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Review Article

TYPE II DIABETES MELLITUS AND MANAGEMENT OF ISOLATED HYPERGLYCEMIA: A REVIEW

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ABSTRACT

Type II Diabetes mellitus (T2DM) is the most common of two types of Diabetes disease. T2DM is a metabolic disease characterized mainly by insulin resistance, reduction of insulin secretion, and hyperglycemia. T2DM is a major public health cause of concern not only by the increase in morbidity and mortality associated with patients with the disease, but also by the significant reduction in quality of life and productivity among the economically active population. Isolated hyperglycemia refers to patients with T2DM with normal fasting plasma glucose and no ketoacidosis. With the rise of T2DM and the presence of hidden symptoms, it is vital to determine a diagnostic sequence, blood-glucose control with sulfonylureas or insulin, and diet and exercise.

Keywords: Type II Diabetes mellitus, Insulin resistance, Hyperglycemia, Hyperinsulinism, Polydipsia, Polyuria, Polyphagia

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INTRODUCTION

T2DM is the most common of two types of Diabetes disease and is considered a global pandemic [1]. Diabetes is classified in type 1 and 2, and more than 90% of patients with diabetes have T2DM [2]. T2DM implies costs for governments directly, indirectly, and intangibly. Direct medical costs represent the burden in medicine and personnel to attend the patient. Indirect costs are due to labor reduction in economic active population, costs associated with health insurance and medical visits. Intangible costs are due to the behavioral changes in a patient and associated productivity reductions [3]. Hyperglycemia is the peak of glucose after loading glucose to the body. Isolated hyperglycemia in patients with T2DM refers to patients with a normal fasting plasma glucose level without ketoacidosis. Detecting glucose abnormalities early and preventing progression from prediabetes to diabetes may be crucial, since hyperglycemia duration could predict adverse outcomes [4].

Among the clinical features of T2DM, the patient may show: Hyperglycemia [5] (thirst, polyuria, weight loss, and blurry vision), a random blood glucose value of 200 mg/dL (11.1 mmol/L) or higher, insulin deficiency (pancreatic beta cell failure) [6], increased gluconeogenesis, glycogenolysis, dehydration [7-9], polyuria, polydipsia, osmotic diuresis [10], compensatory thirst weight loss, sweet cravings, glycosuric calorie loss, and inadequate glucose utilization, muscle pain, and abdominal discomfort [11], lactic acid accumulation, hypokalemia, electrolyte/acid-base derangements, metabolic alkalosis and/or acidosis [12], electrolyte disturbances, and formation of ketone bodies (ketogenesis) [13,14].

A number of screening tests are available, such as a glycosylated hemoglobin test (A1C), fasting plasma glucose, or a two-hour oral glucose tolerance test (OGTT) [15]. A1C 2 test is used to confirm diabetes mellitus in patients with the classic symptoms of hyperglycemia [16]. Both tests can successfully identify asymptomatic cases of diabetes; however, there is a debate about which test is optimal for screening [17]. Some patients with type 2 diabetes also have symptoms of hyperglycemia and blood glucose levels above ≥200 mg/dL [18].

Hyperglycemia is the high level of sugar in the blood triggered by insulin deficiency. Isolated hyperglycemia, with glycemic greater than 200 mg/dl usually detected during control tests or capillary blood glucose, is not accompanied by other metabolic problems neither with acidosis or hyperosmolarity [19]. Although a recent review shows the benefits and harms of intensive glycemic control in patients with T2DM [20], little is known about the control and management protocols for isolated hyperglycemia. This review provides a systematic and comprehensive summary of the body of knowledge about T2DM and early warning signs in patients without prediabetes, but in which management of isolated hyperglycemia is needed.

EPIDEMIOLOGY

T2DM is more common in older adults than in any other population. However, its incidence increases among young adults and children due to increased incidence of obesity, sedentary lifestyle, and inadequate diet [21].

The international diabetes federation, IFD, produces a Diabetes Atlas every 2 years. In its ninth edition of 2019, it is estimated that 463 million adults between 18 and 70 years of age have diabetes worldwide. Furthermore, IFD estimates that in 2025 T2DM will exceed 500 million [22,23].

In South and Central America and the Latino community of the United States, the levels of T2DM are worryingly high, with an estimated 31.6 million people between the ages of 18 and 79 having diabetes, and affecting disproportionately more women than men in all group ages (Fig. 1). A total of 9.4% of people between 18 and 79 years have T2DM, globally. However, the estimated prevalence and number of people with high blood glucose surpasses the 62 million. Therefore, it is worrying that 41.9% are not diagnosed with the disease [24].

About 80% of these people live in urban areas in middle-income countries. The region is also the fifth country with the most people with diabetes. In Brazil, 16.8 million people are living with T2DM. Furthermore, the disease's prevalence increases as the individual's age increases; this is the case in world statistics and is kept in the region [25] (Fig. 2).

Some factors increase the risk of having T2DM. High caloric foods, among them white rice, plain bread, and soft drinks, are directly related

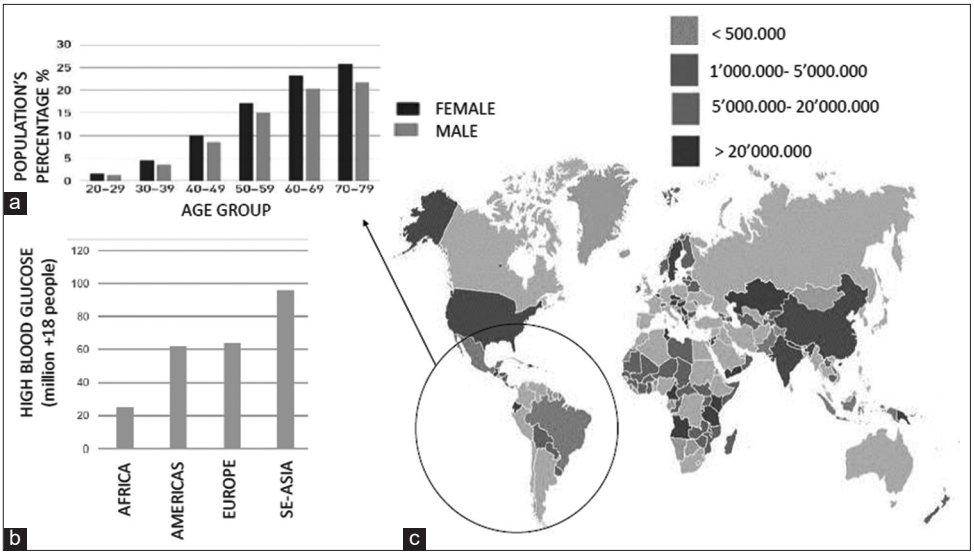

Fig. 1: Main statistics of Diabetes worldwide: a) Percentage of population by age group and gender with T2DM; b) Number of people with high blood glucose by region, c) Global map showing the regions with higher number of people with T2DM and high blood glucose.

to T2DM. In addition, physical inactivity, obesity, and overweight are factors affecting T2DM incidence. In 2019, the IDF estimated that the prevalence of T2DM in people aged 20–79 years was 5.5% [26].

PHYSIOPATHOLOGY

The primary regulator of blood glucose in humans is insulin. The beta cells of the pancreatic islets are responsible for its production, which produce it as proinsulin, which will be processed into proinsulin, which is broken down into insulin and C-peptide [27].

Levels above 70 mg/dl of glucose cause its entry into the beta cells of the pancreas through the GLUT transporter. Once in the pancreatic islets, glucose is processed by glucokinase from which pyruvate and ATP will result which activates the sensitive potassium channels causing insulin secretion [28,29].

In T2DM, there is a combination of insulin resistance (IR) and a defect in insulin secretion that favors hyperglycemia. But understanding the pathology is complicated because insulin resistance and deterioration are not measured in the clinical setting [30]. It is believed that the cause of IR is related to a sedentary lifestyle and therefore obesity, with genetics and aging being minor contributions. Instead, the decrease in insulin secretion is mainly due to genetics, the function of β cells in the uterus. That is why hyperglycemia causes impaired pancreatic beta cell function [31].

In general, type 2 diabetes is often accompanied by alterations in the metabolism of lipids, proteins, and carbohydrates, thus increasing cardiovascular risk. Hyperinsulinism caused by insulin resistance may be necessary for the origin of these alterations. In addition, increased levels of free fatty acids, oxidative factors, and inflammatory cytokines in fat have been mainly related to type 2 diabetes and cardiovascular problems [32,33].

Impaired secretion and insulin resistance have seen as independent risk factors in type 2 diabetes. In addition, the change intolerance to glucose intolerance is characterized by analogous decreases in the elimination of glucose: Insulin-stimulated glucose and glucose-stimulated secretion [34].

Glucose needs to enter the cell through glucosamine (GlcN) activated sugar for which it uses the GLUT-2 transporter. GLUT2 is expressed in the B cells, renal, and hepatic cells [35]. A high-fat diet has been shown to damage this transporter leading to glucose intolerance [36,37].

It is also important to mention that the high-fat diet damages beta cells by generating reactive oxygen species within them, which do not have endogenous antioxidants like other cells.

Although one of the criteria for diagnosing T2DM is fasting blood glucose above 126 mg/dl, it is clear that beta-cell function is abnormal with glucose levels >100 mg/dl [38].

Insulin resistance (IR) is not a diagnosis of T2DM because most patients develop it with a genetic risk of type 2 diabetes. This is evident since IR becomes more severe with a high weight and increasing age, demonstrating a defect in beta-cell function in people likely to cause high glucose tolerance. In patients with normal weight, but with a high risk of suffering type 2 diabetes, post-glucose, fasting hyperinsulinemia predispose to weight gain that leads to hyperglycemia; which can contribute to a greater deterioration of beta cells through glucotoxicity, decreasing the expression of the insulin gene [39].

The breakdown proinsulin gives normal production of insulin which represents 10–15% of the insulin secreted. In T2DM, the pancreatic B cells fail to produce or process enough insulin that the body needs to work. Whereas, the production of proinsulin in T2DM increases in the basal state [40]. When the rise in proinsulin secretion persists after looking at the degree of obesity, this indicates a dysfunction of the beta cells, not only the increased demand imposed by the insulin resistance of obesity. Furthermore, it indicates that proinsulin processing into insulin within beta cells is impaired [41,42].

CLINICAL FEATURES

In general, a patient with isolated hyperglycemia does not present cardinal signs of hyperglycemia (polydipsia, polyuria, polyphagia, and weight loss) and much less ketoacidosis (hyperventilation, asthenia, nausea, vomiting, and ketone stench). It would not be an isolated hyperglycemia but rather a diabetic ketoacidosis or non-ketosic hyperosmolar hyperglycemic decompensation [43].

DIAGNOSIS

Complementary tests should be performed after performing the diagnostic sequence to confirm isolated hyperglycemia and rule out ketosis. Studies aimed at ketogenic acidosis should be carried out if any degree of ketosis is found in these tests, which will not be seen in this section. Diagnosing type 2 diabetes with urine glucose measurement is not recommended due to its lack of sensitivity [44].

A diagnostic sequence is summarized in Fig. 2.

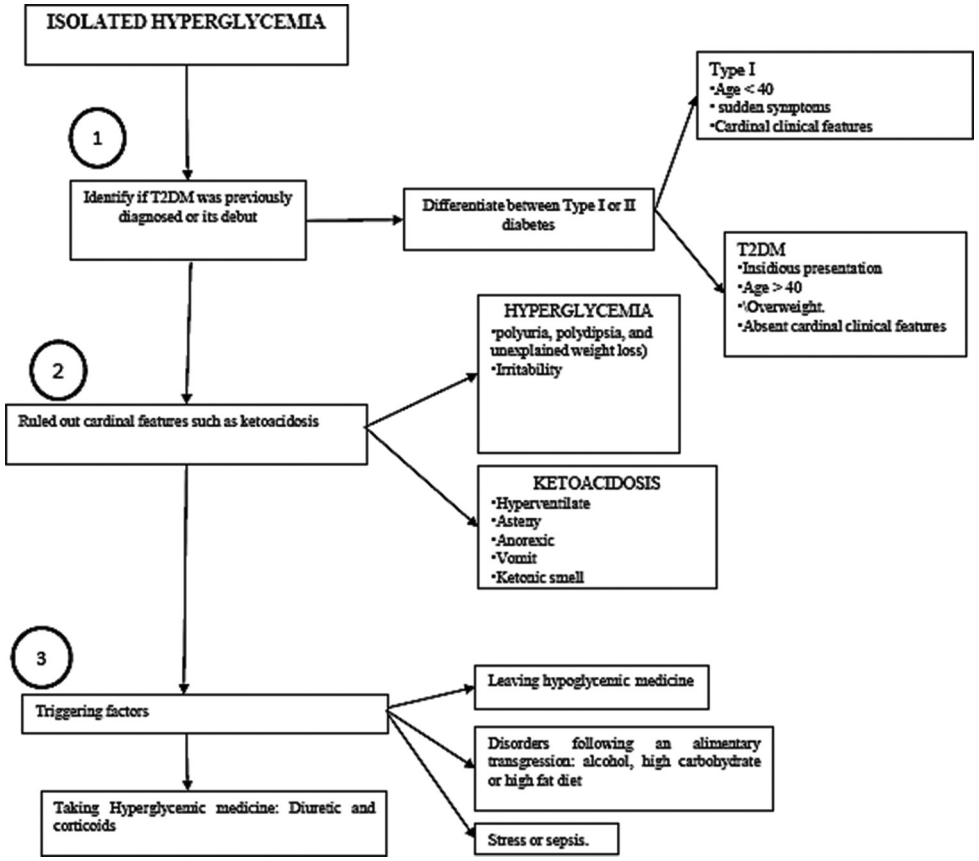

Fig. 2: Diagnostic sequence of Diabetes and triggering factors at three stages of the disease

MANAGEMENT

Treatment of T2DM should be comprehensive, including hypoglycemic drugs, lifestyle changes, physical exercise, and a diet focused on maintaining normal weight or achieving a BMI<25 [45]. Preventing the progression of microvascular disease, including retinopathy, nephropathy, and neuropathy, is possible when hyperglycemia is treated [46]. Weight loss and moderate exercise are the initial recommendations for patients with type 2 diabetes who are overweight (BMI between 25 and 29.9 kg/m) or obese (BMI >30 kg/m). Patients should lose 5–10% of their initial body weight and accumulate 30 min of moderate exercise most days of the week [47].

Treatment should be instituted in blood glucose levels greater than 250 mg/dl or in those patients with ketosis. The first line of treatment is subcutaneous ultra-fast acting insulins. For more severe hyperglycemia (greater than 400 mg/dl) or in the presence of ketosis, rapid-acting intravenous insulin is preferred. The dose is 100 IU diluted in 100 ml of saline and infused at a rate of 0.1 IU/kg/h [48].

The insulin dose required to correct blood glucose is calculated from the actual blood glucose level, the target blood glucose level (170 mg/dL), and the patient's insulin sensitivity factor (ISF). The ISF calculates the drop in blood glucose for each unit of rapid insulin.

$$ISF = 1800/t$$

where, t is the total dose administered to the patient [49]. Fluid replacement is performed in patients with blood glucose greater than 400 mg/dl, dehydration, and ketosis. Crystalloids will be used if the patient tolerates the route and subcutaneous administration, oral rehydration salts, water, or lemon juice are preferred.

In patients with glucose >400 mg/dl, it is important to perform a reassessment and capillary blood glucose should be taken again. If ultra-rapid insulin was used, the reassessment will be performed in 2–3 h; on the other hand, if rapid-acting human insulin was used, it will be performed at 3–4 h [50].

If the blood glucose in the reassessment is still greater than 200 mg/dl, a second dose will be administered, this time calculating the blood glucose obtained in the reassessment [51].

Final recommendations for patients with isolated hyperglycemia are to: (i) Control excessive food intake to avoid hyperglycemia, (ii) distribute food intakes to >5 to avoid hypoglycemia, (iii) restrict the consumption of slow-absorbing carbohydrates, (iv) consume Mediterranean diet, and (v) perform physical exercise for glycemic and metabolic control.

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COMPETING INTEREST

The authors declare no conflict of interests.

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