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Type 1 Diabetes, Cardiovascular Complications and Sesame (芝麻 Zhī Má)

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ABSTRACT

Diabetes is a major concern among medical practitioners, with the annual mortality rate increasing up to 26.9% in a person aged 65 years or older and 11.3% in the adult. There are many serious complications associated with diabetes, particularly cardiovascular complications due to microvascular diseases. A prerequisite to reduce the risk of microvascular and neurologic complications of type 1 diabetes is normoglycemia. Insulin therapy is the most common treatment used nowadays in type 1 diabetes. However, this method still has many disadvantages such as increased episode of severe hypoglycemia, hypoglycemia unawareness, increased weight gain, transient exacerbation of pre-existing retinopathy, etc. Using insulin pump (the insulin pump is a medical device used for continuous subcutaneous insulin infusion to manage the insulin level in the treatment of diabetes mellitus), is associated with known disadvantages including increased ketoacidosis, infection at the infusion site, and the treatment being less suitable in young children (less than 7 years of age). Therefore, alternative treatment for diabetes is still in great demand. We took the approach of traditional Chinese medicine to discuss this matter. Sesame (芝麻 Zhī Má), a herb, has been used medicinally for thousands of years in almost all the countries in the world. The beneficial effects of sesame in remediating diabetes, such as hypoglycemic effects, antioxidant, anti-inflammatory, and hypolipidemic effects, improving fat metabolism, and reducing cholesterol, have been demonstrated in many studies,. However, reports on the effects of sesame in remediating cardiovascular complications in diabetic patients are limited, which necessitates further studies on the effects of sesame on cardiovascular complications.

Key words: Cardiovascular diseases, Chinese herbal medicines, Type 1 diabetes

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disease in which individuals have elevated blood glucose levels. DM is a current global health problem impacting children, adolescents, and adults. The World Health Organization (WHO) has reported that 347 million people worldwide suffer from diabetes, with about 3.4 million people dying in 2004 due to consequences of high fasting blood glucose.[1] In 2030, the seventh leading cause of death globally will be diabetes.[2] Diabetes can lead to a variety of complications, including cardiovascular diseases such as ischemic heart disease, peripheral vascular disease, cerebrovascular disease, and many types of ocular disease such as retinopathy, nephropathy, and neuropathy[3] [Figure 1].

Cell-mediated autoimmune destruction of pancreatic islet beta cells causes decreased insulin production, which leads to

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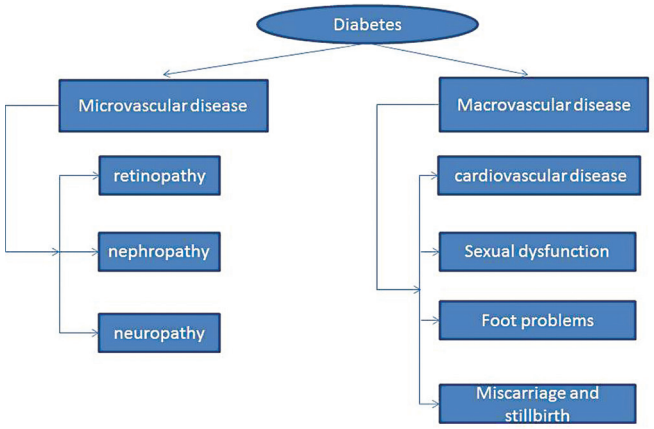

Figure 1. Diabetes and its complication of vascular diseases

type 1 diabetes mellitus or T1DM.[4] Although only about 10% of world population suffers from T1DM, the risk of death from T1DM is high.[5,6] The current annual rate of increase in cases of T1DM globally is 3–5%. If this trend continues, the number of new cases of T1DM in European children younger than 5 years is predicted to double between 2005 and 2020 and rise by 70%, with the condition common in children younger than 15 years. In the United States, about 215,000 people aged 20 years or older are diagnosed with diabetes and the number of new cases with diagnosis of diabetes is about 1.9 million. It is expressed in 0.26% of all people in this age group.[7]

Health care and social care related to T1DM are significant burdens for the economy of any country.[8] In developed countries, diabetes is one of the leading causes of retinopathy, kidney disease, and foot problems and the main cause of deaths from cardiovascular disease, all of which place a heavy burden on their economies.[9] In addition, a study from US has shown that T1DM subtracts 5–20 years from a patient's lifespan.[10] This is similar to the finding of a European study, which reported that when a child has T1DM, the standardized mortality rate (SMR) increases up to fourfold.[11] T1DM not only affects economies and the lifespan of patients, but also causes major psychological impacts, particularly in adolescents.[12]

The development of long-term microvascular and macrovascular complications is the main cause for the increased morbidity and mortality related to T1DM.[9] While testing the ratio of microvascular and acute diabetes complications and the relationship between diabetes duration and blood glucose control, Stephenson and Fuller found a significant correlation between microvascular and acute complications and the duration of diabetes and glycemic control.[13] In addition, degradation of long-term control of glucose metabolism and blood pressure and the development of retinopathy, neuropathy, and atherosclerotic complications lead to increasing trends in patient mortality. These are usually simultaneously caused by diabetic kidney disease.[14] For example, glomerular basement membrane thickening, increased mesangial matrix, and reduced glomerular filtration surface density are caused by renal disease which has long been considered the worst complication in patients with T1DM.[15] These pathologies have been shown to be related to albumin excretion rate and decreased glomerular filtration rate, which usually occur in most patients with T1DM.[15] Recent studies report that the relationship between diabetes and cardiovascular dysfunction has become clearer and more pernicious.[16-18]

CARDIOVASCULAR DISEASE IN PATIENTS WITH TYPE 1 DIABETES

Ischemia leads to mortality rates higher than those due to other complications in the T1DM population at all ages. Occurrence of ischemia is extremely high not only in young women with T1DM but also in men under the age of 40.[16] In younger population, imaging techniques have demonstrated that children with T1DM are exposed to greater risk of atherosclerosis than children without T1DM. The leading cause of mortality in young patients with T1DM, i.e. nephropathy, has been replaced by cardiovascular disease.[18]

Macrovascular complications cause damage to several organs. Coronary atherosclerosis occurs in most of the diabetic population, and 20% of the deaths of diabetic patients are due to myocardial infarction. Early diastolic dysfunction and late systolic dysfunction are characteristics of diabetic cardiomyopathy, in which intracellular calcium and sodium levels are maintained but potassium is reduced. In addition, left ventricular hypertrophy is a complication related to diabetes.[19] The following are the risk factors related to microvascular and macrovascular complications in T1DM: reformative factors, including glycemic monitoring, hypertension, dyslipidemia, diet, sedentary lifestyle, and tobacco use; and non-reformative factors, including diabetes monitoring and duration, genes, and puberty.[17,20] Impairment in remodeling of microvasculature related to hyperglycemia is the main indicator and the main factor leading to target organ damage.[21] According to a recent study, 86% of young people suffering from T1DM have at least one risk factor for cardiovascular disease, 45% are exposed to at least two factors, and 15% have at least three modifiable risk factors related to the disease.[22]

Clinical methods for detecting vascular dysfunction can help experts use appropriate treatment methods to prevent the development of complications.[20] Maintaining the blood glucose levels as close to normal as possible is the most effective way to manage diabetes. Variability in hemoglobin A1c (HbA_{1c}) and diabetes duration are the modifiable risk factors closer to development of complications.[23,24] In another study, the authors reported a relationship between significantly increased incidence of congestive heart failure and higher HbA levels in individuals with diabetes.[25]

In 2008, Cheung *et al*.[26] reached the conclusion in their article that the rate of incidence of heart failure is closely related to diabetic retinopathy. They observed an increase in the development of heart failure in patients with retinopathy (cumulative incidence of 21.6%) compared to individuals without retinopathy (cumulative incidence of 8.5%).

Experts suggest that individuals with T1DM who have a strong family history of cardiovascular disease should practice a fasting lipid blood screening at 2 years of age.[27] To avoid an atherogenic lipoprotein profile, glycemic control is necessary, and if there is an abnormal lipid profile, annual monitoring is required. If the

lipoprotein density value is greater than 4.1 mmol/l or 3.4 mmol/l and the individual has at least one other evident cardiovascular risk factor, the individual should follow a diet that restricts dietary fat to 7% of total calories and dietary cholesterol to 200 mg/d.[28] Age of onset, duration, blood glucose monitoring, and cardiovascular risk factors affect the appearance of complications such as neuropathy, retinopathy, and especially renal disease.[29,30]

Several studies have described the relationship between hyperglycemia and cardiovascular disease, but the relationship in the setting of T1DM is still unclear and incompletely understood.[31,32] Moreover, psychological factors, in particular depressive symptomatology, are not only the leading factors in angina and insulin resistance but also barely predict coronary artery disease (CAD) – the buildup of plaque in the arteries, cause of atherosclerosis status, leading to the interruption of blood flow[33] – end points.[32]

Because the incidence of cardiovascular dysfunction in patients with T1DM is higher than in those without T1DM, to prevent heart disease with its long asymptomatic latent period, the estimated global risk scores for cardiovascular risk should be provided.[4,34] Normoglycemia is a prerequisite to reduce the risk of microvascular and neurologic complications related to T1DM. By observing the symptoms of cardiovascular disease, such as nonfatal myocardial infarction, stroke, death from cardiovascular disease, confirmed angina, or the need for coronary artery revascularization, researchers have realized a significant percentage reduction in cardiovascular disease occurrence (42%, $P = 0.02$) and the risk of nonfatal myocardial infarction, stroke, or death from cardiovascular disease (52%, $P = 0.02$) in diabetic patients. In addition, decreasing glycosylated hemoglobin content has a positive effect in intensive therapy on the risk of cardiovascular disease. There is a close relationship between microalbuminuria and albuminuria and an increased risk of cardiovascular complications.[35] Intensive treatment, either by external insulin pump or three or more daily insulin injections, guided by frequent blood glucose monitoring improved the resistance and retarded the appearance of complications such as diabetic retinopathy, nephropathy, and neuropathy in patients with T1DM.[36,37] Furthermore, self-monitoring of blood glucose can also provide an accurate assessment of blood sugar levels. Results of self-monitoring blood glucose are helpful in preventing hypoglycemia and adjusting medication use, physical activity, and diet.[38] Self-monitoring has been identified as an integral part of diabetes education, and self-management of diabetes medical nutrition therapy is essential for patients with diabetes. Physical activity has been shown to cause significant improvement in glycemic control. It also helps in prevention of cardiovascular risk factors, leads to weight loss, and improves health in diabetic subjects.[39] Strictly controlled dietary behaviors improve diabetic subjects' health status.[24] A protein-deficient diet (0.6–0.7 g/kg/d) minimizes the complications of diabetic nephropathy.[40] More than 150 min of intense physical activity per week supports the melioration of metabolic control.[41] Consumption of carbohydrates might be increased by an active lifestyle in patients who underwent islet cell transplantation.[42]

Supporting knowledge of diabetes is also important in reducing negative psychological impacts on the patient. A Danish study showed that patients with a positive view in life will have lower complication rates than the patients with psychosocial distress.[43]

TRADITIONAL CHINESE MEDICINES IN DIABETES

Traditional Chinese medicines or functional foods are also positive treatments to improve the health of patients with diabetes status.[44-47] The pharmacological activities of herbal medicines, such as ameliorating insulin sensitivity, promoting insulin secretion, increasing glucose uptake by adipose and muscle tissues, inhibiting sugar absorption in the intestines, and increasing the storage of sugar in the liver, have been demonstrated in many studies.[48,49] Moreover, traditional Chinese medicines have been shown to have an effective impact on the treatment of cardiovascular complications in diabetic patients.[50] In type 1 diabetes, most of the herbal in some way protect the beta cells from attack by the immune system. KRG extract not only protects against streptozotocin (STZ)-induced destruction of pancreatic tissue but also restores insulin secretion. Also, the histopathologic results showed the recovery of lymphocytes in lymphoid organs.[46] The herbal was a success in the fight against CD8(+) – a cytotoxic T cell – and inhibited infiltration of lymphocytes into islets.[46] But in type 2 diabetes, these receptors are encouraged to produce as well as increase its efficiency by the effects of herbal, thereby reducing the blood glucose level.[49]

Certain herbals have been demonstrated to have properties that can improve the health of diabetics.[51,52] Korean red ginseng (紅參 Hóng Shēn; *Panax ginseng*), one type of traditional Chinese medicine, has been demonstrated to ameliorate diabetes. Extracts of this herb reduced glycemia and simultaneously reduced STZ-induced destruction of pancreatic tissue, while regenerating insulin secretion.[44] Green tea (綠茶 Lǜ Chá; *Camellia sinensis*) has also shown a positive antihyperglycemic and antioxidant activity after 4 weeks of treatment at a dose of 200 mg/kg in STZ-induced rats.[53] Ginger (生薑 Shēng Jiāng; *Zingiber officinale*) not only increases glucose tolerance but also increases serum insulin levels; this is likely related to participation of 5-hydroxytryptamine (5-HT) receptors.[54] The use of cucurbitaceae (苦瓜 Kǔ Guā; *Momordica charantia* L.) juice also showed a hypoglycemic effect similar to *Camellia* and *Z. officinale*, but its side effect is still a troubling issue and unclear.[55] Another herb, *Polygonatum odoratum* (玉竹 Yù Zhú; TFP), has also been investigated for its antihyperglycemic effects. Oral administration of TFP for 9 days lowered the blood glucose levels. Insulin level was also increased by TFP in type 2 diabetic rats.[56] The hypoglycemic activity of *To-kai-san* (TS) – a complex Chinese medicine – was reported by Miura *et al*.[57] TS not only exhibits hypoglycemic action but also decreases plasma insulin levels after 20 days of oral administration.[57] Chinese herbs, including holy basil leaves (*Ocimum tenuiflorum*), Xianzhen Pian (*C. sinensis*), Qidan Tongmai (a tablet of Chinese herbs), traditional Chinese formulae (TCT), Huoxue Jiangtang Pingzhi, and Inolter, exhibited significant hypoglycemic effects when compared with placebo. Moreover, seven herbal medicines, including Bushen Jiangtang Tang (a Chinese herbal recipe), composite Trichosanthis (瓜蔞 Guā Lóu; *Trichosanthes*

kirilowii), Jiangtang Kang, Ketang Ling, Shenqi Jiangtang Yin (*Schisandra* (五味子 Wǔ Wèi Zǐ), *Astragalus* (黄耆 Huáng Qí), *Dioscorea* (懷山藥 Huái Shān Yào), *Rehmannia* (熟地 Shóu Dì), *Rubus Chingii Hu* (覆盆子 Fù Pén Zǐ), *Wolfiporia* (茯苓 Fú Ling), *Trichosanthes kirilowii,* Xiaoke Tang, and Yishen Huoxue Tiaogan, were found to exhibit better metabolic control than the hypoglycemic drugs such as glibenclamide, tolbutamide, and gliclazide.[58] Furthermore, there have been no reports about the side effects from herbal medicines.[58] Most of the herbs are used as a mixture form.[59] So, the effect of each herb is not clear and this causes difficulties in the treatment of diabetes.

BENEFITS OF SESAME IN DIABETES

Since ancient times, sesame (芝麻 Zhī Má; *Sesamum*) has been considered a rare herb that can treat or prevent diseases. Sesame oil has been shown to reduce the risk of cardiac hypertrophy in mice with high blood pressure. Regression of left ventricular hypertrophy in hypertensive rats has been shown by its effects in reduction of cardiac mass, left ventricular thickness, and cardiomyocyte diameter, showing that sesame oil can have a positive effect on the status of cardiac hypertrophy in hypertensive rats.[60]

In recent studies, sesame and its ligands have been shown to have beneficial effects in treating, preventing, and ameliorating diabetes. The combined consumption of sesame oil and glibenclamide not only reduced the blood glucose levels significantly (36% in treatment compared to no treatment) but also decreased plasma total cholesterol, and this significantly improved the condition of subjects with type 2 diabetes.[61] Incubation of beta cells damaged by STZ with sesamin significantly improved cell viability, insulin secretion activity, activities of superoxide dismutase (SOD) and glutathione peroxidase (GSHpx), and reduced glutathione (GSH) content. Significant reductions in malondialdehyde (MDA) content, nitric oxide (NO) production, the enzyme activities of NO synthase (NOS), and induced NOS (iNOS) were observed in these cells when they were incubated with sesamin. The status of the damaged cells changed in a positive way. Sesamin can reduce beta cell-damaging factors such as oxidative stress and NO synthesis.[62] Hypoglycemic and hypolipidemic activity has been observed in KK-A^y mice, an animal model of type 2 diabetes and insulin resistance, when they were given sesamin orally. Such activity might be due to increased insulin sensitivity and improved insulin resistance by sesamin.[63] Blood glucose in adult female albino Wistar rats was significantly reduced from 322.61 ± 9.49 mg/dl to 222.02 ± 8.27 mg/dl when they were fed with sesamin. Elevated levels of glycosylated hemoglobin, vitamin E, thiobarbituric acid-reactive substances (TBARS), and lipid hydroperoxides were found to decrease on administration of sesamin. In contrast, the levels of hemoglobin, vitamin C, and GSH increased on oral administration of sesamin.[64]

Other than the cardiovascular system, sesame also demonstrates benefits in other systems. Bone loss due to estrogen deficiency was reduced by oral administration of diets supplemented with soybean oil and sesame oil in ovariectomized rats.[65] Sesame oil and sesamol have also exhibited effectiveness in treating heavy metal poisoning.[66] Concentrations of vitamins E and K increased in rat tissue on using sesame seeds and ligands as the main diet.[67] In another study on the inhibition of systemic IgE levels in allergic asthma, sesame oil reduced pulmonary edema and neutral bronchitis; meanwhile the interleukin (IL)-1β and IL-6 levels were significantly decreased in bronchoalveolar lavage fluid.[68]

Sesamin is the active agent and one of the most abundant lignans in sesame. It exhibits a variety of actions and functions, and is of much value as a pharmaceutical.[69] Numerous studies have demonstrated that sesamin has numerous health benefits, including improvement in fat metabolism, antioxidant action, hypolipidemic activity, reduction of cholesterol, anti-inflammatory action, enhanced potency of vitamin E, etc.[69]

CONCLUSIONS

Surpassing nephropathy, cardiovascular diseases have become the most serious complications resulting in high morbidity and mortality rates in diabetic subjects. Microvascular abnormalities in diabetes cause cardiovascular complications. To minimize these complications, detecting early onset of microvascular disease is essential. In addition, other risk factors associated with macrovascular diseases such as diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy require attention during disease process monitoring.[70] Numerous studies have provided a variety of methods for improving the diabetes status and related complications, including intensive treatment, pumping and injecting insulin, hypoglycemia drugs, and placebos.[36,37] A current interest is the application of natural medicines in disease treatment to limit the adverse effects of chemical drugs. Traditional Chinese medicines have a role in such treatments, especially in diabetes.[57] Sesame (芝麻 Zhī Má) has long been regarded as a precious herb. Effects of sesame in reducing glycemia and improving the diabetes status and its complications have long been demonstrated. However, few reports suggest that sesame can aid in improving cardiovascular complications in diabetic patients, and therefore necessitates further research [Figure 2].

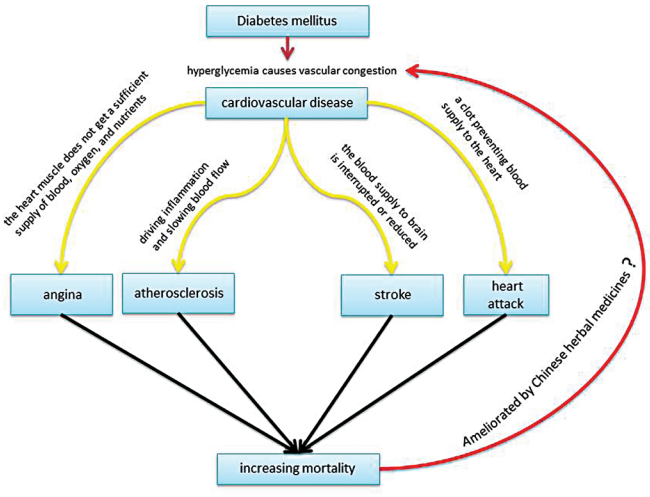

Figure 2. Overview of type 1 diabetes research

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