Beta-glucans in the treatment of diabetes and associated cardiovascular risks

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Abstract: Diabetes mellitus is characterized by high blood glucose level with typical manifestations of thirst, polyuria, polydipsia, and weight loss. It is caused by defects in insulin-mediated signal pathways, resulting in decreased glucose transportation from blood into muscle and fat cells. The major risk is vascular injury leading to heart disease, which is accelerated by increased lipid levels and hypertension. Management of diabetes includes: control of blood glucose level and lipids; and reduction of hypertension. Dietary intake of beta-glucans has been shown to reduce all these risk factors to benefit the treatment of diabetes and associated complications. In addition, beta-glucans also promote wound healing and alleviate ischemic heart injury. However, the mechanisms behind the effect of beta-glucans on diabetes and associated complications need to be further studied using pure beta-glucan.

Keywords: diabetes mellitus, hyperglycemia, prevalence, pathogenesis

Introduction

Diabetes mellitus (diabetes) is a chronic condition characterized by high blood glucose level (hyperglycemia) with typical manifestations of thirst, polyuria, polydipsia, and weight loss (Rother 2007). There are 171 million people worldwide suffering from diabetes in 2000 according to World Health Organization (WHO) statistics and this number would be more than double by 2030 (WHO 2008). The disease is responsible for 3.2 million deaths every year (WHO 2008). Three types of diabetes have been described. Type 1 is caused by T-cell mediated autoimmune destruction of islet insulin-secreting beta-cells (Rother 2007). Type 2 is characterized by the resistance to insulin with both hyperglycemia and hyperinsulinemia followed by the deficiency of insulin. Type 3 specially refers to that in pregnancy, which has both decreased insulin and increased resistance to insulin (Schinner et al 2005; Carpenter 2007; Kreier et al 2007). Among them, type 2 diabetes accounts for 90% of total incidence of diabetes (WHO 2008). Furthermore, prevalence of type 2 diabetes is increasing due to population growth, ageing, unhealthy diets, obesity, and sedentary lifestyles (James 2008). At present, diabetes is treated by injection of insulin (type 1) and combined with diet, exercise, weigh loss, and diabetic drugs (type 2). However, the control of diabtes associated mortality and decreased life quality is not satisfactory.

Beta-glucans are polysaccharides consisting of glucose residue jointed by beta linkage (Chen and Seviour 2007). They are found at a high level in the cell wall of fungi, yeast, oat, barley, as well as bacteria (McIntosh et al 2005). Their structures are diverse with fungal beta-glucans being beta-1,3 linkage branched by 1,6 while oat and barley beta-glucans linked by linear 1,3 and 1,4 bonds (Chen and Seviour 2007; Sadiq Butt et al 2008). However, beta-glucans are also excreted into growth medium, and this could facilitate purification and production (Schmid et al 2001). Natural products containing beta-glucans have been used for thousands of years for the benefits of human health, but beta-glucans were only identified as active components recently (Lucas et al 1958;

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Williams and Di Luzio 1980). Since then, they have been studied extensively for immune stimulation effects and developed for the treatment of several diseases including cancer, infectious diseases (Chen and Seviour 2007). Studies also showed that beta-glucans have great potential for the treatment of diabetes and associated cardiovascular diseases. The foods containing beta-glucans have been used for clinical trial in the treatment of diabetes. In this review, we will summary the possible mechanisms for beta-glucans in the treatment of diabetes and the prevention of its most severe complication of diabetes: cardiovascular risks.

The pathogenesis of diabetes and cardiovascular risks

Diabetes is caused by a defect in insulin secretion or insulin action. Insulin is the main hormone regulating glucose uptake from blood into muscle and fat cells (Schinner et al 2005; Lanner et al 2008). It binds to insulin receptor, which is composed of two extracellular alpha and two transmembrane beta subunits. After binding of insulin to extracellular subunit, the intracellular subunit tyrosine kinase domain will be activated (Czech and Corvera 1999). Consequently, four members of insulin receptor substrate family (IRS1-4) are activated. IRS-proteins in turn activates PI3K/Akt pathway, which is a critical signal pathway regulating many cellular functions such as apoptosis, cell growth (Manning and Cantley 2007; Asano et al 2007; Chen 2008; Chen and McMillan 2008). The pathway also regulates glucose transporter 4 (GLUT4) to relocate it to cell surface for the transportation of glucose into cells (Watson and Pessin 2001). The importance of PI3K/Akt was demonstrated by the fact that overexpression of constitutively active, membrane-targeted PI3K component p110α increased the translocation of GLUT4 to cell surface and increases glucose transportation into cells, irrespective of the presence of insulin (Okada et al 1994; Katagiri et al 1996; Martin et al 1996). Activation of PI3K also leads to glycogen synthesis in the liver to reduce blood glucose levels (Shepherd et al 1995; Sutherland et al 1995; Gabbay et al 1996). Recently it has been also shown that stimulation of PI3K downstream protein Akt2 activity is also sufficient for the GLUT4 translocation (Ng et al 2008). The defects in insulin signal pathways caused either by the insufficiency of insulin or the resistance to insulin play a central role in all forms of diabetes. It has been found that PI3K/Akt pathway is abnormal in diabetes patients (Asano et al 2007). In Zucker fatty rat, a model of early-stage type 2 diabetes induced by overeating and overwight, IRS-1 and IRS-2 mRNA was decreased with corresponding decrease of PI3K activity (Anai et al 1998). Responses of PI3K /Akt activity to insulin-stimulation was also severely impaired in the livers of diabetic (ob/ob) mice and Zucker fatty rats (Folli et al 1993).

Diabetes has a 2-fold higher death rate than in the non-diabetes population (Fox et al 2004). Most risks of diabetes are from its complications that often result in death. Acute complications include hypoglycemia, ketoacidosis, and non-ketotic hyperosmolar coma while chronic complications are cardiovascular diseases (CVD), chronic renal failure, retinal damage, nerve damage, and poor healing (Greenhalgh et al 1990). Due to the use of insulin and the control of blood glucose level, the likelihood of death caused by acute complications have been greatly reduced (Siperstein 1992). Thus, chronic complications are main danger in diabetes.

Chronic complications of diabetes are catalogued into microvascular diseases including diabetic retinopathy, nephropathy, and neuropathy; and atherosclerotic macrovascular diseases including ischemic heart disease and cerebrovascular and peripheral vascular disease (Klein 1995). When diagnosed as diabetes, one third of patients have already some forms of diabetic retinal lesions (Stolk et al 2008), which is the most common cause of blindness in middle aged-subjects (Frank 2004).There are 25% of patients with nephropathy after 10 years of diagnosis and it is the most common reason for renal failure (Gross et al 2005; Stolk et al 2008). Diabetes also causes a high prevalence of CVD (Stamler et al 1993). The relative risk for CVD in patients with diabetes is 2–4 times greater than those without diabetes (Fox et al 2004). Diabetes patients with CVD events have poor prognoses with 2–3 times greater mortality than those patients without diabetes (Fox et al 2004). Thus, CVD is responsible for a majority of the morbidity and mortality in diabetes (50%–80%) (Kannel and McGee 1979; Pyorala et al 1987; Haffner et al 1998). It has been demonstrated that combination of diabetes and other CVD risk factors such as hypertension and dyslipidemia resulted in higher risk than either risk factor along (Goff et al 2007). Thus, the key in the treatment of diabetes is to prevent the death caused by diabetes-associated CVD.

The management of risk factors including hyperglycemia, hypertension, and hyperlipidemia is critical to reduce diabetes associated CVD death. The importance for glucose in control of diabetes associated complications is demonstrated by the fact that each 1% increase in glycosylated hemoglobin increases the risk for CVD by approximately 18% (Goff et al 2007). Randomized trials also have shown that lowering LDL cholesterol reduces CVD event rates by 17%–43% in

patients with diabetes and reducing systolic blood pressure to <140 mm Hg results in 30%–60% reductions in CVD events (Goff et al 2007). Beta-glucans have been tested to be effective in lowing blood glucose concentrations and decreasing hyerlipidemia and hypertension (Kim et al 2005; Goff et al 2007). It may provide another approach to cure diabetes.

The effects of beta-glucans on the blood glucose concentration and the responsible mechanisms

Both oat and fungal beta-glucans reduce blood glucose concentrations after oral administration in animal experiments and clinical trials (Lo et al 2006). In diabetic rats, orally ingested fruiting bodies and the acidic polysaccharide of both *Tremella mesenterica* and *T. aurantia* reduced blood glucose concentrations (Kiho et al 1995). A crude exopolysaccharide produced from submerged mycelial cultures of *Phellinus baummi* also exhibited hypoglycemic effects in stretozotocin-induced diabetic rats (Kiho et al 2000). In genetically diabetic mice, oral administration of 20% whole mushroom maitake powder and its chemically derived fractions prevented an increase in blood glucose levels by increasing insulin sensitivity (Mayell 2001). Another beta-glucan prepared by hot water extraction of *Agaricus blazei* basidiocarps showed antihyperglycemic, antihypertriglyceridaemic, antihypercholesterolemic and antiarteriosclerotic activity in diabetic rats (Kim et al 2005). All of these studies have used impure beta-glucans and thus the active component was not identified. However, the preparations from *Agaricus blazei* basidiocarps were digested by an endo beta-(1-6)-glucanase from *Bacillus megaterium* and the resulting di- and tri-saccharides had doubled the antidiabetic activities shown by the parent beta-glucans, which indicates that their derived oligosaccharides are the effective agents (Kim et al 2005).

Oat beta-glucans have been used in several clinical trials to reduce glucose. Studies showed that oat beta-glucan lowered postprandial glycemia (Tappy et al 1996; Jenkins et al 2002). It was also shown that oat bran flour was more effective than oat bran crisp explained by the three times higher of beta-glucan content in oat bran flour (Saris 2003; Tapola et al 2005). The problem is also that no purified beta-glucan whose chemical structure has been fully characterized has yet been tested against diabetes. Consequently, the need is to clarify the structural features required and to identify the nature of the beta-glucan binding receptors related to their antidiabetes activities.

The effect of beta-glucans to reduce blood glucose could be mediated possibly by delaying stomach emptying so that dietary glucose is absorbed more gradually (Kiho et al 1995). After ingestion of the oat (bran flour or crisp), the blood glucose levels were lower at 15, 30, and 45 min but higher at 90 min after 12.5 g glucose loading (Tapola et al 2005). Thus, the peak level is much smoothed and the shape of the plasma glucose response curve is much flatter (Tapola et al 2005). These changes reduce the feeling of hunger caused by rapid decrease in blood glucose (Ludwig 2003; Saris 2003). Thus, beta-glucans may decrease appetite and reduce food intake.

Another possible mechanism for beta-glucans to reduce blood glucose level is mediated by signal pathway through PI3K/Akt activation. Decreased PI3K/Akt activity has been shown to play a key role in the pathogenesis of diabetes. Beta-glucans have been demonstrated to increase PI3K/Akt through several receptors (Hsu et al 2002; Chen and Seviour 2007). These receptors stimulated by beta-glucans include Dectin-1, complement receptor 3, lactosylceramide, scavenger and toll like receptors; each induces specific signal pathways. The interaction between beta-glucans and their receptors has been reviewed in detail (Brown 2006; Chen and Seviour 2007). The most relevant fact is that administration of beta-glucans could restore decreased PI3K/Akt in diabetes. For example, zymosan and mushroom extract have been shown to activate PI3K/Akt pathway mediated by syk kinase (Hiller et al 2000; Li et al 2006; Lee et al 2008). These beta-glucans can bind to dectin-1 receptor to stimulate the signal pathway (Underhill et al 2005; Trinidad et al 2006; Brown 2006; Olsson and Sundler 2007). Another beta-glucan lentinan binds to scavenger receptors which can also activate src tyrosine kinase and PI3K/Akt pathway (Rice et al 2002; Mineo et al 2003). However, how it works in diabetes is not studied. It will be interesting to test if beta-glucans could restore PI3K/Akt activity in diabetes animal models.

Reduction of blood cholesterol level

Diabetes associated dyslipidemia is a major risk factor for CVD (Turner et al 1998). The dyslipidemia is caused either by insulin resistance or adipocytokines. In diabetes, adipose cells are insulin resistance, thus, insulin-mediated uptake of free fatty acids in skeletal muscle is impaired. Increased circulating free fatty acids flux to the liver, resulting in increased triglyceride synthesis and the assembly of very low-density lipoprotein (VLDL) (Assmann et al 1997; Jeppesen et al 2003; Hobbs 2006). Thus, the characteristics of dyslipidemia in the patients with diabetes is hypertriglyceridemia.

Hyperglycemia and low insulin may also contribute to VLDL production (Hobbs 2006). In diabetes, adiponectin is reduced, which increases muscle free fatty acid uptake and reduce plasma free fatty acid level (Yamauchi et al 2001; Faraj et al 2004). This mechanism is independent of insulin-resistance (Tschritter et al 2003; Schulze et al 2004). In addition, high-density lipoprotein (HDL) may also decrease (Harris 1991; Laakso 1996).

Beta-glucan has been shown to decrease LDL cholesterol and increase HDL to alleviate possibly dyslipidemia and reduce CVD (Anderson 1995; Reyna-Villasmil et al 2007; Kapur et al 2008). Oats were first found to have a cholesterol-lowering effect and the active component was identified as beta-glucans (Kerckhoffs et al 2002). Oats reduced both serum total choleterol and LDL cholesterol compared with control (Davidson et al 1991; Van Horn et al 1991; Gerhardt and Gallo 1998; Kerckhoffs et al 2003; Karmally et al 2005; Naumann et al 2006; Reyna-Villasmil et al 2007; Theuwissen and Mensink 2007). In 20 hypercholesterolemic male patients, oat bran was shown to be better than wheat bran in lowing choleterol (Anderson et al 1991). Barley has also been shown to have a similar effect (Davy et al 2002; Behall et al 2004; Shimizu et al 2008). Although reduced LDL in diabetes has been shown to decrease CVD incidence by 25%–50%, oat and barley beta-glucans do not reduce triglyceridemia (Collins et al 2003; Colhoun et al 2004). Thus, it will be needed to further characterize lipid alteration by beta-glucans in diabetes. There is possibility that combinational use of beta-glucans with other fibers, which decrease triglyceride such as a corn fiber, α-cyclodextrin (trade name FBC) could produce better treatment effect (Artiss et al 2006).

Obesity is closely related with diabetes and responsible for increased number of diabetes in recent years (Mokdad et al 2003; Fox et al 2006; Hoenig 2008). Several factors in obesity including hyperlipidemia, hyperinsulinemia, hyperleptinemia, and insulin resistance could contribute to the development of type 2 diabetes (Olefsky 1981; Kissebah et al 1989). Obesity has been associated with increased triglyceride, VLDL, total cholesterol, and decreased HDL and thus, is also a cause of CVD (Denke et al 1994). Administration of oat and barley may help to reduce appetite and weight gain. Many studies have shown beta-glucans reduced body weight (Artiss et al 2006; Reyna-Villasmil et al 2007). For example, Sanchez and colleagues (2008) showed the lowing body weight effect of oat bran beta-glucan at the concentration of 10%. In a clinical trial, barley beta-glucan reduced LDL, total cholesterol, waist circumference and visceral fat (Shimizu et al 2008). However, controversial results have also been presented. In a randomized single blinded crossover study, Keogh and colleagues (2007) found that soluble fibre and amylose from barley Himalaya 292 increased subsequent energy intakes rather than reduce although it decreased blood glucose and insulin levels. They have also reported that barley beta-glucan was not effective on LDL (Keogh et al 2003). This could be due to lower beta-glucan contents used or different properties of beta-glucans in different preparation. Recent trials by Shimizu and colleagues (2008) also showed that 7.0 g beta-glucan from barley per day for 12 weeks caused marked decrease in LDL cholesterol. Therefore it is important to study specific effects for structurally different beta-glucans.

The mechanism for beta-glucans to lower LDL is considered to be mediated by bile acids binding property of beta-glucans. Therefore beta-glucans increase exclusion of bile acids (Lia et al 1995; Marlett 1997; Ellegard and Andersson 2007), and this in turn activates choleterol 7α-hydroxylase and upregulates low-density lipoprotein receptor (LDLR) and thus increase the transport of LDL into hepatocytes and the conversion of cholesterol into bile acids (Nilsson et al 2007). Other soluble dietary fibres that are resistant to digestion by human enzymes such as pectins, guar gums, psyllium can also have similar effects (Anderson et al 1990; Anderson 1995). The advantages for beta-glucans are that they exhibit high viscosities at very low concentration (1%) and are stable with pH (Sadiq Butt et al 2008). The viscosity determined by water solubility and molecular weight has been shown to affect the hypocholesterolemic effect of beta-glucans (Sadiq Butt et al 2008). Thus, different structure of beta-glucans may have different properties to cause viscosity. Some beta-glucans may have no effects. It is important to characterize what sort of structure features are essential for lowering lipids and antidiabetic effects. There is possibility to modulate the synthesis of beta-glucans to increase their effect as the successful alteration of the resistant starch by siRNA interference of starch-branching enzyme (SBE) II (SBEIIa and SBEIIb) in wheat has been used (Regina et al 2006). In addition, Oat and barley beta-glucans have also been shown to be fermented by human fecal microbiota to produce short-chain fatty acids, which have also hypocholesterolemic effect (Han et al 2004; Drzikova et al 2005; Alminger and Eklund-Jonsson 2008; Hughes et al 2008).

The effects of beta-glucans on hypertension

Hypertension is a risk factor in diabetes and diabetes itself can increase hypertension (Klag et al 1996; Martin et al 1996).

Beta-glucan has been shown to be able to reduce hypertension. In genetically modeled rats with spontaneous hypertension (SHR), a diet containing 5% Shiitake (*Lentinus edodes*) or maitake (*Grifola frondosa*) caused a decrease in the mean systemic blood pressure (Kabir et al 1987, 1988; Kabir and Kimura 1989). Moreover, consumption of whole maitake basidiocarps and the water-soluble extract also led to a decrease in blood pressure in Zuker fatty rats, a diabetes rat model (Talpur et al 2002a, 2002b, 2003).

A clinical trial with food containing oat beta-glucan showed it reduced blood pressure in the subjects with body mass index above medians (31.5 kg/m^2) (Maki et al 2007). This is further demonstrated by another trial that also showed effective role of oat (He et al 2004). However, no pure beta-glucan has been used for these studies and thus, it is difficult to identify which components are effective. Other components from mushroom have also been shown to decrease blood pressure such as pepetides (Talpur et al 2003; Hyoung Lee et al 2004).

Increase wound healing

Vascular injury may contribute to the pathogenesis of CVD (Liuba and Pesonen 2005; Kibos et al 2007). Beta-glucan such as zymosan has been shown to be beneficial in wound healing (Kenyon and Michaels 1983; Browder et al 1988). It may increase collagen synthesis (Portera et al 1997; Wei et al 2002). The study has shown that beta-glucan can help the healing of wound in db/db mice (Berdal et al 2007). This is related beta-actin activation of macrophage. There is also possibility that beta-glucan could help the healing of vascular injury. But no such experiments have been performed.

In addition, cardiomyopathy is 75% more in diabetes patients (Bertoni et al 2003) and could be caused by insulin resistance in diabetes (Karnik et al 2007). It is also caused by the impaired PI3K/Akt pathway (Shulman 2000; Kim et al 2001). Insulin sensitizer has been demonstrated to be beneficial (Sasaki et al 2007). Thus, beta-glucan induction of PI3K/Akt to sensitise insulin could be important for the prevention of cardiomyopathy in diabetes. Furthermore, activated Akt also increases cell survival (Hsu et al 2002). Indeed, most of cardiomyopathy is ischemic (Frustaci et al 2000; Domanski et al 2003). Beta-glucans have been shown to protect heart ischemic injury (Li et al 2004).

Conclusions

In conclusion, beta-glucans are potentially beneficial in the treatment of diabetes and associated cardiovascular risks. Studies have shown that beta-glucans could reduce hyperglycemia, hyperlipidemia, and hypertension. Thus, beta-glucan could produce new approaches for the treatment of diabetes. However, no pure beta-glucan has been used. Thus, it is not known if other components in products used could also have effects. Beta-glucans are diverse in their structure and some may be not effective on diabetes. Thus, characterization of structure features essential for antidiabetic effects is of importance and the modification of beta-glucan structure may lead to compounds that are more effective for the treatment of diabetes. Further studies will be also needed to elucidate how beta-glucan affect PI3K/Akt in diabetes.

Disclosure

The authors report no conflicts of interest in this work.

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