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Review

The role of incretin-based therapies in prediabetes: A review

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ABSTRACT

Prediabetes, a high-risk state for future development of diabetes, is prevalent globally. Abnormalities in the incretin axis are important in the progression of B-cell failure in type 2 diabetes. Incretin based therapy was found to improve B cell mass and glycaemic control in addition to having multiple beneficial effects on the systolic and diastolic blood pressure, weight loss in addition to their other beneficial effects on the liver and cardiovascular system. In prediabetes, several well-designed preventive trials have shown that lifestyle and pharmacologic interventions such as metformin, thiazolidinediones (TZD), acarbose and, nateglinide and orlistat, are effective in reducing diabetes development. In recent small studies, incretin based therapy (DPP IV inhibitors and GLP-1 agonists) have also been extended to patients with prediabetes since it was shown to better preserve B-cell function and mass in animal studies and in clinical trials and it was also shown to help maintain good long term metabolic control. Because of the limited studies and clinical experience, their side effects and costs currently guidelines do not recommend incretin-based therapies as an option for treatment in patients with prediabetes. With future clinical trials and studies they may be recommended for patients with impaired fasting glucose or impaired glucose tolerance.

Contents

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1. Introduction

Type 2 diabetes is a globally growing public health concern. However a much larger segment of the world's population is actually diagnosed with prediabetes, which is defined as having blood glucose concentrations higher than normal, and not yet meeting the definition of diabetes per se. Based on the World Health Organization (WHO), individuals with prediabetes have impaired fasting glucose concentration (IFG) ranging between 110 mg/dl and 126 mg/dl, and/or impaired glucose tolerance (IGT), defined as plasma glucose concentration 2 h post 75 g oral glucose load, ranging between 140 mg/dl and 199 mg/dl. The American Diabetes Association (ADA), uses the same WHO definition for the post-load threshold values for impaired glucose tolerance however a lower cutoff value for impaired fasting glucose is used and it ranges between 100 and 125 mg/dl. Furthermore, the ADA stated that glycated hemoglobin (HbA1c) between 5.7 and 6.4% can also be used for diagnosing prediabetes. It is important to note that the ADA and the WHO recognize that HbA1c level $\geq$6.5% is indicative of diabetes [1–4]. As per the International Diabetes Federation, 382 million people worldwide, or 8.3% of adults, were found to have diabetes in the year 2013 and by the year 2035 this will rise to 592 million. Around 316 million people worldwide, or 6.9% of adults are estimated to have impaired glucose tolerance and by 2035 this is projected to increase to around 471 million which is around 8.0% of the total adult population [5]. Prediabetes represents a high-risk state for future development of diabetes where it was found that around 10% of patients with prediabetes develop diabetes annually and around 70% will eventually develop diabetes during their lifetime [6].

2. Pathophysiology of prediabetes

The pathophysiology of type 2 diabetes is now known to be very complex with associated increased insulin resistance in the skeletal muscle and liver and enhanced hepatic glucose output along with impaired insulin secretion due to a progressive decline of pancreatic B-cell function [7]. However, in addition, other mechanisms augment the pathological pathways including altered fat metabolism in the adipocyte secondary to insulin resistance, deficiency of incretin secretion by the gastrointestinal tract and/or resistance to incretin action due to their receptors downregulation, increased glucagon production by the pancreatic α-cells and enhanced glucose reabsorption by the kidneys [8]. Chronic hyperglycemia and secondary increase in free fatty acids are significantly associated with glucolipotoxicity, which leads to B-cell failure with accelerated apoptosis and decreased proliferation with a decreased expression of the insulin gene [9]. Insulin sensitivity was noted to be reduced 13 years before the onset of diabetes, with a further steeper decrease noted 5 years before the diagnosis. However there is a compensatory increase in B-cell mass and insulin secretion 3–4 years before the conversion to diabetes finally occurs [6,9]. Therefore it seems that insulin resistance actually starts several years before the onset of diabetes and decreased B-cell function is already present, even in the prediabetic stage. Diabetes development occurs once B-cells are unable to compensate for the insulin resistance and consequently glucose concentrations start to increase rapidly. Five stages of diabetes development have been proposed by Weir et al. [10]. The first stage is defined by a long period of insulin resistance but a compensatory increased rate of insulin secretion and an increased B-cell mass. The second stage is the stable adaptation period when B cells are no longer fully able to compensate for the increased insulin resistance and hence the decrease in acute insulin secretion with the changes of B-cell phenotype occurs. This causes fasting and post-load glucose values not to be maintained and glucose levels will start to rise into the 89–116 mg/dl range. This is considered to be the prediabetics stage. These people will develop progressive hyperglycemia and eventually go to the third stage, which is also known as the unstable early decompensation period, where the B cells become unable to compensate for insulin resistance and during this phase glucose levels would start to reach approximate 130 mg/dl, and this is the period where diabetes manifests. In the subsequent two stages, stable and severe decompensation occurs [10].

Although both isolated IFG and isolated IGT are considered to be states of insulin-resistance, they do differ in their pathophysiology, where those who have isolated IFG have hepatic insulin resistance but normal insulin sensitivity at the level of the muscle. These people were noted to have a decrease in first-phase insulin secretion in response to both intravenous glucose (0–10 min) and to oral glucose (0–30 min) but with a normal late-phase (60–120 min) plasma insulin secretion, due to the fact that they have normal muscle insulin sensitivity. On the other hand patients with isolated IGT have normal to slightly decreased insulin sensitivity at the level of the liver with a moderate to severe insulin resistance at the level of the muscle. Isolated IGT patients were also noted to have a defect in both the early-phase insulin secretion in response to an oral glucose load, and had a severe deficit in late phase insulin secretion as well. B-cell dysfunction seems to be required for the development of impaired glucose tolerance (IGT) or diabetes [11,12]. Not surprisingly, individuals who have both IFG and IGT manifest muscle and hepatic insulin resistance. There are a wide variety of interventions which have shown to alter the natural history of progression of the IFG/IGT to developing diabetes [13,14].

Patients with prediabetes were also found to have alterations in circulating incretin concentrations [15]. In a large study of individuals with prediabetes, decreased GLP-1 concentrations were found after a glucose challenge and this was not related to defects in first phase basal insulin secretion. Hence GLP-1 was found to be mainly decreased in patients who had impaired glucose tolerance who are already known to have a state of insulin resistance [16,17]. Moreover early glucagon suppression was found to be impaired in patients with IGT, and since it is known that GLP-1 is an insulin secretagogue, and it also suppresses glucagon secretion, hence defects in GLP-1 secretion could contribute to the pathogenesis of pre-diabetes [18].

Mechanism of Action of Incretin Therapies Abnormalities in the incretin axis are also important in the progression of B-cell failure in type 2 diabetes. The two main incretin hormones