospective Study

Observational Study

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 30 October 26, 2022

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 30 October 26, 2022

Contents

World Journal of Clinical Cases

Thrice Monthly Volume 10 Number 30 October 26, 2022

Contents

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MINIREVIEWS

Ketosis-prone diabetes mellitus: A phenotype that hospitalists need to understand

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Abstract

Diabetes has been classified mainly into types 1 and 2. Some type 2 diabetes patients, when developing ketosis, have been labeled as having atypical diabetes. Lately, syndromes of ketosis-prone diabetes, primarily in patients who we previously classified as type 2 diabetics, have emerged, and calls are being made to even reclassify diabetes. This mini-review will extensively deal with the historical, molecular, phenotypical, and clinical basis of why ketosis-prone diabetes is different than the traditional principles of type 1 and 2 diabetes and should be classified as such. Clinicians, especially those who are not diabetologists or endocrinologists, as well as hospitalists, intensivists, and primary care providers, will greatly benefit from this review.

Key Words: Diabetic ketoacidosis; Diabetes; Diabetes prone ketosis; Ketosis; Acidosis

Core Tip: Diabetes is one of the most common chronic diseases globally. Ketosis-prone diabetes is now being increasingly recognized. The majority of patients with ketosis-prone diabetes are being diagnosed at the time of their presentation as diabetic ketoacidosis. Its presentation is unique, and it has components of both type 1 and type 2 diabetes. This article helps the clinician understand the pathophysiology of this phenotype.

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INTRODUCTION

The earliest record of diabetes was described on the Ebers Papyrus. An Egyptian document is believed to be from approximately 1500 before Christ (BC)[1]. At present, diabetes is estimated to affect over 420 million people worldwide, with expectations that this number will rise to over 500 million by the end of this decade. According to the Report of the global Diabetes Summit, co-hosted by the World Health Organization and the Government of Canada[2-4].

Diabetes is broadly categorized as diabetes mellitus, diabetes insipidus, and gestational diabetes, with diabetes mellitus and diabetes insipidus having further subcategorizations of type 1 and type 2. Gestational diabetes is defined as glucose intolerance that is first discovered during pregnancy. It affects 2%-5% of pregnant women and risk factors include a strong family history of diabetes and obesity. Diabetic ketoacidosis (DKA) can develop as a life-threatening complication for both the mother and the fetus. The incidence of occurrence of DKA ranges from 0.5%-10.0% in gestational diabetes. Its pathophysiology can be characterized by insulin resistance and respiratory alkalosis. Considered a physiologic mechanism to preserve glucose for the fetus, insulin sensitivity for the mother is decreased. Furthermore, increased alveolar ventilation in the mother results in respiratory alkalosis that is offset by increased bicarbonate secretion which can lead to ketoacidosis. Additionally, the fetus uses a significant amount of maternal glucose, which leads to decreased fasting glucose of the mother, which in relation to the insulin deficiency leads to increased production of free fatty acids that are converted to ketones in the liver[5].

Different forms of diabetes have been increasingly recognized in the last few decades. Some published work includes the characterization of ketosis-prone diabetes (KPD), also called ketosis-prone type 2 diabetes mellitus (KPDM), Flatbush diabetes, idiopathic type 1 diabetes, or atypical diabetes[6,7]. KPD is unique in that its presentation and the clinical course contain elements of both types 1 and 2 diabetes mellitus[6].

Here we aim to review the contemporary literature and outline the background, molecular, phenotype, and clinical basis of why this ketosis-prone diabetes is different and must be classified as so to benefit clinicians. This review provides the current understanding of KPD with recent literature and can serve as a resource for medical professionals during their clinical decision-making.

BACKGROUND AND HISTORY OF KPD

KPD, commonly known as "Flatbush Diabetes", refers to a hybrid form of diabetes that has various characteristics of type 1 diabetes and type 2 diabetes[8]. Type 1 diabetes is caused by the autoimmune loss of insulin-producing beta cells in the pancreas. Patients become dependent on insulin as a result of this, and the lack of natural insulin makes patients vulnerable to DKA. On the other hand, type 2 diabetes differs from type 1 diabetes because it is caused by insulin resistance in the body in elderly patients, which leads to beta-cell burnout over time[5]. KPD is a type 2 diabetes-like illness that involves DKA but occurs later in life and can regain beta cell activity, similar to type 2 diabetes. KPD has similar biochemical and acid-base parameters to type 1 diabetes[5].

KPD has been recognized as a medical condition since 1984. Most of the early studies were focused on African American individuals but have shifted to sub-Saharan African, Hispanic, and Asian populations in recent years. Studies show that Blacks and Hispanics account for 20%-50% of KPD patients in the United States[8]. KPD predominantly affects African American men who are overweight, have a family history of KPD, and have a low prevalence of autoimmune markers[8].

KPD is believed to commence with ketoacidosis in people who lack autoimmune markers, islet cell antibodies, and glutamic acid decarboxylase (GAD) autoantibodies[9]. People dealing with these conditions require insulin replacement, but it may be possible for them to end insulin treatment in the

future, depending on the progress of treatment and the condition of the individual. This unusual condition that does not fit traditional categories is described as KPD[9]. Furthermore, at the initial stage of diagnosis, many individuals will have impaired insulin secretion in addition to complications such as ketosis or DKA[10]. Studies have found that up to 75% of people who have KPD had DKA at the diagnosis level. The classification of KPD is dependent on testing for GAD, anti-islet cell antibodies, and fasting C-peptide levels[8].

PATHOPHYSIOLOGY

KPD departs from the classical presentations of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). Whereas T1DM is the autoimmune destruction of pancreatic B-cells, and T2DM is characterized by insulin resistance and B-cell dysfunction, KPD has unique pathogenesis. It lacks the immunologic markers to distinguish it as T1DM but also lacks the insulin requirements to be considered T2DM. Considered the third type of diabetes, there are four classifications for KPD: The American Diabetes Association (ADA) classification, the modified ADA system, the BMI system, and the Aß system[11]. The Aß system distinguishes four subgroups based on the presence/absence of autoantibodies and ß cell function. The four subgroups include autoantibodies present beta-cell function absent (A+ß-), autoantibodies present beta-cell function present (A+ß+), autoantibodies absent beta-cell function absent (A-ß-), and autoantibodies absent beta-cell function present (A-ß+) (Table 1).

Differentiating A+ß- from A+ß+ KPD allows exploration into autoimmune pathways that lead to distinct patterns of beta-cell loss. The more moderate clinical course of A+ß+ KPD patients compared with A+ß- KPD patients may be related in part to epitope-specific antibodies to the 65-kDa isoform of glutamic acid decarboxylase (GAD65)[12]. Furthermore, a specific amino-terminal epitope defined by monoclonal antibody DPD is correlated with a higher beta-cell functional reserve and was associated with the milder A+ß+[13]. However, the mechanisms that create the autoantibody specificity and result in variable beta-cell functional reserve remains to be known. In healthy individuals, GAD65 antibodies (GAD65Ab) are present in the sera but are masked by anti-idiotypic antibodies[13]. Masked GAD65Ab specific for the epitope DPD is strongly associated with preserved beta-cell function among patients with KPD[13]. Additionally, circulating insulin DNA is a biomarker for A+ß+ KPD patients, though absent in A+ß- KPD patients[14].

A-ß- KPD is characterized by beta cell failure and undetectable autoimmunity. Some A-ß- KPD patients may be misclassified as "A-" because of a decline in autoantibody titers over time though a decline in antibody titer is less likely as GAD autoantibodies are reportedly durable[11]. Most A-ß- KPD patients have relatives with a strong family history of diabetes, which suggests a familial trait and defects in genes responsible for beta-cell development and function[15]. Significant variants in the genes encoding the key beta-cell transcription factors hepatocyte nuclear factor-1-alpha (HNF1a), PAX-4, pancreas-duodenum homeobox-1 (PDX-1), TCF1, PAX-4, PDX-1, are enhanced in A-ß- KPD which may contribute to a monogenic etiology for some patients with the A-ß- phenotype[15].

Finally, the A-ß+ phenotype is characterized by partially reversible beta-cell dysfunction, which may be due to metabolic, genetic, or viral etiologies[16]. Dysfunctional pathways of branch chain amino acid (BCAA) and arginine/citrulline metabolism in A-ß+ patients were discovered by a plasma metabolomics survey[10]. A-ß+ patients had impaired ketone oxidation and fatty acid oxidation, resulting in increased leucine catabolism which highlights an aberrant mechanism for energy production and ketosis in A-ß+ KPD[10]. It was also found that A-ß+ patients in acute episodes of DKA had impaired catabolism and accelerated fatty acid conversion of ketones, similar to the T1DM patients [17].

CLINICAL PRESENTATION

The clinical presentation of KPD follows a similar constellation of symptoms across those affected. The majority affected are considered to be of middle age, are classified as obese, and have recently received a diagnosis of diabetes mellitus[18]. These individuals present abruptly with DKA and classically follow a similar history prior to presentation (increased urination, increased thirst, and associated weight loss), with a predilection of men *vs* women being affected by the condition[18]. Of those who present with KPD, they classically do not have the standard phenotypic expression of autoimmune type I diabetes, which is what one may expect in a patient presenting with DKA. That is, many present with features similar to type 2 diabetes, including the previously listed symptoms of obesity and diagnosis of diabetes in middle age, in addition to strong family history, hypertension, and beta-cell functional reserve[19]. Regarding findings obtained in labs, these individuals present with severe hyperglycemia, ketosis +/- acidosis, and will commonly have negative panels for autoantibodies against beta-cell antigens[20], further distinguishing this pathology from type 1 or type 2 diabetes mellitus. Certain ethnicities are more commonly associated with KPD as well. In a 2004 study performed by Maldonado *et al*[21], 321 patients were interviewed over a span of 3.5 years, in which information was collected to analyze group

Table 1 Aß system for four ketosis-prone diabetes subgroups based on the presence/absence of autoantibodies and ß cell function

	A+: Anti-GAD65 and IA-2 antibodies present in serum	A-: Anti-GAD65 and IA-2 antibodies not present in serum
ß+: Fasting serum C-peptide concentration greater than or equal to 1 ng/mL (0.33 nmol/L) or a peak serum C-peptide response to glucagon greater than or equal to 1.5 ng/mL (0.5 nmol/L)	A+ß+: Autoantibodies present, beta cell function present	A-ß+: Autoantibodies absent, beta cell function present
ß-: Fasting serum C-peptide concentration is less than 1 ng/mL (0.33 nmol/L) or a peak serum C-peptide response to glucagon less than 1.5 ng/mL (0.5 nmol/L)	A+ß-: Autoantibodies present, beta cell function absent	A-ß-: Autoantibodies absent, beta cell function absent

GAD65: Glutamic acid decarboxylase; IA-2: Anti-islet tyrosine phosphatase 2.

differences. They found that 44% of individuals were African American, 40% were Hispanic, and 16% were Caucasian.

Finally, the course of this pathology can follow a similar timeline of events. In a review performed in 2006 by Umpierrez *et al*[18], they collected data from biomedical literature from 1966-2005 and concluded that individuals with KPD who present with an acute error of insulin production will usually have near-resolution of symptoms within several weeks of insulin treatment and later will progress to a nearly normoglycemic state that can last for months to years. This unique presentation and course of events further help to distinguish this subtype of diabetes from others and can help tailor the approach to treatment for patients.

Several studies have found that coronavirus disease 2019 (COVID-19) infection triggers the onset of KPD, but the exact mechanism is still unknown. Further investigation is needed to understand the distinct relationship between COVID-19 and KPD. A possible theory is that COVID-19 infection triggers changes in the human body that result in insulin resistance or cause pancreatic beta cells to be destroyed. Another possibility is that antibodies against COVID-19 can affect the role of endogenous insulin in the body[22].

CLINICAL MANAGEMENT OF KPD

Management of KPD is divided into three stages: acute management of DKA, evaluation of the KPD subgroup after DKA resolution, and long-term health maintenance. KPD patients who present with DKA should be managed according to standard care methods for DKA, regardless of subtype. These inpatient protocols include aggressive fluid replacement to restore circulatory volume, regular IV insulin therapy, evaluation and treatment of precipitating factors, correcting the hyperglycemia, stabilizing the electrolyte disorders, and alleviating ketoacidosis[23]. This treatment plan should be followed with a transition from IV insulin therapy to subcutaneous regimens[23]. Additionally, all KPD patients should be given a discharge plan that provides 24-h insulin coverage. Insulin may be discontinued only after a thorough evaluation and accurate classification of the KPD subtype and assessing the patient's predictive factors. This evaluation should be performed at the first outpatient visit following discharge from the hospital, preferably after 1-3 wk.

Evaluation of the KPD subgroup is performed *via* assessment of beta-cell secretory reserve and beta-cell immunology (Table 1). This evaluation is usually performed at least 1-3 wk after the resolution of DKA to minimize the effects of glucose toxicity and beta-cell desensitization on the diagnostic parameters. The beta-cell secretory reserve is measured with C-peptide levels during a fasted state or after glucagon stimulation, and it is a strong predictor of long-term glycemic control[24] and insulin discontinuation[25]. Patients are classified as ß+ if they have adequate beta-cell reserve with a fasting serum C-peptide concentration greater than or equal to 1 ng/mL (0.33 nmol/L) or a peak serum C-peptide response to glucagon greater than or equal to 1.5 ng/mL (0.5 nmol/L)[11]. Patients are classified as ß- if they have inadequate beta-cell reserve with a fasting serum C-peptide concentration is less than 1 ng/mL (0.33 nmol/L) or a peak serum C-peptide response to glucagon less than 1.5 ng/mL (0.5 nmol/L)[11]. This classification scheme is used due to its high accuracy and predictive value[26]. Quantitative assessment of beta-cell auto-antibodies is also valuable for this clinical evaluation, especially in patients with the A+ß+ KPD phenotype. The serum autoantibodies measured include anti-glutamic acid decarboxylase (GAD65) and anti-islet tyrosine phosphatase 2 (IA-2), and increased accuracy of this classification is also often done by measuring serum titers of autoantibodies to the zinc transporter 8 (ZnT8) antigen[11]. Patients are then classified as A+ or A- based on the presence of a significant number of autoantibodies.

Once the patient has been classified with a KPD subtype, began on appropriate therapy, and been assessed for risk factors for subsequent ketotic episodes, the standard protocol for diabetes management should be followed for long-term management of KPD. In addition to other forms of diabetes mellitus,

all subtypes of KPD should be managed with lifestyle changes, including appropriate diet and adequate exercise. A registered dietician is recommended, along with a diabetic educator as needed. Additional measures include weight loss in obese patients, smoking cessation, if applicable, and physical activity multiple times a week[27]. Insulin discontinuation in ß+ can be achieved by evaluating for factors such as new diagnosis of diabetes, older age at onset, and high beta-cell secretary reserve. The presence of beta-cell autoantibodies can also be used to determine beta-cell function in the future and insulin discontinuation. Although KPD patients with autoantibodies tend to have a lower beta-cell function at the time of diagnosis and at follow-up, approximately 50% of A+ß+ KPD patients maintain a long-term beta-cell secretory reserve[28]. Due to the unpredictability of beta-cell reserve, A+ß+ KPD patients can also come off insulin therapy initially but require close monitoring for at least two years. HLA subtyping is useful in predicting long-term outcomes because it can elucidate those patients who will most likely have a more severe experience.

CONCLUSION

Syndromes of ketosis-prone diabetes have been described in the literature, and much has been learned about the condition. However, much is still unknown about the etiology, treatment, and why it affects certain ethnicities more than others. The wide range of presentations and classifications poses an obstacle to proper preventative and clinical management of KPD since the pathophysiology of each subtype is different. The role of genetics and genotyping in KPD has yet to be elucidated, but further understanding of both the etiology and risk factors of KPD will guide clinicians in determining the most effective therapies for the management of the condition and the prevention of ketosis.

FOOTNOTES

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