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Review Article

CURRENT TREATMENTS FOR TYPE 2 DIABETES, THEIR SIDE EFFECTS AND POSSIBLE COMPLEMENTARY TREATMENTS

ARSHPREET KALSI*, SHIVANGI SINGH*, NANCY TANEJA, SAMIKSHA KUKAL, SHALINI MANI#

Jaypee Institute of Information Technology, Noida, Assistant Professor, PhD (Medical Genetics).
Email: akalsi91@gmail.com

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ABSTRACT

Diabetes mellitus is a chronic metabolic disorder in the endocrine system and characterized by a varied and complex pathophysiology. World-wide there is a dramatic increase in the number of patients for type 2 diabetes, and hence it is becoming a serious threat to the health of mankind. Commercially a large number of drugs belonging to different classes such as biguanides, sulfonylureas, meglitinides and thiazolidinediones are available to control and treat the type 2 diabetic patients. However, none of these drugs are known to completely cure the diabetic phenotype. On the other hand, a long term usage of these drugs exhibits several side effects and complications to different organs of the body which ultimately lead to cardiovascular problems, liver disease, kidney disease and weight gain too. Like many other drugs, these anti-diabetic drugs are also known to interfere and interact with other non anti-diabetic drugs, if the patient is taking them for a long time. To combat the side effects of these drugs, complementary treatments may be found as a preventive measure and more promising in the management of disease phenotypes in these patients. As per reports available from a large number of studies, these complementary therapies may include physical exercise, dietary supplements and Nutraceuticals.

Keywords: T2D, Drugs, Complementary medicine, Anti-oxidants, Nutraceuticals, Oxidative stress.

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia with defective carbohydrate and fat metabolism. These defects are mostly due to impaired insulin secretion from pancreatic β cells and/or insulin resistance to the target cells like skeletal muscles, adipose tissues, and liver etc.

The vast majority of cases of diabetes fall under two major categories of diabetes mellitus as defined by the World Health Organization in 1980 [1]. The first category is Type1 diabetes (T1D) where the cause of hyperglycemia arises as an absolute deficiency of insulin secretion. The occurrence of this type of diabetes among the population is identified by the evidence of autoimmune pathologic process in pancreatic β-cells as a cause of the low insulin secretion. The second category of diabetes named as Type 2 diabetes (T2D) is the most prevalent form that develops due to the combined action of both insulin resistance and insufficient insulin secretion.

The high blood sugar is the main characteristic of diabetes and it produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger) in patients. But apart from these chief clinical complaints, other co-morbidities such as, retinopathy, nephropathy neuropathy and cardiovascular problems also associate with T2D patients over the time [2].

Along with genetic, the epidemic of T2D is associated with a large number of environmental factors also. A sedentary lifestyle, lack of proper nutrition (excessive calories and low fiber intake), stress, smoking and alcohol consumption are a few of the important factors generally observed in the urban population and associated with the development of T2D. The important risk factors which make a person more prone to developing this disease include obesity (BMI>25Kg/m2), age (>40 years) and an imbalance between energy intake and expenditure [3].

T2D is one of the most important health challenges faced by the global population today. According to the International Diabetes Federation, in 2013 there were 382 million people worldwide suffering from DM which is estimated to be 8.5% of the world's population and if left unchecked this number may rise to 592 million by the year 2035. Diabetes Atlas, 2006 published by the International Diabetes Federation, there are around 40.9 million diabetic patients in India and which is expected to increase to 70 million by 2025 unless preventive measures are taken [4]. The most disturbing change in the trend towards its prevalence is a decrease in the age of onset with the greatest number of people with diabetes present between 40 and 59 years of age [5].

Due to the pathogenic complexity of the disease, the cure and its management are also not very straight forward and thus the economic burden of diabetes mellitus is also immense. A global expenditure exceeding USD 548 billion was done to treat, prevent or manage diabetes mellitus and its associated complications [5]. However, none of the drug/therapy is proven to completely cure this disease. Thus, a proper health care system to manage and treat this disease afflicting people of all economic backgrounds is the need of the hour. In the current article, we are summarizing all the current treatments available for diabetic patients and their side effects. Further, we are also highlighting the evidences in support to some common complementary treatments and put forth the explanation towards their usage to avoid the side effects of drugs and better management of T2D.

Current treatments for T2D and their side effects

T2D cannot be completely cured but its severity and symptoms can be managed by the use of drugs and lifestyle modifications. Some of the most commonly used pharmacological agents for the treatment of T2D include drugs from different classes such as biguanides (ex. metformin), sulfonylureas (ex. glyburide and glipizide), meglitinides (ex. repaglinide and nateglinides) and thiazolidinediones (ex. pioglitazone). The drugs belonging to these classes are administered as the first line of defense to prevent deterioration of the diabetic state.

Thiazolidinediones

Thiazolidinediones (TZDs) are insulin sensitizers which primarily work by improving insulin sensitivity on target organs like liver and muscles. The mechanism by which TZDs exert their anti-diabetic effect involves the activation of a transcription factor, peroxisome proliferator-activated receptor (PPAR γ). This factor alters the transcription of several genes involved in glucose and lipid metabolism and energy balance, including fatty acyl-CoA synthase, malic enzyme, glucokinase and glucose transporter 4 (GLUT4) etc. By doing so, TZDs reduce the insulin resistance in adipose tissue, muscle and the liver [6]. One of the main side effects of activation of the PPAR γ receptors is the enhanced proliferation of peripheral adipocytes to

increase uptake of free fatty acids. This effect may adversely lead to weight gain and increased peripheral fat mass [7]. Several recent studies and analyses have revealed the potential impact of TZD on cardiovascular events in patients with type 2 diabetes. In this context, meta-analyses of adverse event data from randomized controlled trials have shown a possible association between the use of thiazolidinedione and an increased risk of ischemic myocardial events in diabetic patients [8]. Another adverse effect associated with the use of TZDs is fluid retention. It has been proposed that TZD induced edema formation in the kidney may be a result of the stimulation of the sodium-coupled bicarbonate absorption from the renal proximal tubule. The enhancement of sodium and fluid re absorption from the renal tubule leads to increased kidney volume [9]. The results of these studies have ignited debate and instilled uncertainty regarding the use of TZDs in diabetes treatment strategies.

Biguanide

Biguanides are another insulin sensitizer and metformin is one of commonly prescribed anti-diabetic drugs belonging to this class. The hypoglycemic action of metformin involves improvement in glucose utilization by its action on insulin receptors and glucose transporters present on target cells like the skeletal muscle and the liver cells [10]. Metformin is known to decrease the pyruvate dehydrogenase activity and hence leads to lactic acidosis, which is a rare but potentially fatal complication associated with the use of metformin. The increased risk of metformin induced lactic acidosis generally arises in patients with renal, pulmonary or cardiac insufficiency or with a history of liver disease [11].

Sulfonylureas

Sulfonylureas are secretagogue and they aim to increase insulin output from pancreatic β- cells. The primary targets of the drugs belonging to the class sulfonylurea are the ATP-sensitive potassium (K_{ATP}) channels, which control the pancreatic β-cell membrane potential. Binding of the drug to the sulfonylurea receptor (SUR) subunit of the K_{ATP} channel causes the depolarization of the cell membrane leading to an influx of calcium ions. This results in the exocytosis of insulin granules from the pancreatic β-cell [12]. Diabetic hypoglycemia is a major concern for those patients who have been consuming sulfonylureas (like glyburide) for a longer time. Elderly patients and patients who frequently skip meals are more prone to the risk of hypoglycemia associated with the use of sulfonylureas. Sulfonylureas are also associated with an increased cardiovascular risk. As per studies, it is shown that while stimulating the closure of the K_{ATP} channels of the pancreatic β-cell to stimulate insulin secretion, this drug may also lead to the closure of the myocardial K_{ATP} channels, leading to a greater cardiovascular incidence in those patients [13].

Meglitinides

The mode of action of meglitinides resembles that of sulfonylureas; however, its action is mediated through a different binding site on the SUR of the β-cell when compared with sulfonylureas [14]. A number of other drugs are also administered along with the anti-diabetic drugs discussed above to manage the various co-morbidities associated with T2D.

Certain anti-diabetic agents are susceptible to drug-drug interactions resulting in adverse events and adding to the complications for the diabetic patient. For example, sulphonamides, a known structural analogue of sulfonylurea, replaces it from the plasma protein, making it more freely available for its activity. This potentiates the risk of hypoglycemia caused by sulfonylurea [15]. Some sulfonylureas are metabolized by liver metabolic enzymes and thus inducers of hepatic drug metabolism, such as rifampicin increases the clearance of sulfonylureas and hence decrease the plasma concentrations sulfonylurea and its efficacy [13]. Thus, knowledge of the benefits as well as the risks of the vast array of drugs available today is essential for the optimal treatment of T2D patients.

Insulin

Insulin is a hormone, produced by the pancreatic β cells in the body and regulates the body's sugar level in the bloodstream as well as allowing excess glucose to be stored in the liver. Although T2D patients produce their own insulin but as the disease progresses, either the amount of produced insulin is not enough or there is a further low response towards insulin in target cells of these patients. Hence, in most of the cases, insulin therapy is chosen as the final step for glucose lowering therapies [16]. The major disadvantages associated with long term use of insulin therapy are hypoglycemia and weight gain. These symptoms are very well justified because there is a decrease in glycosuria and less energy consumption in these patients as the glycemic level is improved by this therapy [17]. Further, a serious problem is known to be associated with hyperinsulinemic hypoglycemia is its indirect effect on cell proliferation. Hyperinsulinemia (due to its growth promoting properties) may enhance the specific cell proliferation and survival pathways, resulting in the risk of the progression of cancer in different organs such as liver, pancreas, colon and many others [18-20]. In Addition to it, as insulin is injected into the subcutaneous layer, there is the formation of the fatty lumps over the sites of injections which are termed as lipohypertrophy. It's most common in people who frequently receive multiple daily injections, which may affect the absorption of insulin, leading to alterations in the blood glucose levels [20].

Complementary treatments for management of T2D

The risks associated with the use of conventional anti-diabetic agents are high. In some cases, they may prove toxic and may adversely affect the health of the patient. As an approach to combat this disease and to improve the quality of living for the diabetic patients, several studies that have suggested that lifestyle interventions based on improvement in physical activity and nutrition may help in better management of the disease.

Exercise

It is a well known fact that frequent and regular exercise boosts the overall quality of life and likely to prevent various lifestyle associated diseases like cardiovascular disease, obesity and T2D. During a regular stretch of physical exercise, the skeletal muscles increase their uptake of glucose by several fold and hence reduces the hyperglycemic conditions in the blood [22]. The intensity and duration of the physical exercise are the two important factors that determine the type of fuel being utilized during exercising. As the muscle glycogen is progressively depleted, there is a shift in the energy source towards circulating glucose, free fatty acids and greater carbohydrate oxidation. The origin of circulating glucose also shifts from hepatic glycogenolysis to gluconeogenesis [23]. A meta-analysis with 8538 patients showed that a structured exercise training for more than 150 minutes which includes aerobic exercise, resistance training or a combination of both led to greater HbA_{1c} declines than that of 150 minutes or less per week [24]. On the similar lines, a systemic review with 10 prospective cohort studies indicates that a moderately intense physical activity like walking is also associated with a lower risk of T2D [25]. Different Clinical trials suggest decrease in HbA1c in diabetic patients with the help of aerobic, resistance, stretching, upper and lower body exercises. In continuation to these clinical trials Boule´ *et al*. also studied the effects of different exercises for 8 weeks to study its effect on HbA1C and body mass of 504 T2D patients and was analyzed using statistical models, which supports the above study [26]. Additionally, study conducted by Ishii *et al*., supports improvement in insulin sensitivity with the help of effective exercises [27].

Cuff *et al*., studied 28 postmenopausal T2D women patients assigned with aerobic resistance training for 16 weeks and outcomes were measured by glucose disposal by hyperinsulinemic-euglycemic clamp and computed tomography scans of abdominal and mid-thigh skeletal muscles, resulting in the increase of the infusion rates and reduction in muscle density of exercise group in comparison to the control group with no exercise [28]. Other studies conducted by Castanenda *et al*., Dustan *et al*., further add evidence in the similar lines [29-30].

Yoga

Yoga, a physical and spiritual exercise regimen hold immense potential as a co-intervention in the improvement in the quality of

life for diabetic patients. It involves various body postures and movements (known as asanas), breathing techniques and meditation, which are all designed to promote physical comfort and mental composure.

An Indian study on 123 diabetic patients showed that yoga resulted in significant reduction in BMI and glycemic control. There was also an increase in the levels of glutathione and vitamin C which led to an effective decrease in the oxidative stress in diabetic patients**.** Oxidative stress has been implicated as the root cause underlying the development of insulin resistance, β-cell dysfunction, diabetes, and its associated clinical conditions such as atherosclerosis, micro vascular complications, and neuropathy [31]. A 12-week yoga program among 23 adults at high risk for T2D demonstrated that the yoga group participants experienced improvements in weight, blood pressure, insulin, triglycerides as compared to the control group [32]. In a study conducted by V Malhotra *et al,* in 2004 it was observed that there was a noticeable change in lipid profile and blood glucose levels of 20 T2D patients who followed and performed various asanas continuously for 40 days [33]. Further a clinical trial in hypertensive diabetic patients who were practicing yoga for 1 hour along with diabetic drugs was carried out for 3 months by Nisha *et al.,* in Kerala. The control for this study was those diabetic patients who were only taking diabetic drugs, but not practicing yoga, After 3 months, blood pressure and blood sugar were compared in both the groups and it was found that blood pressure and blood sugar level were comparatively low in patients following yoga [34]. Similarly, a study conducted by Savita and colleagues, on twenty-four T2D cases favor metabolic and clinical evidence of improvement in blood glucose level control and cardiac functions after 20-40 minutes of yoga with different asanas per day for 40 days assigned by the experts [35].

Diet

Diet is considered as a most vital factor governing the health of an individual. There are ample of studies suggesting the significance of diet for a healthy life. Studies have shown that low fat vegetarian diets consist of fruits, vegetables; grains etc. are associated with increased insulin sensitivity, glycemic control, weight loss etc. and thus helpful in controlling diabetes. High dietary fiber, low carbohydrate and low fat containing diet are highly recommended to diabetic patients as these are known to prevent a rise in the blood glucose levels. High fiber carbohydrates, which are also known as slow release carbohydrates helps in maintaining blood sugar levels as they are digested slowly, thus preventing high insulin production in the body [36-38]. Dietary fat is also of particular interest because fatty acids influence glucose metabolism by altering cell membrane function and enzyme activity of various enzymes helping in glucose metabolism. Fatty meal is also known to slow down the action of insulin, leading to the high blood glucose level after the meal. Control in the diet helps in regulating the blood glucose levels, which are validated with the help of different studies [39]. In a trial conducted on 99 T2D individuals in America, it was found that the low-fat vegan diet contribute greatly in controlling glycemia and plasma lipid concentrations [40]. Another randomized control trial (RCT) performed in America on 99 individuals further proved the fact that low fat vegan diet improves glycemic, plasma lipid and weight control in individuals with T2D [41]. In a prospective cohort study carried out on 35,988 older Iowa women initially free of diabetes, it was found that dietary carbohydrates influence the development of T2D [42]. A randomized, crossover study conducted with 13 T2D patients concluded that diet predominantly rich of soluble fiber improves glycaemia control, decreases hyperinsulinemia and lowers plasma lipid concentrations in them [43]. Thus there should be more emphasis in recommending a fibre rich diet to these patients.

Vitamins

Several studies have suggested that vitamins have strong potential to cure diseases like T2D when given as a supplement [44]. It has been hypothesized that diabetes is a disease marked by oxidative damage [45]. So there is a significant association between antioxidants and oxidative stress. On the other hand, many of the vitamins such as vitamins D, C and E are known potential antioxidants, hence could be used to cure diabetes by lowering the oxidative stress.

Vitamin D

Most of the requirement of vitamin D is covered from sunlight, but with the change in lifestyle the exposure to sunlight has greatly been reduced and thus leading to vitamin D deficiency which in turn could cause several health issues. As per large number of association based studies, it has been proposed that people who have the lowest vitamin D levels in their blood are at an increased risk of developing T2D [46]. As per recent studies most of the diabetic patients are also found to be deficient for their vitamin D levels as compared to the non diabetic individuals [46]. Several vitamin D receptor and vitamin D binding proteins are present in pancreatic tissues, linking its possible role in insulin synthesis and secretion [46]. A meta-analysis including 21 prospective studies has related lower circulating vitamin D levels to hyperglycemia and insulin resistance [47]. In a RCT with 92 adult patients at a risk of T2D, short-term supplementation with vitamin D showed improved pancreatic βcell function[48]. The cross-sectional studies have shown that low serum concentrations of 25-hydroxyvitamin D are associated with impaired glucose tolerance and diabetes [48]. The role of vitamin D in reducing the risk of T2D was suggested by the study conducted on 83,779 women for 20years [49]. It has also been observed that glucose tolerance is restored when the levels of vitamin D return to normal [50].

Vitamin E

Vitamin E is a fat soluble vitamin which plays several important biological roles including an antioxidant. Common food sources of vitamin E are vegetable oils, nuts, green leafy vegetables and fortified cereals. As an anti-oxidant, it scavenges reactive oxygen species (ROS) during oxidation of fats in the tissues. Oxidative stress due to increased production of ROS and decreased level of antioxidants has been associated with the pathogenesis of T2D and its complications. A meta-analysis conducted among American women showed an evidence of five randomized placebo-controlled trials with a sample size from 15 to 57 participants, showed that vitamin E supplementation with dosages from 600 to 1,600 IU reduced oxidative stress and improved glycemic control among diabetic patients during a period of 4–16 weeks [51]. On the other hand, a Heart Outcomes Prevention Evaluation trial of 3654 participants who were diabetic as well as at a risk of developing cardiovascular problems showed that in spite of the daily administration of 400 IU vitamin E, there was a neutral effect on the glycemic control and cardiovascular outcomes in diabetic patients. There is a need to conduct more trials to understand the effects of vitamin E supplementation in T2D patients [52].

Vitamin C

Vitamin C plays a vital role in regulating the in blood glucose levels by acting as an antioxidant [53]. Various studies have been performed in order to determine the significance of vitamin C in curing T2D. A population-based prospective cohort study conducted on 21,831 individuals, suggested that the higher level of vitamin C in plasma decreased the risk of T2D [54]. Another study conducted on 10 healthy and 10 diabetic individuals, concluded that infusion of vitamin C plays an important role in improvement of non-oxidative glucose metabolism as well as in modulating insulin action in diabetic patients [55].

Nutraceuticals

The term is applied to products that range from isolated nutrients, dietary supplements and herbal products which are administered with the intent of improving the health of the individual. In recent years, growing evidence has come into light which point towards the therapeutic use of Nutraceuticals for management and complementary treatment of patients of T2D and other diseases as well [56]. Amongst these Nutraceuticals, berberine, garlic and cinnamon are some of the common supplements that are proposed to be beneficial for improving the health of the diabetic patients.

Cinnamon

Cinnamon is proposed to have several health benefits such as ability to control blood glucose, total cholesterol and triglyceride levels, etc. Cinnamonaldehyde, an active component present in cinnamon

contributes primarily in promoting insulin secretion and glucose uptake [57]. It enhances glucose uptake by activating kinase activity of insulin receptor thus leading to auto-phosphorylation of an insulin receptor which in turn activates the cascade of pathway which finally results in GLUT4 activation [58]. First clinical trial to study the effect of cinnamon in controlling T2D was conducted in Pakistan on 60 diabetic person who were supplemented with different dose of cinnamon and it was found that after 40 days there was significant reduction in the mean fasting serum glucose, triglyceride, low density lipid, cholesterol and total cholesterol levels, as compared to placebo groups which did not consume cinnamon [59]. The significant effect of cinnamon on blood glucose could be well demonstrated from the meta-analysis of 10 RCTs with sample size of 543 patients, which concluded that the consumption of cinnamon is associated with a statistically significant decrease in levels of fasting plasma glucose, total cholesterol, low density lipid-cholesterol (LDL-C) and triglyceride levels [57]. Thus, from different studies, it could be hypothesized that cinnamon inclusion in the diet could be beneficial in curing diabetes.

Garlic

It has been used for imparting flavor and aroma in the food all over the world. Beside this its antioxidant activity has made it useful for various medical purposes. Studies have shown that S-allyl cysteine sulfoxide an antioxidant which is isolated from garlic may contribute to its beneficial effect in diabetes [60]. From the clinical trial conducted in a group of 50 T2D patients with hyper-lipidemia, it was observed that consumption of 900mg/day garlic powder tablets for 6 weeks will significantly decreased total cholesterol, LDL-C, systolic blood pressure and increase high density lipid –cholesterol(HDL-C) [61]. Its anti-diabetic effects were further demonstrated by another randomized, single-blind, placebo controlled study, which was conducted on 70 T2Dpatients with newly diagnosed dys lipidemia for 12 weeks and it was found that garlic exhibits a short term benefit on lipid profile and greater reduction in total cholesterol and LDL-C and moderate increase in HDL-C than that with placebo [62]. In order to further evaluate the anti-diabetic properties of garlic, some more studies are need to be conducted.

Berberine

Berberine is a plant alkaloid with a long history of medicinal use in both Ayurvedic and Chinese medicine. It has a wide range of effects that includes mainly the antimicrobial (against bacterial diarrhea, intestinal parasites, fungal infections, *Candida albicans*, yeast, and possibly methicillin resistant *Staphylococcus aureus*) and anti-inflammatory responses. It can be found in the roots, rhizomes and stem bark of several plants like *Hydrastiscanadensis*, *Coptischinensis*, *Berberisaquifolium*, *Berberis vulgaris*, and *Berberisaristata* [63]. Berberine has been shown to have antidiabetic properties, although its mode of action is not well elucidated. One of the mechanisms, suggesting the health benefits of berberine by its action on the adenosine monophosphate-activated protein kinase (AMPK), which leads to the phosphorylation of important targets such as the enzymes involved in lipid metabolism, lipolysis, fatty acid oxidation and glucose uptake. Experiments conducted in rat models have shown that berberine-induced activation of AMPK stimulates a cascade of events which leads to the translocation of GLUT4 in muscles and lipid lowering in adipocytes [64]. There are few case control studies which provide the evidence of the hypoglycemic effect of berberine. A RCT conducted in China with 106 T2D patients also suffering from dyslipidaemia, showed significant reductions in the levels of fasting and postprandial plasma glucose as well as HbA_{1c}levels when participants received a daily dose of 1 gm berberine for 3 months [65]. A meta-analysis conducted with 14 RCTs involving 1068 participants suggested that berberine has beneficial effects on blood glucose control in the treatment of T2D patients and exhibits efficacy comparable with that of conventional oral hypoglycemics (metformin, glipizideandrosiglitazone). Additionally, no serious adverse effects were noted for berberine in this study [66]. However, long term studies with larger sample sizes are needed to better understand the mechanism, efficacy and safety of berberine as an anti-diabetic agent.

The above mentioned part of the review highlights the importance of complementary approaches for the management of the diabetic phenotype. Table 1 summarizes the evidences in support of these complementary treatments.

Table 1: Summary of studies supporting various complement approaches towards the management of T2D

Comparative therapy	Mode of action	Evidence
Exercise	Increase in insulin sensitivity	a) Meta analysis on 8538 patients [24] b) 10 Prospective cohort studies with 301,221 participants [25] c) 8 weeks to study its effect on HbA1C and body mass of 504 T2D [26] d) Studies with 28 postmenopausal T2D women patients [28]
Yoga	Decrease in oxidative stress	a) 3 month trial with 123 diabetic patients [31] b) RCT on 23 adults [32]
Diet	Increase in insulin sensitivity, control and weight loss	a) RCT on 99 individuals [40] b) RCT on 99 individuals [41] c) A cohort study of 35988 women [42] d) Randomized, crossover study of 13 patients [43]
Vitamins a) Vitamin D	Improves insulin secretion and action, anti-oxidant activity.	a) Meta-analysis, including 21 prospective studies [47] b) RCT with 92 adult patients [48] c) Meta-analysis with 83,779 women [49]
b) Vitamin E	Reduction in oxidative stress	a) Meta-analysis on 38,716 [51] b) HOPE trial with 3654 patients [52]
c) Vitamin C	Antioxidant activity, modulating insulin action	a) Cohort study with 21831 individuals [54] b) Study on 10 healthy and 10 diabetic patients [55]
Nutraceutical a) Cinnamon	Promotes insulin secretion and glucose uptake	a) Meta-analysis of 10 RCT (543 patients) [57] b) RCT on 60 individuals [59]
b) Garlic	Antioxidant activity	a) Clinical trial on 50 patients [61] b) RCT on 70 patients [62]
c) Berberine	Activation of AMPK which leads to increase in glucose uptake	a) RCT on 106 T2DM patients [65] b) Meta-analysis of 14 RCTs (1068 participants) [66]

CONCLUSION

The prevalence of T2D is on an increase worldwide owing to the change in lifestyle. Several reports have come into the light which point towards various pharmacological agents like metformin, rosiglitazone etc., which have wide ranging side effects, including weight gain, hypoglycemia and risk of coronary heart disease. Since, T2D is a lifelong ailment thus prolonged exposure to drugs further deteriorates the quality of life of the patient.

Further, the cost of the prolonged treatment only adds to the woes of the patient. There is an urgent need to come up with complementary treatments that can be used as therapy along with the drugs to reduce the dependence on the drugs and better manage the disease.

Daily exercise, inclusion of nutritious diet and vitamin and nutraceutical supplements in everyday life can significantly improve the well being of diabetic patients.

ABBREVIATION

DM: Diabetes mellitus; T1D: Type1 Diabetes; T2D: Type2 Diabetes; TZD: Thiazolidinediones; PPARγ: Peroxisome Proliferator-activated receptor gamma; $K_{ATP:}$ ATP-sensitive potassium channels; SUR: Sulfonylurea receptor; GLUT4: Glucose Transporter 4; RCT: Randomized Controlled Trial; ROS: Reactive Oxygen Species LDL: Low Density Lipids; LDL-C: Low Density Lipid Cholesterol; HDL-C: High Density Lipid Cholesterol.

CONFLICT OF INTERESTS

No potential conflict of interest relevant to this article was reported.

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