Type 2 Diabetes: Modulation of Metabolism, Cell Therapy and Other Options Beyond Insulin Therapy

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ABSTRACT

Type 1 diabetes is often hereditary, but type 2 diabetes is primarily lifestyle dependent. The world is currently threatened by the ever increasing trend of T2D that is also associated with diabetes-associated complications such as heart disease, diabetic nephropathy, diabetic retinopathy and so on. As 85-90% of all the diabetes cases in the world are T2D, it becomes all the more important to find avenues to cure T2D. Lifestyle dependency of T2D presents as insulin resistance. Hence, conversion of insulin resistant state to an insulin sensitive state is an essential process for mitigation of this lifestyle associated disorder. Insulin administration is the standard therapy for all kinds of diabetes that has been recently proven to be a contributor to obesity. However, in the case of T2D lifestyle management is more important. This short review focuses on other modalities of managing T2D with or without combining conventional insulin therapy primarily modulation of metabolism using various options, in addition to, diet and exercise.

KEYWORDS

Type 2 diabetes; Incretin; Cell therapy; Leptin; Brown adipose.

INTRODUCTION

It is a well-known fact that the modern lifestyle makes people prone to obesity. Currently, obesity is considered to be a metabolic syndrome and affects over 150 million people worldwide [1]. Also, obesity is considered to be the underlying reason for the pandemic disease, the type 2 diabetes (T2D) [2]. North America, China, India, Europe are the countries in which obesity is the major risk factor for about 70-90% of T2D [2-4]. The category prediabetics is often associated with overweight individuals often having higher levels of atherogenic lipoprotein profile [5, 6].

Currently, the worldwide standard therapy for long-standing cases of T2D is insulin. Thiazolidinediones (TZD) or glitazones-Pioglitazones and Rosiglitazones are also commonly used cat-egory of drugs that enhance insulin resistance in type 2 diabetics by production of more fat cells, but have side effects such as serious liver damage (reported only in case of first generation TZD). Moreover, increased fat production by TZD might act harmful by contributing to obesity, thereby continuing the vicious cycle of obesity in T2D. Dipeptidyl peptidase 4 (DPP-IV)inhibitors, class of common oral hypoglycemics used in standard therapy for T2D reduce glucagon, increasing incretin levels thereby increasing the insulin levels and hence, blood sugar lowering.

Indeed, the administration of insulin over an extended period induces lipid accumulation in muscle, adipose, and other peripheral tissues, thereby also leading to further obesity [7]. Such rise in obesity due to insulin administration hence has

detrimental effects such as an increase in cardiovascular mortality [8]. Hence, the vicious cycle of increased obesity and insulin resistance/ diabetes continues throughout the lifetime of a T2D individual due to insulin administration. So, there is a need to develop therapeutic modalities in T2D patients, so as to improve their metabolism thereby increasing the insulin sensitivity. Accordingly, such treatment modalities can eventually substitute the administration of insulin in T2D patients in the long run. The various treatment modalities that have been discussed in this short review are standard practices for management of T2D versus their failure or long-term adverse effects, therapies beyond insulin and their advantages and risk factors. Such treatments/management beyond insulin include diet and exercise, bariatric surgeries, improving the levels of brown adipose tissue, cell therapy by transplanting functional β islets. In the end, I have also reflected upon the existing scenario versus feasibility of aforementioned treatment modalities in isolation or combination with insulin therapy for diabetes.

STANDARD PRACTICES FOR THE MANAGEMENT OF T2D VERSUS THE LONG TERM FAILURE OF SUCH PRACTICES

As discussed in the previous section, administration of insulin is the standard therapy for T1D and T2D. Due to the vicious cycle of increased obesity and insulin resistance, improving lipid and glucose homeostasis for the improvement of overall metabolism can rescue a diabetic patient from getting metabolically worse over a period of several years. Hence, the standard therapy of insulin administration that had worked earlier in the same patient does not seem to work so well. The patient eventually develops T2D related complications triggered by inflammatory cytokines such as cardiac complications [9]. Hence, it is important to improve the metabolic status of the diabetic individual using various measures either in isolation or combination.

THERAPIES BEYOND INSULIN AND THEIR ADVANTAGES AND RISK FACTORS

Diet and exercise and management of T2D: Recently published human trials from an Australian study on low carbohydrate, low saturated fat, high unsaturated fat and exercise regimes of 60 minutes each day for three days a week improved the levels of glycated hemoglobin and blood glucose levels in T2D patients [10]. A large number of published literature is available correlating the management of T2D by reducing the insulin resistance, improving the muscle mass, reducing abdominal obesity, and overall metabolism. As low carbohydrate diet and exercise are the most natural means of managing T2D, there are not many risks associated with them. However, certain risks such as heavy exercise related injuries might affect an individual.

Bariatric surgeries

Over the past several years bariatric surgeries in various forms have evolved as efficient tools for treating long-term T2D in obese patients as well as borderline diabetics. Moreover, bariatric surgeries also help in the long run maintenance of weight loss. Bariatric surgeries have assisted in the secretion of incretin from the distal gut along with antidiabetic drugs and have enhanced excellent long-term glycemic control of the T2D patients [11]. As these are surgeries, they are often associated with the general surgical risk factors.

Cell therapies

Cell therapies for diabetes aim at replenishing the body of defective insulin producing β cells from an external source. This source can be either cadaveric pancreas or else in vitro differentiated from pluripotent stem cells or else, mesenchymal stem cells. We and various groups worldwide have successfully generated such functional insulin producing β cells that have been used for correcting diabetes in animal models [12-19]. However, challenges remain regarding robust glucose responsiveness of these in vitro differentiated pancreatic β cells [20]. Given reaching of the cell-based therapy to an ordinary person suffering from diabetes, it is still far to go for most of the countries. However, Viacyte Inc. USA is the only company whose diabetes cell therapy product named VC-01™ is in clinical trials [21]. This product involves a combination of pancreatic β cells differentiated from human embryonic stem cells (PEC-01™) cells and a microencapsulation device/drug delivery system (Encaptra®). This product is subcutaneously implanted to act as a secretor of insulin.

With regards to the risks involved in cell therapies, teratoma issues, immune rejections, and risks involved with surgeries can be listed. However, the cell therapy product that can be administered with non-invasive methods poses minimal risk to the patients.

Modulation of glucagon levels in the brain

This novel strategy of treatment of diabetes is via increasing the glucagon action in the brain and simultaneously block the glucagon action in the liver thereby regulating diabetes by using certain drugs. However, drugs modulating glucagon signaling have yet to be used for treating diabetes. The proposed glucagon therapy has been proven to work in mice and rats

[22]. As glucagon induces lipolysis, it might exert its role in reducing obesity in obese diabetic individuals.

As glucagon therapy is not yet practiced extensively and it acts mostly by increasing the glucagon action in the brain, risk factors might involve various neurological effects that need to be validated.

Improving the levels of brown adipose tissue

The adipokine leptin is a hormone that helps to regulate satiety and is often circulated in low quantities in obese individuals. However, this hormone is considered to be useful for diabetes therapy in combination or without insulin therapy [23, 24]. The mechanism of action of leptin is via hypothalamic secretion of the appetite suppressing corticotrophin releasing hormone [25-27]. Intrahypothalamic and ventromedial injections of leptin in rats have been proven to enhance the activity of insulin thereby improving the uptake of glucose by the peripheral tissues [28, 29]. Precise regulation of energy metabolism is the leptin mediated release of sympathetic neurotransmitters such as norepinephrine and epinephrine that increases lipolysis and thermogenesis in white adipose tissue (WAT) and brown adipose tissue (BAT) [30, 31]. Interestingly, leptin and insulin have been reported to work synergistically for the browning of white adipose tissue in mouse models thereby promoting thermogenesis and hence a better energy expenditure [32]. This synergistic action of leptin and insulin is via increasing energy expenditure through hypothalamic neurons. As leptin and insulin are now reported to work in synergy for energy expenditure, the same strategy for administration of leptin along with insulin can be tried in patients with the long-standing history of diabetes. The precise mechanism of action of leptin is via increased glucose uptake in the brown adipose tissue, skeletal and cardiac muscle, and also suppression of glucagon. Hence, leptin can be considered as a promising candidate as an alternative or a combinatorial therapy with insulin for obese and T2D individuals. Regarding the risk factor of leptin administration, in vivo validation for other physiological effects need to be performed.

Therapies in isolation or combination to insulin therapy

As T2D is a progressive disease leading to various complications in the long run when managed with only insulin administration, it is important to administer adjunctive pharmacotherapy to such patients. Adjunctive pharmacotherapy is expected to optimize glycemic control in the T2D individuals. The underlying cause of T2D is obesity or overweight, and hence weight management is the primary goal of managing T2D for improving the overall health and hence overall quality of life. Similar to insulin various glucose-lowering drugs are associated with weight gain that puts the patients and the clinicians in difficult-to-handle situations. Hence, individualized therapies also can be recommended in which glucose lowering drug response and weight gain in each patient needs to be monitored. With the advent of some glucose-lowering medicinal products in the market, it is important to understand the impact of current therapies to manage weight gain. However, till date metformin remains the most commonly used drug for the management of diabetes after diet and exercise. Recently incretins, GI hormones released in response to meals that control postprandial insulin and glucagon release have been explored for their actions on managing diabetes [33]. Two types of incretins namely glucose-dependent insulinotropic polypeptide and Glucagon-like peptide-1 (GLP-1), have several other actions by peripheral and central mechanisms. GLP-1 regulates body weight by inhibiting appetite and delaying gastric, emptying measures that are dependent on central nervous system GLP-1 receptor activation. Hence other classes of drugs can be administered as combination therapies of insulin, an incretin-glucose transporter 2 (Glut2) protein inhibitor or glucagon-like peptide 1(GLP1) agonist. Such a combination that might be useful to achieve a robust glycemic control along with weight loss and minimal risk of hypoglycemia.

More recently, Glucagon like peptide 2 (GLP2), a proglucagon derived peptide synthesized by the intestinal endocrine cells, as well as, neurons housed in the hypothalamus has been found to be beneficial in imparting energy optimization and insulin sensitivity in obese animal models [34, 35]. GLP2 mainly imparts its role in energy absorption in the gut, and might play a role satiety situations in the hypothalamic neurons. Contrarily, GLP2 exhibited an inverse relationship with insulin sensitivity in a pilot study in obese individuals [36]. As GLP2 is a much neglected peptide, in relation to, the treatment modalities of diabetes, more studies need to be carried out for understanding the effect of GLP2 in regulating energy metabolism in humans and whether GLP2 agonists or else, antagonists will be beneficial for treating T2D.

CONCLUSION

All said and done; diabetes remains a major concern to the world. Also, with the advent of novel drugs and therapies, there is a possibility that this disease can be controlled to a certain extent. Moreover, it takes time for the clinicians to adopt novel therapies/combinatorial therapies to diabetes over the traditional insulin therapy. With the discovery of insulin about one hundred years ago, it was thought that we have a cure for diabetes. Although insulin therapy still stands

at the top in diabetes management, the number of cases of diabetes especially T2D have drastically gone up in the past several years. Hence, combinatorial therapy, along with diet, exercise, various peptides/molecules and probably cell therapy might work out as the optimal solution to manage diabetes in the coming years.

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