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New Insights into the Management and Therapeutics of Type 2 Diabetes

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Abstract

Type 2 Diabetes is Insulin dependent diabetes caused due to decrease in the production and secretion of Insulin or resistance to insulin. There may be multiple factors underlying the pathophysiology of the disease, however, maintaining required insulin levels in response to glucose stimulation has been the precise for diverse treatment modalities. With widely used three tier anti-hyperglycemic therapy regimes comprising of monotherapy, dual therapy and triple therapy being unable to avoid therapeutic side-effects and patient morbidity, increasing amount of efforts have to be channelized to find newer targets involved in disease pathophysiology or finding newer therapeutic strategies. Cell based therapies, newer delivery systems and newer leads have shown some promise in laboratory and clinical settings. Promising results have also been obtained from fields which were overlooked in the management of type 2 diabetes. The efficacy of these treatment modalities can be further improved which can be helpful in providing a better, cost-effective and reliable therapeutic approach to manage type 2 diabetes. We present here some of the highlights of such research with considerations for improvising them. Furthermore, we emphasize that lifestyle management of patients enrolled in a particular therapeutic regimen will improvise the efficacy of such treatments. However, while deciding a particular regimen, primary care providers should consider the factors influencing the patient's adherence to such regimens by following a patient-centric approach to ensure maximum efficacy of the chosen regimen. We propose that newer line of drugs or therapies with a conscious effort to include lifestyle management parameters in patients may overcome the current shortcomings in three tier anti-hyperglycemic therapy regime.

Keywords: Type 2 Diabetes; Monotherapy; IDDM; New Therapeutic Approaches; Cell Based Therapies; Anti-Hyperglycemic Therapy

Abbreviations: T2D: Type 2 Diabetes; IDDM: Insulin Dependent Diabetes Mellitus; HSC: Hematopoietic stem cells; ISC: Insulin secreting cells; BMT: One Marrow Transplantation; ESC: Embryonic stem cell

Introduction

Diabetes is a medical condition in which sugar, or glucose, levels build up in the bloodstream. The increase

in glucose is the result of insufficient insulin production which is responsible for triggering sugar uptake into the cells for production of energy. This causes the body to rely on alternative energy sources in your tissues, muscles, and organs. Type 2 diabetes is a progressive condition in which the body becomes resistant to the normal effects of insulin and/or gradually loses the capacity to produce enough insulin in the pancreas. The causes of type 2 diabetes are multifactorial, however, the occurrence of type 2 diabetes is associated with modifiable lifestyle, genetic and family related risk factors. Over a long course of disease progression, it can lead to occurrence of a variety of symptoms and complications. Type 2 diabetes can develop slowly wherein the symptoms may be mild and easy to dismiss at first. The incidences of type 2 diabetes are increasing worldwide due to changes in lifestyle habit and westernization of our diets. The neglect towards regular exercise and eating a healthy diet causes disturbances in the body-fat distribution besides other genetic factors predisposing an individual towards gradual weight gain/obesity and thus to the disease condition. Since the day of diagnosis, the patients are advised to enroll for the first line of oral non-insulin anti-diabetic therapy which in most cases is Metformin. Over a period of time, if Metformin is resisted or rejected by the body, a combination of second non-insulin drug with or without basal amount of insulin injections is prescribed. The two-tier or three-tier therapy often leads to reversion of insulin resistance built up in the system but does not overcome the gradual beta cell loss that occurs during the progression of disease. Most often, secondary disease complications such as Cognitive failures, Atherosclerotic heart disease and Renal disorders are also caused whilst the patients are on combinatorial therapy. Hence, maintaining the recommended level of plasma glucose in the fasting and postprandial state is not the only concern prevailing in the scientific community.

In this article, we provide a perspective on other modes of therapy by reviewing the success and shortcomings of currently used anti-hyperglycemic drugs in monoline or combinatorial therapythat may provide better disease management in terms of glycemia based insulin secretion and overcoming side-effects and/or secondary complications. This review does not offer first hand clinical data but a summary of the findings of other groups in a clinical or an academic setting. The therapeutic strategies that will be discussed in this article have been tested in a limited laboratory or clinical setting, however, holds promise and should be further explored to be used as frontline therapies to overcome the long term consequences of insulin resistance. It must also be considered that many of such studies have been designed and conducted on cohorts of specific age groups, ethnicity and with certain history of the disease. Hence, the findings may not be applicable to all the patients, however, it is also inevitable that further molecular studies be undertaken to understand the targets and mode of action of many such therapies where there is a proven clinical outcome. Improvising the delivery systems for currently available therapies may also provide better disease management and increase patient adherence if they can be cost-effective and are required to be taken only on a periodic basis.

Monotherapy versus Combinatorial Therapies

Metformin is the first line of Oral Antidiabetic Drug of choice after diagnosis of type 2 diabetes. Metformin therapy if tolerated well by the patients can avoid cost-burden, adherence and persistence related problem during the disease management. However, most often Metformin treatment although being highly effective in most cases, often leads to side-effects and other complications thereby decreasing the adherence to the treatment and warranting better disease management [1,2]. Metformin lowers the blood glucose level mainly by decreasing glucose released by liver in blood. It also increases sensitivity of the body cells to insulin. The main advantage of Metformin is that it lowers the risk of other complications like heart attack and stroke [3] but the disadvantage is that after starting the medicine one might feel nausea and can have mild runny stools (diarrhoea). Other class of oral anti-diabetic drug is from the Sulfonylurea class. This category of medicines include glibenclamide, gliclazide, glimepiride, glipizide and tolbutamide. All these medicines increase the amount of insulin that is produced by pancreas. Sulfonylurea class secretagogues are prescribed if a patient cannot take metformin because of the side-effects being intolerable or if one is overweight. However, this class of drugs can also cause hypoglycemia due to insulin surge if the sugar level is not continuously monitored [4].

Another class of first line drugs could be Alpha-glucosidase inhibitors, which help the body to break starchy foods & table sugar. This category of drugs include acarbose and miglitol [5]. The fourth most common choice of anti-hyperglycemic drugs belong to the category of DPP-4 inhibitors which includes alogliptin (Nesina), alogliptin-metformin(Kazano), and many more. It helps the body continue to produce insulin. They work by reducing blood sugar without causing hypoglycemia. However, over a long course of treatment their efficacy to trigger pancreatic beta cells to produce insulin decreases

due to beta-cell overload or loss of beta-cell mass [6]. In some cases, the choice of primary line of oral anti-diabetic drug can be different from Metformin. In a controlled clinical study containing 24 patients with a mean age group of 58.3 years undergoing stable metformin therapy, two different groups of patients were given Vildagliptin and Glimepiride in a cross-over manner. The former drug maintained a more stable blood glucose level suggesting that it can offer long term stable benefits and prevent the development of treatment related complications if chosen as the first line of therapy [7].

In Combinatorial therapy regimen, a two-tier therapy is prescribed if the first line of Metformin therapy fails. These tiers are mostly a combination of other class of drugs along with metformin. The objective of two class of drug combinations is to increase control over maintaining glycemia in the prescribed range. Recent evidences however suggest that the choice of second drug plays a very important role in determining the future need of triple drug combinations or patient adherence and persistence to the two-tier drug regimen which is also influenced by the potential risk of side-effects that develop in the due course of the treatment. In a retrospective study using health-claim data from more than 20,000 patients, 6758 patient pairs were selected to be on Sulfonylurea and DPP-4 inhibitors. When the treatment progression was compared for adherence, persistence and treatment progression of patients with Metformin + Sulfonylurea versus Metformin + DPP-4 inhibitors, a larger fraction of the patients in the Metformin + Sulfonylurea group discontinued the treatment whereas the latter group of patients had better adherence and persistence. Furthermore, the rate of initiation of Insulin therapy in the former group was higher than in the latter [8].

Similarly, in a randomized clinical trial conducted by researchers from Novartis, when Vildagliptin was added to a group of patients on dual drug therapy Metformin + Sulfonylurea, better control over hyperglycemia was obtained without adverse effects such as hypoglycemia and obesity suggesting that Vildagliptin could provide a better alternative as compared to the widely popular oral anti-diabetic drugs [9]. Similarly, besides a three drug combination, two drug and administration of insulin is also one of the commonly used therapy regimen on patients who develop severe long term complications or resist oral anti-diabetic drugs. If the side-effects become too severe, multiple administration of insulin injections on a daily basis is recommended. However, employing multiple drugs in a triple combination therapy severely increases the risk of side effects and long term complications such as atherosclerosis, cognitive impairment and renal failures. The risk of atherosclerotic cardiovascular disease significantly increases in combinatorial drug therapy thereby warranting constant monitoring of blood lipid profile and related changes [10]. Hence, in order to avoid therapy related complications, newer candidates such as Incretins and Secretagogin have to be validated for their use as anti-diabetic drugs [11,12].

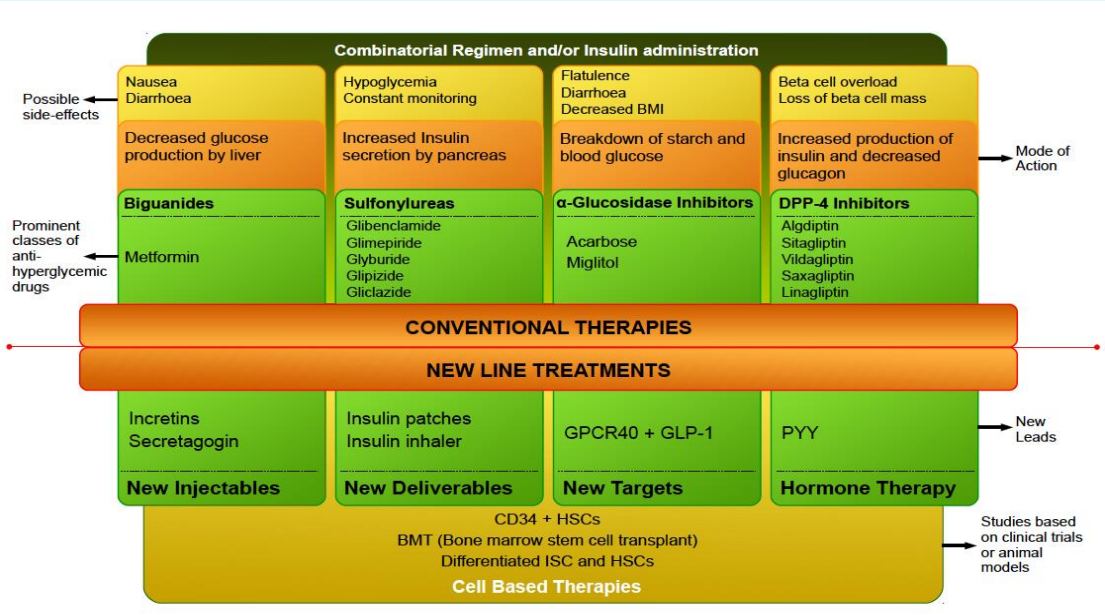

Figure 1: A schematic representation of most prominent class of anti-hyperglycemic drugs used in conventional therapy with proposed new line of treatments and therapies. Adapted from Izucchi et al. [13].

New Delivery Systems and New Leads

In order to avoid therapy related complications, newer candidates such as Incretins and Secretagogin have to be validated for their use as antidiabetic drugs [11,12]. A recombinant protein Exenatide, that mimics Incretin hormones have been found helpful in controlling the blood glucose levels in patients with Type II Diabetes. This injection is especially found to be effective when the blood glucose levels cannot be maintained by oral medications. The function of Incretin hormone is to stimulate Insulin release and make the person feel satiated. Hence the Exenatide injections trick the patients into feeling satiated thereby decreasing their urges for meal intake and hence leading to weight loss. However, some minor side effect like nausea has been reported in this method because the patients are not really feeding themselves to the brink of satiation. However, the short coming of this recombinant protein is its short half-life of two and half hours. Hence, there is an ongoing effort to create a sustained release form of the exenatide by gene modification or combinatorial chemistry that only warrants its usage to once a week thereby increasing patient adherence [14]. Similarly, in a 56 week long double blind study on 505 obese type 2 diabetic patients comprising of 80% caucasian patients and mean age of 54 years, sustained release formulations of Naltrexone and Buproprion resulted in desired weight loss, decrease atherosclerotic risk factors and enhanced glycemic controls with minimal to no side-effects [15]. Such studies point that sustained release formulations of already available pharmacotherapeutic agents can also improve therapeutic markers in the management of type 2 diabetes.

Smart Insulin patches have been one such new delivery systems that holds great promise for the treatment of diabetes including type 2 diabetes. Although, the preliminary reports for design and usage of glucose responsive microneedle based insulin releasing patches have been cited for animal models of type-1 diabetes, the precise of using a biocompatible nanovesicle or a biocompatible material that has a minimally invasive effect embedded with a smart glucose/hypoxia signal amplifier and capable of delivering insulin for a prolonged period of time holds much promise for the next generation of disease management [16-18]. Similar attempt was also made when in 2014, FDA approved the use of Afrezza – a human insulin inhalation powder. Afrezza proved to be effective in blood glucose in the control study group however due to the nasal route of administration caused serious side-effects such as bronchospasms, cough and throat irritations. Such delivery systems will have to overcome the inherent limitations caused by the route of administration if they are to see the light of the day.

Research efforts channelized in the direction of reducing therapeutic complications or finding newer targets to better manage the disease have led to the identification of newer targets. Sometimes, the leads have come from an unsuspected area such as Cancer. In a new study, GPR39 has been found to be a new target for type 2 diabetes. GPR39 agonists were tested to check if they can improve beta cell function which is important to overcome long term beta cell loss and thus increase insulin secretion [19]. Similar attempts have been also made in cell line and animal diabetes models by combining agonists of G-protein coupled receptor 40 and GLP-1 peptides with promising results [20]. In an unsuspected discovery, a commonly used cancer drug Gleevec for treatment of CML was found to be effective in lowering insulin resistance by blocking PPAR thereby decreasing hyperglycaemia and obesity in high-fat fed mice which are important parameters of controlling type 2 diabetes [21]. Another group of researchers have found a new hormone PYY to be a key player in causing improved islet function and possibly remission of type 2 diabetes after bariatric surgery using a diabetic Goto-Kakizaki (GK) rat model [22]. Such a hormone therapy may hold potential to also overcome therapy related side-effects found in current mode of therapy. Recent discoveries also point towards a potential role of newly found beige adipocytes in adult humans that may be of special interest as new targets for management of type 2 diabetes [23]. With a change of perspective, many of the aging related phenotypes such as inflammation and senescence-associated secretory phenotype (SASP) have been also found to be shared by type 2 diabetes. Focusing future therapeutic options on SASP linked oxidative stress, ER stress and endothelial dysfunction can prove to be effective in controlling the disease associated morbidity [24].

Cell Based Therapies

Irrespective of any chosen mode of therapeutic regimen, the long term consequences lead to decline in beta cell function or beta cell death thereby reducing insulin secretion potential of the pancreas. Hence, supplementation of already existing disease management systems with cell based therapies in combination or isolation may improve treatment efficacy and decrease instances of beta cell loss in the long run. When a group of 95 patients with a mean age group of 57.1 years, with a previous history of diabetes and experiencing diabetes associated complications were injected with human embryonic stem cell lines, their dependence on insulin

and other drugs decreased significantly [25]. In a similar meta-analysis carried out on the clinical data of 524 patients, all type 1 diabetic patients who underwent infusion of CD^{34+} HSCs (human embryonic stem cells) decreased insulin dependency in the advanced stage of the disease [26]. This study also extrapolates a potentially beneficial role of CD^{34+} HSC transfusions in type 2 diabetic patients. Although side-effects in this treatment modality were reported, further studies relate the occurrence of these side effects to the mode of administration of such stem cells and their homing efficacy. In the recent past, an attempt combining autologous bone marrow stem cell transplantation (BMT) with hyperbaric oxygen treatment to treat type 2 diabetes improved glucose control and reduced the requirement of insulin or other anti-diabetic drugs although transiently [27]. In order to achieve a rather long term solution to overcome the dependency on endogenously supplied insulin in the advanced stages of type 2 diabetes, a combination of adipose tissue derived-mesenchymal stem cell (MSC) differentiated insulin secreting cells (ISC) and hematopoietic stem cells (HSC) were infused through different routes in different groups of patient. Over a course of more than 30 months, it was observed that exogenous insulin requirements substantially decreased with no observable side-effects thereby portraying MSCs or a combination of MSCs with ISCs as promising cell-based therapies [27,28]. Thus, although in primary stage of development, stem cell therapies hold great future for the management of type 2 diabetes and controlling associated risks of the current therapy regimes.

Conclusion

Current therapeutic modalities for the treatment of type 2 diabetes has many side-effects and faces problems of patient adherence, persistence and associated secondary complications with the disease. Moreover, in developing countries, the cost of treatment also influences the success of disease management. Hence, a long term treatment regimen will also incur heavy expenses on patients. Furthermore, lifestyle management is one key factor often overlooked while deciding which treatment modality should be employed for a particular patient. Involving patients to make a bilateral decision based on the lifestyle choices and preferences of the patients keeping in mind the expenditure to be incurred by the patient will give better insights to the primary care providers in deciding for the treatment that best suites the patient's requirements. Moreover, newer leads, delivery systems and cell based therapies offer a very promising future in improvising the therapeutic modalities with more predictable, safer and reliable outcomes for improving the success rates of such therapies.

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