Complementary and alternative approaches to diabetes care

Continuing Education Module

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**Goal:**

The goal of this module is to promote an understanding of diabetes mellitus. The effects of nutritional supplements on diabetes management will also be discussed.

**Objectives:**

Following the successful completion of this module, the healthcare professional will be able to:

- Discuss the different types of diabetes.
- Understand the pathogenesis of type II diabetes.
- Recommend CAMs products effective in diabetes management.
- Discuss the relationship between diabetes, oxidative stress and nutritional deficiencies.

1. Introduction

Patients with diabetes experience a host of problems related to the condition, including problems with their eyes, circulation, teeth, feet, and the heart. Diabetes also increases the risk of several gastrointestinal conditions ranging from reflux to faecal incontinence (Pray, 2007).

Besides being the earliest manifestation of neuropathy, microalbuminuria is an independent marker of increased cardiovascular morbidity and mortality for patients with type I or type II diabetes. Death rates from CVD in adults with diabetes are two to four times higher than for adults without diabetes. Heart disease is also the leading cause of diabetes-related deaths, accounting for about 65% of deaths among people with diabetes. Thus, detecting microalbuminuria is an indication for vascular disease screening and aggressive intervention to reduce all cardiovascular risk factors, including LDL-C, hypertension, blood glucose, obesity, inactivity, and smoking (Iltz et al., 2006).

According to Diabetes South Africa (www.diabetessa.co.za) there are three main types of diabetes. It is believed that 90% of people living with diabetes have type II diabetes, with one in five people over the age of 35 estimated to have type II diabetes. The International Diabetes Federation reported that there were 4.6 million deaths due to diabetes in 2011 alone (www.discovery.co.za).

2. Diabetes mellitus

2.1 Type I

Type I diabetes results when the pancreas produces insufficient amounts of insulin to meet the body's needs. A trigger – either an illness or stress – cause the immune system to attack and destroy the beta cells of the pancreas. As a result the pancreas stops producing insulin. The primary treatment for type I diabetes is to take insulin injections every day to survive. This form of diabetics is also called insulin dependent diabetes mellitus (IDDM). Type I develops suddenly in childhood or adolescence (Fatima et al., 2012). It is interesting that niacinamide may play a role in preventing the further progression of this type of diabetes.
2.2 Type II

Type II diabetes results when the pancreas produces insulin, but the cells are unable to use it efficiently; this effect is called ‘insulin resistance’. Type II diabetes is far more common than type I and approximately 90% of all diabetes cases are type II. There is a strong genetic predisposition for type II diabetes. Age, obesity and sedentary lifestyle are also risk factors. This form of diabetes is called non-insulin dependent diabetes mellitus (NIDDM). Type II mainly affects people over the age 40 and is more common in overweight people (Fatima et al., 2012).

2.3 Gestational diabetes mellitus (GDM)

In GDM glucose intolerance is recognized during pregnancy. It can complicate pregnancy leading to prenatal morbidity and mortality, so clinical detection is important. GDM occurs as a result of hormonal changes during pregnancy and affects 2-4% of women, usually in the second or third trimester (Mossman, 2007). Gestational diabetes is fully treatable but requires careful medical supervision throughout the pregnancy. About 20-50% of affected women develop type II diabetes later in life.

2.4 Other specific types of diabetes

Maturity onset diabetes of youth (MODS) is due to an impaired insulin secretion, or minimal or no insulin resistance - hyperglycaemia is noticed at an early stage. Genetic inability to convert pro-insulin to insulin causes mild hyperglycaemia (Fatima et al., 2012).

3. Diabetic control

Pathological features of diabetes mellitus are due to the following factors (Fatima et al., 2012):

- Decrease in utilization of glucose by the body cells. This results in an increase in the blood glucose concentration to 300 - 1 200 mg/dl.
- Increase in mobilization of fats from the fat storage areas. This results in abnormal fat metabolism and deposition of cholesterol in arterial walls causing atherosclerosis.
- Tissues get protein depleted.

There is worldwide an epidemic of both type I and type II diabetes. The effects of uncontrolled diabetes are experienced daily in all medical institutions, with short and long term complications being costly and drain on our already strained budget. The following should be controlled in diabetes (Van Zyl, 2007):

3.1 Blood glucose

Blood glucose should be measured both before and after meals. Before meals the blood glucose ideally should be less than 6.5 mmol/l, and after meals not higher than 8.5 mmol/l (Lowy and Phillips, 2005). Due to costs patients can be taught to monitor at different times on different days to gain an overall picture of the blood glucose trends.

3.2 Haemoglobin A1c

Every three to four months it is important to have blood drawn to evaluate HbA1c. The ideal is between 5% and 6%. This reflects a blood sugar between 4.5 and 6.7 mmol/l. For each percent the average blood sugar rises approximately 2 percentage points. The HbA1c allows evaluation of true long-term success of blood sugar control - most strive for a value of less than 7% (Phillippou, 2012; Mollentze, 2013).

By reducing the HbA1c by 1%, the Diabetes Control and Complications Trial (DCCT) showed that this could reduce the complications of retinopathy by 38%, nephropathy by 28% and neuropathy by 35% in type I diabetics (DCCT, 2005). The United Kingdom Prospective Diabetes Study (UKPDS) showed that reducing the
HbA1c in type II diabetics by 0.9% could reduce any diabetic end point by 12%, reduce any microvascular end point by 25%, reduce MI by 16%, reduce retinopathy by 21% and reduce microalbuminuria at 12 years by 34% (Holman et al., 2008).

### 3.3 Lipids

Diabetes is a metabolic disease, which commonly has an effect on the lipid status of the individual. Triglycerides should be measured at each visit to the health care professional, and levels to aim for are as follows:

- Fasting < 1.7 mmol/l and
- Post-prandial levels ≤ 2.3 mmol/l.

Total cholesterol should be kept at < 5.2 mmol/l, while HDL cholesterol should be > 0.9 mmol/l.

### 3.4 Blood pressure

Blood pressure is very important in all types of diabetes, and it is essential that it is measured at each visit to a health care professional. Blood pressure is treated aggressively in diabetes (Phillips, 2007).

### 3.5 Urine albumin/microalbuminuria

Urine should be monitored for protein at least once annually.

### 4. Pathogenesis of type II diabetes (Pirie, 2005)

Insulin enhances glucose uptake into some cells and also increases the utilization of glucose by these cells. Insulin levels may actually increase in some obese patients with type II diabetes mellitus. Untreated diabetes mellitus is characterized amongst others by cells starving for glucose.

The hyperglycaemia of type II diabetes develops when pancreatic β-cell insulin secretion is insufficient to compensate for the prevailing degree of insulin resistance. In the initial stages, postprandial hyperglycaemia occurs, but with progression, fasting hyperglycaemia also develops. In most people with type II diabetes, the disorder is a condition of both insulin resistance and β-cell dysfunction in different proportions. It appears that both components are required for the clinical expression of the disease (Pemba, 2012). Glycosylation of proteins in diabetics is believed to be partly responsible for many of the long-term complications of the disease.

Rare conditions exist in which overt diabetes develops with either extreme insulin resistance alone or severe defects in insulin secretion alone, without the corresponding metabolic defect. Insulin resistance appears to be the initial metabolic defect in most subjects destined to develop the disease and is often demonstrable many years before the onset of any abnormality in glucose tolerance. Evidence in favour of the presence of β-cell dysfunction was provided by the United Kingdom Prospective Diabetes Study (UKPDS; Holman et al., 2008), in which it was estimated that approximately 50% of β-cell function is lost by the time type II diabetes is diagnosed. In addition, the UKPDS showed that β-cell function continued to decline over time, indicating that type II diabetes is a progressive disease.

Insulin resistance commonly occurs in association with obesity and the relationship between insulin sensitivity and body mass index (BMI) has been shown in numerous studies. Not all obese subjects with insulin resistance develop diabetes, however, thus substantiating the fact that an additional factor (β-cell dysfunction) is required for the disease to develop. Furthermore, at least some of the β-cell dysfunction appears to be reversible by optimal glycaemic control. In the early stages of the disease, improvement in insulin secretion through optimal glycaemic control may be sufficient to induce clinical remission for a variable length of time.
The predominant metabolic disturbances which result from combined insulin resistance and inadequate insulin secretion include decreased glucose uptake by skeletal muscle and liver, decreased hepatic glycogen synthesis and increased hepatic glucose production. Insulin resistance at the level of the adipocyte causes increased lipolysis, resulting in an increase in circulating free fatty acids with deleterious effects on both insulin sensitivity and insulin secretion (lipotoxicity) (Pirie, 2005).

Type II diabetes is classified as a single entity by the World Health Organization, but is qualified as being due to either predominant insulin resistance or predominant insulin secretory dysfunction, which means that the disorder is heterogeneous. Population-based prevalence studies have also shown ethnic heterogeneity (Pirie, 2005). Application of a common therapy to a condition with a uniform clinical expression (hyperglycaemia) but variability in the pathogenetic factors is not logical. Clinical judgment is needed to select the most suitable therapies to treat hyperglycaemia in individual cases. Recognising that the disease is, in all probability, inexorably progressive despite optimal glycaemic control, is critical to the long-term follow-up of patients with type II diabetes. This requires continued surveillance of metabolic control and corresponding adjustment of therapy in all cases.

The UKPDS demonstrated that good glycaemic control can result in reduction of micro vascular complications of diabetes. This means that any clinician managing patients with type II diabetes must ensure that glycaemic targets are achieved and maintained as strictly as possible in each individual case (Pirie, 2005). The Society for Endocrinology, Metabolism and Diabetes of South Africa (SEMDSA) has published guidelines for metabolic control and these include a fasting glucose concentration of 4-6 mmol/l, postprandial glucose concentration of 4-8 mmol/l and glycated haemoglobin level <7.0%.

Both non-pharmacological and pharmacological interventions can help attain these goals. Non-pharmacological interventions include weight loss through calorie-restricted diets and regular physical exercise. Both are effective in reducing hyperglycaemia and should be the initial management in most subjects with newly diagnosed type II diabetes. It has been well established that regular participation in physical exercise reduces the risk of developing type II diabetes (Schwellnus and Derman, 2005). Since physical exercise can reduce blood glucose levels and insulin resistance, regular aerobic exercise can improve metabolic control in type I diabetes (Valerio et al., 2007).

Although diet and exercise will be insufficient as sole therapies for long-term management in most cases, they should remain part of the management, since drug therapy is more effective in subjects on continued diet and exercise programs (Ignarro et al., 2007).

5. Diabetic peripheral neuropathy (Farvid et al., 2011)

Diabetic peripheral neuropathy is a degenerative complication of diabetic patients, characterized by a progressive loss of nerve fibres and is the leading cause of painful or insensitive extremities, most foot ulcers and amputations. The pathogenesis of diabetic neuropathy is not yet clearly defined. For a long time hyperglycaemia and diabetes duration were viewed as major. The other possible important etiologic factors are hypertension, age, smoking, alcohol, hypoinsulinemia, hyperinsulinemia and dyslipidaemia. However the influence of some factors may have been overestimated in some studies.

Hyperglycaemia can induce oxidative stress via various mechanisms, such as glucose auto-oxidation, and subsequent formation of advanced glycation end-products (AGEs), polyol pathway hyperactivity, and altered essential fatty acid metabolism. Also, there is a growing body of scientific evidence pointing to oxidative stress as a critical factor in the development of diabetic peripheral neuropathy.

Enhanced oxidative stress produces lipid peroxidation, protein modification and DNA oxidation, which may cause damage to the tissue and play an important role in the development of diabetic complications. Higher levels of lipid peroxides have been reported in patients with diabetic neuropathy and patients with diabetic foot ulcers (Al-Rawi, 2011).

Although tight glycaemic control is the most effective way of preventing or delaying neuropathy, not all patients
with diabetes achieve this goal. In diabetes, vitamins C and E reduction contributes to the development of neuropathy. Vitamin E supplementation in diabetic rats had a neurotrophic role by maintaining neuronal cellular bodies. Defective nerve conduction in diabetic subjects is also affected by pharmacological treatment with vitamin E supplementation. Low levels of vitamin B₆ and hypomagnesaemia have been reported in patients with diabetic neuropathy but not in diabetic patients without neuropathy. Therefore, antioxidant vitamins and minerals that have beneficial effects in oxidative stress reduction in diabetic patients through improving glycaemic control and/or applying antioxidant activity might be recommended as adjunctive therapy in diabetic patients to improve symptoms of neuropathy.

Because of the known synergistic action between vitamins E and C, vitamin E and zinc, and vitamin E and magnesium, a further important question is whether a combination of antioxidants provides better protection, thus, in their double blind, randomized, placebo-controlled clinical trial, Farvid and co-workers (2011) investigated the effect of magnesium in combination with zinc, vitamin E and vitamin C, on neuropathy indices in subjects with type II diabetes and additionally examined the combining of these micronutrients with the vitamin B group. The authors concluded that their studies suggest that micronutrients supplementation might ameliorate diabetic neuropathy symptoms (Farvid et al., 2011).

Finally, a number of studies showed that hyperhomocystenemia occurred and was associated with macro/micro complication in diabetes, and was independently associated with the occurrence of diabetic neuropathy (Jianbo et al., 2011; Fonseca et al., 2013).

6. Diabetes, oxidative stress and nutritional deficiencies

High blood sugar levels strain the body and its organs – as a result oxidative stress can occur. Diabetics are also more inclined to have low levels of antioxidants, minerals and vitamins in their bodies due to their condition - oxidative stress associated with altered cellular function in diabetes may therefor respond favourably to antioxidant treatment. Thus diabetics are prone to nutritional deficiencies and may benefit from appropriate and targeted supplementation.

A relationship between diabetes and minerals is frequently reported. Trace elements as a component of oxidative stress are suggested to be a good indicator for diagnosing various diseases. Oxidative stress is an important contributing factor in the pathogenesis of many diseases, including diabetes (Viktorinova et al., 2009; Kangralkar et al., 2010)). Several studies have confirmed that hyperglycaemia plays a key role in inducing oxidative stress in diabetes.

Copper and zinc play a pivotal role in the oxidant/antioxidant mechanism, imbalance of which leads to increased susceptibility to oxidative damage of tissues, thereby leading to the pathogenesis of diabetes or diabetic complications. Copper acts as a pro-oxidant and may participate in metal-catalysed formation of free radicals. On the other hand, Cu and Zn act as structural and catalytic components of some metallo-enzymes. Copper is necessary for the catalytic activity of enzymes such as Cu/Zn superoxide dismutase (SOD) that is involved in the protection of cells from superoxide radical. Zinc acts as an antioxidant by protecting the sulfhydryl groups of proteins and enzymes against free radical attack in the body (Fang et al., 2002; Viktorinova et al., 2009). Dietary deficiencies in zinc can also contribute to single- and double-strand DNA breaks and oxidative modifications to DNA that increase the risk for cancer development (Ho, 2004).

Experimental and clinical data suggest that the supplementation of insulin resistant or diabetic states with antioxidants like vitamins C, E, and selenium, normalises oxidant stress and improves both endothelium-dependent vasodilation and insulin sensitivity (Laight et al., 2000; Ceriello et al., 2007).

It is well known that zinc plays a key role in the synthesis, storage, and secretion of insulin. Hyperglycaemia causes the increased urinary losses of zinc and decreased zinc levels in the body. The decreased levels of zinc affect adversely the ability of the islet cell to produce and secrete insulin (Viktorinova et al., 2009; Carneiro et al., 2013).

Magnesium is an essential component in various enzymatic pathways involved in glucose homeostasis. The
relationship between hypomagnesaemia and insulin resistance, impaired glucose tolerance, as well as decreased insulin secretion has been suggested by numerous studies (see Viktorinova et al., 2009 for a review). Reduced plasma levels of magnesium have been documented in both type I and type II diabetes, especially in poorly controlled diabetes mellitus. The cause of hypomagnesaemia was attributed to osmotic renal losses from glycosuria, decreased intestinal absorption, and redistribution of magnesium from the plasma into blood cells caused by insulin effect (Guerrero-Romero and Rodriguez-Moran, 2005; Viktorinova et al., 2009; Carneiro et al., 2013).

Magnesium deficiency may also have some effects on the development of diabetic complications with other risk factors (Johnson, 2001; www.naturalmedicine.co.za). Patients with diabetes have altered metabolism of copper, zinc, and magnesium; and this may be related to increased values of glycated haemoglobin. In their research Viktorinova and co-workers (2009) concluded that impaired metabolism of these elements may contribute to the progression of diabetes mellitus and diabetic complications (Viktorinova et al., 2009).

Magnesium participates in several intracellular processes in many tissues and is relevant for glucose metabolism. It has been shown that insulin is an important regulatory factor of intracellular magnesium accumulation. Once inside the cell, magnesium plays the role of a second messenger for insulin action (mainly oxidative glucose metabolism). Intracellular magnesium deficiency may result in disorders of tyrosine kinase activity during insulin signalling and glucose-induced insulin secretion, leading to impaired insulin sensitivity in muscle cells and adipocytes (Carneiro et al., 2013).

There is increasing evidence suggesting that vitamin D deficiency has adverse effects on glucose tolerance, insulin resistance, and the risk of diabetes mellitus, independently of the degree of obesity (Carneiro et al., 2013). Vitamin D is a hormone essential for regulation of calcium and phosphorous metabolism. Vitamin D may predispose to glucose intolerance and altered insulin secretion and type II diabetes, either through a direct action, via vitamin D receptor (VDR) activation, or indirectly, via calcium metabolism. Pancreatic β cells express VDR, 1 alpha-hydroxylase enzyme and calcium binding proteins and respond to 1,25 (OH)2D in vitro with increased insulin secretion. The mechanisms by which 1,25 (OH)2D might act on insulin secretion also involves calcium and the parathyroid hormone (Carneiro et al., 2013). The results of a large prospective study (Pittas et al., 2006) suggest a potential beneficial role of both vitamin D and calcium intake in reducing the risk of type II diabetes especially in women; a systematic review and meta-analysis by the same authors (Pittas et al., 2007) concluded that vitamin D and calcium insufficiency may negatively influence glycaemia, while combined supplementation with both nutrients may be beneficial in optimizing glucose metabolism. Results of Skalli and co-workers (2012) also showed an association between vitamin D deficiency and clinically assessed neuropathy in type II diabetic patients.

The trace mineral selenium is essential for human health. As selenocysteine, it is the key component of a number of selenoproteins with essential enzymatic functions that include redox homeostasis, thyroid hormone metabolism, and protection from oxidative stress and inflammation (Thurnham, 2009; Rayman and Stranges, 2013).

The vitamin B family of vitamins play an active role in energy provision (see table 6); while rare in Western diets, deficiency of thiamine still occurs in populations who consume large amounts of polished rice.

7. Diabetes and complementary and alternative medicine (CAMs)

Vitamins, minerals and trace elements are essential factors and cofactors in many biological processes regulating directly or indirectly the body glucose metabolism. The accumulated evidence for example suggests that low plasma vitamin D, zinc or magnesium concentrations are associated with impaired glucose metabolism and an increased risk of type II diabetes. The role of these vitamin and minerals in the pathogenesis of diabetes, however, still remains to be explained (Carneiro et al., 2013).

The worldwide prevalence of diabetes has caused a tide of research in the field of diabetic medication and complications. Metformin, an old medication, which is mainly benefiting from the medicine itself and losing body weight it caused, has been widely prescribed to patients with diabetes. Great interest has been roused in
recent years for the beneficial effects of metformin on reducing risks of cardiovascular diseases, all-cause mortality and even probably cancers, which is attributed to its roles in regulating AMPK/mTOR pathway. The established advantages and safety of metformin have made it the first-line treatment in patients with type II diabetes.

However, some studies have demonstrated that long-term use of metformin combined with other antidiabetic agent increased the risk of vitamin B\textsubscript{12} and folate deficiency, and thus influenced the homocysteine metabolism and contributed to the progression of diabetic peripheral neuropathy (Xu et al., 2013).

There are many products on the market targeting diabetic patients and include capsules, tablets, energy drinks and powdered nutritional shakes. These shakes may be substituted for meals or part of meals, or used as a dietary supplement to increase calorie or protein intake, to gain or maintain weight and to support a balanced nutritional program. These shakes are typically:

- Low GI
- High in fibre - support for the healthy functioning of digestive tract and removal of toxins; fibre may also assist in providing a more sustained release of energy)
- High in protein
- High in vitamin B\textsubscript{3} - may assist with circulation and the metabolism of carbohydrates, fats and proteins
- High in vitamin B\textsubscript{6} (support protein metabolism and immune function)
- High in zinc - anti-viral support
- High in chromium - may assist to stabilise blood sugar levels
- Source of magnesium - promotes healthy muscles and supports energy production
- High in omega 3 fatty acids – heart/vascular support
- Low in saturated fat

Herbs, vitamins and minerals (as contained in tablets and capsules) that have proven to be effective in diabetes management are:

7.1 Gymnema sylvestre

*Gymnema sylvestre* is an Indian herb used in Ayurveda; its primary application was for adult-onset diabetes (NIDDM), a condition for which it continues to be recommended today in India. The gradual hypoglycaemic action of Gymnema leaves, first documented in the 1930, differs from the rapid effect of many prescription hypoglycaemic drugs. Gymnema leaves raise insulin levels according to research in healthy volunteers possibly due to regeneration of the β-cells in the pancreas (Joffe, 2001; Ahmed et al., 2010; Patel et al., 2012). The leaves are also noted for lowering serum cholesterol and triglycerides. A water-soluble acidic fraction of the leaves provides hypoglycaemic actions, and is possibly gymnemic acid (Shanmugasundaram, et al., 1990).

Results from case reports and studies in humans suggest that gymnema works in several ways to help control both type I diabetes and type II diabetes (Baskaran, et al., 1990; Shanmugasundaram, et al., 1990; Patel et al., 2012; El Shafey et al., 2013). First, the acids contained in gymnema sylvestre decrease the amounts of sugar that are absorbed from foods. As a result, blood sugar levels may not increase as much as usual after meals. Secondly, gymnema sylvestre stimulates the production of insulin by the body. Gymnema sylvestre stimulates the pancreas to develop more β cells. It also makes body cells more responsive to the insulin that is available.

Gymnema sylvestre also reduces body weight, blood cholesterol, and triglyceride levels. Although the exact reasons are not clear, gymnema sylvestre blocks the absorption of dietary fats into the bloodstream. More fats are then eliminated instead of being stored. Some individuals taking gymnema sylvestre for diabetes have also seen a reduction in cholesterol and/or weight.

<p>| Table 1. Summary of studies done on Gymnema Sylvestre and diabetes (Natural standards) | 7 |</p>
<table>
<thead>
<tr>
<th>Condition</th>
<th>Study design</th>
<th>Author, Year</th>
<th>N</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type I diabetes</td>
<td>Controlled trial, non-randomized, non-blinded</td>
<td>Shanmugasundaram, 1990</td>
<td>64</td>
<td>GS4 (gymnema) plus insulin vs. insulin alone. 11 dropouts. 40 non-diabetics also studied. Author affiliated with manufacturer</td>
</tr>
<tr>
<td>Type II diabetes</td>
<td>Before and after study, non-randomized, non-blinded</td>
<td>Baskaran, 1990</td>
<td>47</td>
<td>GS4 (gymnema) added to oral hypoglycaemic drugs improved fasting glucose and HbA1c levels</td>
</tr>
<tr>
<td>Type II diabetes</td>
<td>Case series</td>
<td>Kothe, 1997</td>
<td>21</td>
<td>Gymnema administered over 6-month period. Uncontrolled. Limited reporting of numerical results</td>
</tr>
<tr>
<td>Type II diabetes</td>
<td>Case series</td>
<td>Khare, 1983</td>
<td>16</td>
<td>10 days of gymnema reduced serum glucose levels in both diabetic and non-diabetic patients</td>
</tr>
</tbody>
</table>

### 7.2 Cinnamon

A number of medicinal plants have a history of traditional use in treating raised blood sugar levels and cardiovascular risk factors. One such compound that has been the subject of intense research is cinnamon, a compound with Generally Regarded as Safe (GRAS) status by the FDA. Cinnamon offers a great potential as a dietary strategy to improve glycaemic control because it contains doubly linked type-A polyphenol compounds (Akilen et al., 2013).

Insulin resistance might be encouraged by activation of the renin–angiotensin–aldosterone system and is associated with increased free radical formation. Occurring in cardiovascular, muscle, and liver tissue, local insulin resistance appears to contribute to the development of endothelial dysfunction and hypertension. Diminished insulin sensitivity is related to the signs and symptoms of the metabolic syndrome including increased BP, visceral obesity, fasting plasma glucose (FPG), low density lipoprotein, and decreased high-density lipoprotein (Akilen et al., 2013).

In 1990, it was reported that compounds found in cinnamon (cinnamon cassia) have insulin-potentiating properties and may be involved in the alleviation of the signs and symptoms of diabetes and cardiovascular disease related to insulin resistance (Anderson, 2008). Naturally occurring compounds that have been shown to improve insulin sensitivity include polyphenols found in cinnamon (Anderson, 2008). The potential glucose-lowering effect and pharmacologic mechanisms of cinnamon have been identified in in vitro and in vivo animal studies (Akilen et al., 2012). Cao and co-workers (2007) reported that purified cinnamon extracts and cinnamon polyphenols increased insulin receptor proteins and glucose transporter (GLUT4) proteins. These proteins are involved in the insulin signalling transduction pathways that function in insulin receptor substrate activation and insulin-regulated glucose transportation, respectively (as cited by Akilen et al., 2012). Aqueous extracts and polyphenol compounds of cinnamon have been shown, in an in vitro assay to potentiate insulin activity more than 20-fold, higher than any other compound tested at comparable dilutions (Akilen et al., 2012).

The polyphenolic polymers found in cinnamon may function as antioxidants, potentiate insulin action, and may be beneficial in the control of glucose intolerance and diabetes (Khan et al., 2003). Sixty people with type II diabetes took 1, 3, or 6 grams of cinnamon in pill form daily, an amount roughly equivalent to one quarter of a teaspoon to one teaspoon of cinnamon. After 40 days, all three amounts of cinnamon reduced fasting blood glucose by 18 to 29%, triglycerides by 23 to 30%, LDL cholesterol by 7 to 27%, and total cholesterol by 12 to 26% (Khan et al., 2003; McCarty, 2005).

Cinnamon consumption has been found to associate with the attenuation of diabetes mellitus. The misfolding of human islet amyloid polypeptide (hIAPP) is regarded as a causative factor of type II diabetes mellitus. Jiao and co-workers (2013) investigated whether cinnamon has any beneficial effect on the toxic aggregation of hIAPP. They found that cinnamon water extract (CWE) inhibited the amyloid formation of hIAPP in a dose-dependent manner, and identified proanthocyanidins as the major anti-amyloidogenic compounds of CWE. Proanthocyanidins affected the secondary structures of hIAPP and delayed the structural transition from unstructured coils to β-sheet-rich structures. Further studies showed that proanthocyanidins not only inhibited the formation of hIAPP oligomers, but also significantly attenuated the membrane damaging and cytotoxic effects caused by the hIAPP aggregation. Together, these results suggest a possible way by which cinnamon shows beneficial effects on type II diabetes mellitus, and indicate a potential pharmacological usage of
proanthocyanidins as an anti-diabetic drug candidate (Jiao et al., 2013).

In a meta-analysis of 10 RCTs (n = 543 patients), Allen and co-workers (2013) found that cinnamon doses of 120 mg/d to 6 g/d for 4 to 18 weeks reduced levels of fasting plasma glucose (-24.59 mg/dL; 95% CI, -40.52 to -8.67 mg/dL), total cholesterol (-15.60 mg/dL; 95% CI, -29.76 to -1.44 mg/dL), LDL-C (-9.42 mg/dL; 95% CI, -17.21 to -1.63 mg/dL), and triglycerides (-29.59 mg/dL; 95% CI, -48.27 to -10.91 mg/dL). Cinnamon also increased levels of HDL-C (1.66 mg/dL; 95% CI, 1.09 to 2.24 mg/dL). No significant effect on haemoglobin A1c levels (0.16%; 95%, CI -0.39% to 0.02%) was seen. High degrees of heterogeneity were present for all analyses except HDL-C ($I^2$ ranging from 66.5% to 94.72%) (Allen et al., 2013).

The authors concluded that the consumption of cinnamon is associated with a statistically significant decrease in levels of fasting plasma glucose, total cholesterol, LDL-C, and triglyceride levels, and an increase in HDL-C levels; however, no significant effect on haemoglobin A1c was found (Allen et al., 2013).

Table 2. Summary of studies done on Cinnamon and diabetes (Natural standards)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Study design</th>
<th>Author, Year</th>
<th>N</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>Meta-analysis</td>
<td>Baker, 2008</td>
<td>5 trials; 282 participants</td>
<td>Patients with type 1 and type 2 diabetes</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Systematic review</td>
<td>Dugoua, 2007</td>
<td>3 trials</td>
<td>Patients with type 2 diabetes</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Systematic review</td>
<td>Kleefstra, 2007</td>
<td>5 human trials</td>
<td>Authors concluded that cinnamon is not effective for improvements in glycaemic control</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Systematic review</td>
<td>Pham, 2007</td>
<td>3 trials</td>
<td>Patients with type 2 diabetes. Authors concluded that cinnamon may have modest effects in lowering plasma glucose levels</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Systematic review</td>
<td>Nahas, 2009</td>
<td>5 trials</td>
<td>One trial not randomized, one trial investigated adolescents with type 1 diabetes. Other three were randomized controlled trials. FBG level reduction in two of three trials</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Randomized controlled trial</td>
<td>Altschuler, 2007</td>
<td>72</td>
<td>Adolescents with type 1 diabetes</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Randomized controlled trial</td>
<td>Blevins, 2007</td>
<td>77</td>
<td>Patients with type 2 diabetes</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Randomized controlled trial</td>
<td>Mang, 2006</td>
<td>79</td>
<td>Patients with diabetes type 2. Reduced fasting plasma glucose concentration</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Randomized controlled trial</td>
<td>Vanschoonbeek, 2006</td>
<td>25</td>
<td>Small sample size, limited collective, inadequate description of blinding; 1,500mg of cinnamon daily</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Randomized controlled trial</td>
<td>Suppapitiporn, 2006</td>
<td>60</td>
<td>Patients with type 2 diabetes. Single-blind</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Randomized controlled trial</td>
<td>Khan, 2003</td>
<td>60</td>
<td>Unblinded; no information on standardization of dosing. 1, 3, or 6g of cinnamon daily</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Randomized controlled trial</td>
<td>Crawford, 2009</td>
<td>109</td>
<td>Unblinded. 1g daily cinnamon capsules for 90 days</td>
</tr>
</tbody>
</table>

2.3 Pine bark extract

The PubMed entries on pycnogenol and human diabetes gives 12 articles, among these the most authoritative is that of Liu and co-workers (2004) where a double-blind, placebo-controlled, randomized, multi-centre study was performed with 77 diabetes type II patients. The study reports that conventional diabetes treatment supplementation with 100 mg pycnogenol for 12 weeks, lowers glucose levels and improves endothelial function.

Pycnogenol, a standardized extract of the bark of the French maritime pine (Pinus pinaster), is known to increase capillary resistance and strengthen the walls of all blood vessels (D’Andrea, 2010). Diabetic microangiopathies in the eye lead to the development of retinopathy involving gradual loss of vision. Pycnogenol has been tested for the treatment and prevention of retinopathy in five clinical trials with a total number of 1289 patients since the late 1960’s. All the available data indicate that pycnogenol slows the progression of retinopathy and partly recovers visual acuity (Schonlau and Rohdewald, 2001 as quoted by D’Andrea, 2010).
A study done by Kim and co-workers (2005) on the effect of pine bark extract on alpha-amylase and alpha-glycosidase indicated that pine bark extract can be used to suppress postprandial hyperglycaemia of diabetic patients. Another double-blind, placebo-controlled, randomized study was performed with 77 diabetes type II patients to investigate the anti-diabetic effects of pine bark extract. The results showed that supplementation with 100 mg pycnogenol for 12 weeks lowers glucose levels and improve endothelial function (Liu, et al., 2004).

Pine bark extract also has antioxidant activity (D'Andrea, 2010); pycnogenol helps to limit free radicals - the mechanism of action of pycnogenol may thus be related to its free radical scavenging, anti-inflammatory and capillary protective activities.

Table 3: Summary of studies done on Pine bark extract and diabetes (Natural standards)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Study design</th>
<th>Author, Year</th>
<th>N</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes (type II)</td>
<td>Randomized controlled trial</td>
<td>Liu, 2004</td>
<td>77</td>
<td>100mg 12 weeks with standard therapy. Decreased glucose</td>
</tr>
<tr>
<td>Diabetic microangiopathy</td>
<td>Controlled trial</td>
<td>Cesarone, 2006</td>
<td>60</td>
<td>50mg three times daily for four weeks. Improved level of microangiopathy</td>
</tr>
<tr>
<td>Diabetic microangiopathy</td>
<td>Controlled trial</td>
<td>Belcaro, 2006</td>
<td>30</td>
<td>Systemic (150mg daily), and local application (100mg daily) tested</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>Randomized controlled trial and open trial (combined data)</td>
<td>Spadea, 2001</td>
<td>20 + 20</td>
<td>50g three times daily for two months. No deterioration in retinal function and recovery of visual acuity</td>
</tr>
</tbody>
</table>

### 7.4 Chromium

Chromium is an essential trace element that exists naturally in trivalent and hexavalent states. Trivalent chromium (chromium/Cr III), typically found in foods and supplements, appears to have very low toxicity and a wide margin of safety (Shara et al., 2007). Hexavalent chromium (chromic oxide, chromate) is a known toxin; long-term occupational exposure may lead to skin problems, perforated nasal septum, and lung cancer.

Chromium plays an important role in insulin's regulation of blood glucose (increases insulin's binding to receptors), and it acts as a cofactor for a number of enzymes involved in energy production. It has been used to treat diseases in which glucose regulation is dysfunctional (diabetes) and in lipid disorders, and as a supplement for weight loss. Similar to metformin and troglitazone, experts believe that trivalent chromium decreases insulin resistance and, in addition, has an acceptable side-effect profile (Anderson, 2008). Chromium picolinate has gained popularity among Americans, especially those seeking a weight-reduction program (Vincent, 2003; Natural Standards, 2013).

Deficiency states may provide insight into chromium's mechanism of action. Chromium deficiency may yield glucose intolerance, elevated circulating insulin, glycosuria, fasting hyperglycaemia, impaired growth, decreased longevity, elevated serum cholesterol and triglycerides, increased incidence of aortic plaques or coronary artery disease, peripheral neuropathy, brain disorders, and decreased fertility and sperm count (Natural Standards, 2013).

Results from a number of studies show that chromium supplements helps to control type 2 diabetes and suggest potential beneficial antioxidant effect of individuals. Because chromium alters the breakdown of fats in the diet, chromium is also being beneficial for individuals with some types of high cholesterol (Sharma et al., 2011).
<table>
<thead>
<tr>
<th>Condition</th>
<th>Study design</th>
<th>Author, Year</th>
<th>N</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycaemia</td>
<td>Randomized controlled trial</td>
<td>Anderson, 1987</td>
<td>8</td>
<td>200mcg chromium or placebo daily for 12 weeks; significant improvements were seen in insulin binding, insulin receptor number, and hypoglycaemic symptoms. Small study</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Meta-analysis</td>
<td>Althuis, 2002</td>
<td>618</td>
<td>Chromium lacked a significant effect on blood glucose or insulin levels in participants without diabetes. There was dose-dependent HbA1c lowering in one study of diabetics</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Systemic review</td>
<td>Nahas, 2009</td>
<td>3</td>
<td>The reviewers concluded that, based on level 1 evidence, chromium may help control glucose.</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Systemic review</td>
<td>Bartlett, 2008</td>
<td>16</td>
<td>In six studies, treatment with chromium had a statistically significant effect on HbA1c (p&lt;0.05)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Systematic review</td>
<td>Balk, 2007</td>
<td>41</td>
<td>Systematic review of the effect of chromium supplementation on glucose metabolism and lipid levels</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled trial</td>
<td>Kleefstra, 2006</td>
<td>53</td>
<td>500 or 1,000mcg of chromium daily in the form of chromium picolinate for six months did not show reductions in A1c</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled trial</td>
<td>Amato, 2000</td>
<td>19</td>
<td>1,000mcg of chromium daily; no significant changes on insulin sensitivity, lipids, or body composition was found; healthy elderly; high-dose chromium</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled trial, double-blind</td>
<td>Kleefstra, 2007</td>
<td>57</td>
<td>400mcg of chromium daily in the form of chromium yeast for six months in addition to hypoglycaemic agents showed no significant differences in A1c when compared to placebo</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized placebo controlled trial, double-blind</td>
<td>Pei, 2006</td>
<td>60</td>
<td>Chromium-containing milk powder (200mcg of chromium and 20g of milk powder) twice daily for 16 weeks resulted in lowering of FPG, fasting insulin, and improvement of metabolic control</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled trial, double-blind</td>
<td>Singer, 2006</td>
<td>43</td>
<td>600mcg of chromium as chromium picolinate and biotin (2mg daily) in addition to an oral antihyperglycemic agent improved glucose management and several lipid measurements.</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled trial</td>
<td>Lee, 1994</td>
<td>30</td>
<td>200mg of chromium daily for six months; no detected difference in glucose and HbA1c (possibly due to small sample size); predominantly Hispanic NIDDM subjects</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled trial, double-blind</td>
<td>Jain, 2012</td>
<td>83</td>
<td>400mcg of chromium, as chromium dinitocysteinate, for three months lowered insulin levels and insulin resistance vs. baseline. Between-group differences were lacking</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled trial, double-blind</td>
<td>Ali, 2011</td>
<td>60</td>
<td>500mcg of chromium picolinate or 1,000mcg of chromium picolinate lacked significant effects on all parameters</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled trial, double-blind</td>
<td>Krol, 2011</td>
<td>20</td>
<td>Five tablets of chromium brewer's yeast or placebo in three divided doses daily for eight weeks lacked a significant effect</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled trial, double-blind</td>
<td>Martin, 2006</td>
<td>29</td>
<td>Sulfonlylurea plus 1,000mcg of chromium as chromium picolinate for six months significantly improved insulin sensitivity and glucose control</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled trial, double-blind</td>
<td>Racek, 2006</td>
<td>36</td>
<td>400mcg of chromium daily as Cr-enriched yeast reduced fasting glucose levels but lacked an effect on lipids, HbA1c, and fructosamine</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled trial</td>
<td>Gunton, 2005</td>
<td>40</td>
<td>400mcg of chromium picolinate or placebo by mouth twice daily for three months</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled trial</td>
<td>Bahijiri, 2000</td>
<td>78</td>
<td>200mcg of chromium chloride, 23.2mcg of chromium from whole brewer's yeast, or 0.54mcg of chromium from whole torula yeast for eight weeks improved glucose and lipid parameters vs. baseline</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled trial</td>
<td>Anderson, 1997</td>
<td>180</td>
<td>220mg of chromium or 1,000mcg of chromium daily resulted in reduction in fasting insulin, two-hour insulin, and HbA1c for both chromium groups vs. placebo</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled trial</td>
<td>Wilson, 1995</td>
<td>26</td>
<td>220mg of chromium daily for 90 days; significant decrease in post-supplemental insulin levels in 15 patients; healthy, non-obese subjects</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled trial</td>
<td>Uusitupa, 1992</td>
<td>26</td>
<td>Placebo or 160mg of chromium daily for six months; no significant changes in glucose tolerance; elderly; low chromium intake</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled trial</td>
<td>Martinez, 1985</td>
<td>86</td>
<td>200mcg of chromium or placebo daily. At-risk women who were not on medications demonstrated a small significant decrease in glucose response to challenge</td>
</tr>
<tr>
<td>Disease</td>
<td>Design</td>
<td>Reference</td>
<td>Participants</td>
<td>Outcome</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------------</td>
<td>----------------------------</td>
<td>--------------</td>
<td>--------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled</td>
<td>Jovanovic, 1999</td>
<td>30</td>
<td>Compared 4mcg/kg and 8mcg/kg of chromium against placebo; both chromium groups had significantly decreased glucose and insulin when compared to placebo</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled</td>
<td>Anderson, 1996</td>
<td>180</td>
<td>A significant decrease in fasting glucose and two-hour glucose was reported at two and four months for the high-dose group when compared to placebo (p&lt;0.05)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled</td>
<td>Anderson, 1983</td>
<td>76</td>
<td>200mcg of chromium or placebo daily for two-three-month periods; unclear randomization; significant effects after grouping</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled, double-blind</td>
<td>Rabinowitz, 1983</td>
<td>43</td>
<td>150mcg of chromium, brewer's yeast with or without GTF, or placebo daily for 16 months; no significant changes noted; poor description of randomization and blinding methods</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled</td>
<td>Uusitupa, 1983</td>
<td>10</td>
<td>200mcg of chromium for six weeks; no significant changes in glucose tolerance and fasting or two-hour post-glucose serum insulin levels; one-hour post-glucose serum insulin level was lower (p&lt;0.01); unclear randomization</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled</td>
<td>Offenbacher, 1980</td>
<td>24</td>
<td>Single-blinded, torula yeast as low-chromium control</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled</td>
<td>Sharma, 2011</td>
<td>40</td>
<td>Three capsules of brewer's yeast three times daily for three months reduced blood sugar and haemoglobin A1c vs. baseline</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled</td>
<td>Zhang, 2010</td>
<td>240</td>
<td>400mcg of organic chromium twice daily for four weeks reduced FBG and HOMA-IR vs. control group</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>Randomized controlled</td>
<td>Abraham, 1992</td>
<td>76</td>
<td>250mcg of chromium daily for 7-16 months; no changes in fasting blood glucose were noted</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Systematic review</td>
<td>Huang, 2011</td>
<td>1 trial</td>
<td>Treatment with chromium lacked a statistically significant effect on serum lipid profile</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Systematic review</td>
<td>Balk, 2007</td>
<td>41 trials</td>
<td>Systematic review of the effect of chromium supplementation on glucose metabolism and lipid levels.</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Randomized controlled</td>
<td>Amato, 2000</td>
<td>19</td>
<td>1,000mcg of chromium daily; no significant changes were noted; healthy, elderly subjects; high dose</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Randomized controlled</td>
<td>Roebback, 1991</td>
<td>72</td>
<td>600mcg of GTF-chromium or placebo for eight weeks; chromium led to significant increase in HDL; subjects on beta-blockers.</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Randomized controlled</td>
<td>Lee, 1994</td>
<td>30</td>
<td>200mcg of chromium daily for six months; significant reduction in triglyceride levels; no changes in LDL, HDL</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Randomized controlled</td>
<td>Lefavi, 1993</td>
<td>34</td>
<td>200mcg of chromium and 1.8mg of nicotinic acid or 800mcg of chromium and 7.2mg of nicotinic acid for four weeks</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Randomized controlled</td>
<td>Press, 1990</td>
<td>32</td>
<td>200mcg of chromium or placebo daily for 42 days; total cholesterol, LDL decreased significantly; crossover design baseline differences</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Randomized controlled</td>
<td>Riales, 1981</td>
<td>23</td>
<td>200mcg of chromium daily for five days per week for 12 weeks; significant increase in HDL and weight reduction</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Randomized controlled</td>
<td>Wilson, 1995</td>
<td>26</td>
<td>220mcg of chromium daily for 90 days; no change in lipid levels; healthy, young, non-obese patients</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Randomized controlled</td>
<td>Uusitupa, 1992</td>
<td>26</td>
<td>Placebo or 160mcg of chromium daily for six months; no significant changes in lipid levels were seen; elderly subjects; low chromium intake</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Randomized controlled</td>
<td>Hermann, 1994</td>
<td>42</td>
<td>150mcg of chromium or placebo daily for 12 weeks; significant reductions in LDL and total cholesterol with chromium; subgroup analysis on small sample</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Randomized controlled</td>
<td>Offenbacher, 1985</td>
<td>23</td>
<td>200mcg of chromium or brewer’s yeast daily for 10 weeks; no significant change in lipids; healthy elderly volunteers</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Randomized controlled</td>
<td>Anderson, 1983</td>
<td>76</td>
<td>200mcg of chromium or placebo for two three-month periods; no significant effects noted; unclear randomization; six-month trial</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Randomized controlled, double-blind</td>
<td>Rabinowitz, 1983</td>
<td>43</td>
<td>150mcg of chromium, brewer's yeast with or without GTF, or placebo daily for 16 months; no significant changes noted; poor description of randomization and blinding methods</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Randomized controlled</td>
<td>Uusitupa, 1983</td>
<td>10</td>
<td>200mcg of chromium for six weeks; no significant changes in lipid levels were noted; unclear randomization</td>
</tr>
<tr>
<td>Hyperlipidaemia</td>
<td>Randomized placebo controlled</td>
<td>Abraham, 1992</td>
<td>76</td>
<td>250mcg of CrCl3 chromium daily for 7-16 months; significant increase in HDL and decrease in triglycerides</td>
</tr>
</tbody>
</table>
Due to a 3-fold increase in the consumption of herbal remedies in the United States along with a staggering popularity of the ginseng herb as a method of sustaining good health, significant focus have been placed on two widely used types of ginseng, American (Panax quinquefolius L.) and Asian ginseng (Panax ginseng CA Meyer). The usage of ginseng root for medicinal purposes has been recorded for millennia, known as a tonic capable of sustaining longevity as well as maintaining viability. Asian ginseng is said to facilitate blood flow, alleviate fatigue as well as relieve oxidative stress in diabetic conditions through various mechanisms such as the inhibition of lipid peroxidation (Luo and Luo, 2008). Due to presumed side effects, ginseng has been contraindicated by the Commission E for people with hypertension. It seems that ginseng and ginsenosides are beneficial for diabetes therapy. Although single ginsenosides have shown to have positive effects, whether a single component or a mixture of components maximizes the therapeutic effect of ginseng on diabetes is still unclear. Many steps have been taken to standardize the usage of ginseng root through isolating specific ginsenosides, which is an effective way to maintain dosages and specificity. It is more than likely that ginseng affects not only the pancreas to increase insulin production but also other tissue to utilize insulin as well as decrease insulin resistance through its various components (Luo and Luo, 2008).

Ginseng root has been shown to be effective in cell cultures, animal studies, as well as clinical practice. Root extracts and components exhibited anti-hyperglycaemic activities and reduced insulin resistance and increased insulin production. Ginseng root is able to increase insulin production and decrease cell apoptosis in pancreatic β-cells, which signifies that ginseng affects the pancreas directly. Also, ginseng has been shown to mediate various mechanisms related to muscle and fat tissue such as the GLUT4 pathway. Despite the lack of sufficient widespread clinical, mechanistic studies and standardization for immediate therapeutic uses greatly hinders the possibility of practical applications, current reports of ginseng and ginsenosides point to the possibility of ginseng as a candidate for complementary diabetes therapy (Luo and Luo, 2008).

The experience with ginseng suggests that although reproducible efficacy may be achieved using an acute postprandial clinical screening model to select an efficacious ginseng batch, dose, and time of administration, there is a need to develop a basis for standardization that ties the composition of herbs to efficacy.

Ginseng can cause hypoglycaemia, perhaps through activity similar to insulin or by altering hepatic glucose metabolism. A systematic review (as cited by Birdee and Yeh, 2010), found conflicting clinical data of ginseng’s effect on blood glucose in diabetic and non-diabetic populations. Variations in response may reflect chemical heterogeneity of different ginseng batches used in the studies.

### 7.6 Trigonella foenum graecum (fenugreek)

Fenugreek is grown in North America and Asia and often flavours Indian food; it has been used as medicine for diabetes in India and China. Mechanisms proposed for fenugreek in diabetes are decreased carbohydrate absorption and increased insulin secretion. Several clinical trials among patients with type I or type II diabetes suggest a potential effect, but studies thus far have lacked sufficient quality (Birdee and Yeh, 2010). It appears that fenugreek improves metabolism and general health; it was listed in early Greek and Latin pharmacopoeias for treating hyperglycaemia (Assad and Morse, 2013).

The antidiabetic properties of fenugreek were initially thought to be the result of the high fibre content of the seeds. However, it is now increasingly being realized that other seed components in addition to the fibre...
content may also account for its antidiabetic action. These components are believed to act synergistically in inhibiting glucose absorption and promoting pancreatic functions. Results of the extensive in vitro and in vivo studies (Basu and Srichamroen, 2010), have convincingly pointed to the fact that 4-hydroxy-isoleucine, galactomannan, and saponin, the three potential active components isolated from the fenugreek seeds, lower blood glucose, cholesterol (including LDL-cholesterol), triglyceride, free fatty acids, and abdominal fat. Further, the galactomannan component of fenugreek has been shown to markedly reduce glycaemic response in parallel with its insulin response to a glucose load. It has been known for many years that obesity is associated with insulin resistance, hyperinsulinaemia, non-insulin-dependent diabetes mellitus, hyperlipidaemia, and premature atherosclerosis, leading to increased morbidity and mortality from coronary arterial disease, stroke, and vascular disease (Basu and Srichamroen, 2010). This cluster of associated diseases has been termed the ‘insulin resistance syndrome,’ ‘syndrome X,’ or ‘metabolic syndrome.’ It is increasingly being realized that the treatment of these multiple abnormalities is a central focus of management. Weight reduction associated with a decrease in total body and intra-abdominal fat results in a marked improvement in insulin resistance and in blood glucose and lipid profiles. The studies reported by Basu and Srichamroen (2010) show that fenugreek has the potential to lower blood glucose, lipid profiles, insulin resistance, and body weight (including the loss of abdominal fat), and thus fenugreek offers a viable choice in the treatment and prevention of diabetes and its complications.

7.7 Vanadium

Vanadium is a poorly understood trace element that is ubiquitous in nature and believed to have many functions in human physiology. In vitro and animal studies have demonstrated its insulinomimetic effects mediated by inhibition of phosphotyrosine phosphatase enzymes that affect the insulin receptor (Birdee and Yeh, 2010). A recent meta-analysis identified 5 uncontrolled trials (N = 48) in which 50 to 300 mg of vanadium was administered for 3 to 6 weeks. Vanadyl sulphate was used in four trials and sodium metavanadate was used in one trial. All five trials reported reductions in FBG levels, but these were of short duration; none of the trials included controls. Commonly reported side effects included gastrointestinal upset, bloating, and nausea (Nahas and Moher, 2009).

7.8 Vitamin E, biotin, magnesium and manganese

A deficiency of manganese is common amongst diabetics; manganese could be a key co-factor in the way enzymes within the body handle glucose metabolism.

Magnesium tends to decline in people with diabetes, and may fall to dangerously low levels amongst those suffering from severe diabetic retinopathy. A magnesium deficiency has been shown to directly influence the blood sugar control of type II diabetics and may interrupt the insulin secretion process, and also increase insulin resistance. When using supplemental magnesium, diabetics may be able to lower their insulin dosage.

Biotin works in synergy with insulin in the body, and independently increases the activity of the enzyme glucokinase. The enzyme glucokinase is responsible for the first step of glucose utilisation, and is therefore an essential component of normal bodily functioning. Glucokinase activity occurs only in the liver, and in diabetics its concentration may be extremely low. Biotin supplementation may have a significant effect on glucose levels for both type I and type II diabetes.

Vitamin E can improve the activity of insulin; an increased vitamin E intake may decrease the likelihood of developing type II diabetes, and may improve glucose tolerance in type II diabetics. Furthermore, the antioxidant nature of vitamin E may reduce the risk of diabetic complications.

7.9 Vitamin B6, B9 and B12

The link between high levels of homocysteine and diabetes are well established. Dietary intake of folate is a major determinant of blood homocysteine concentration, and vitamin supplements containing folic acid effectively lower homocysteine concentrations (Homocysteine Lowering Trialists’ Collaboration, 2005).
The Homocysteine Lowering Trialists’ Collaboration was established to determine the size of the reduction in homocysteine concentration achieved with different oral doses of folic acid and with the addition of vitamin B\textsubscript{12} and B\textsubscript{6}. Twenty five trials incorporating 2596 participants were initiated to determine both the dose-dependent effect (folic acid and adding either vitamin B\textsubscript{12} or B\textsubscript{6}) on plasma homocysteine concentration. Results on this meta-analysis indicated that homocysteine reduction is achieved by increasing the dose of folic acid above \( \approx 0.8\text{mg/d} \), but combined administration of folic acid with vitamin B\textsubscript{12} will achieve a greater reduction in plasma homocysteine concentration than does that of folic acid alone.

Van Oort and co-workers (2003) designed a dose-response trial with a randomized, double-blind, parallel group, placebo-controlled among 316 Dutch men and women aged 50-75 years. Subjects received folic acid supplementation for 12 weeks (50, 100, 200, 400 600 or 800 micrograms). They concluded that in older adults, daily supplementation with folic acid effectively lowers plasma homocysteine concentration, and a daily dose of approximately 400 micrograms is the minimum dose required for an adequate homocysteine reduction (Van Oort \textit{et al.}, 2003).

Several more studies concluded that a deficiency of folate acid may result in an accumulation of homocysteine and could be corrected by a vitamin B supplementation (Tucker \textit{et al.}, 2004; Carlsson, 2006; Ntaios, \textit{et al.}, 2008; Bazzano \textit{et al.}, 2009; Schroecsksnadel, 2010).

The high prevalence of suboptimal folate, vitamin B\textsubscript{12} and vitamin B\textsubscript{6} status in hyperhomocysteinemic men, as well as the efficacy of vitamin supplementation to normalize circulating homocysteine concentrations, indicated that premature atherosclerotic vascular disease due to hyperhomocysteinemia in the sample studied could have been nutritionally induced by the lack of adequate vitamins in the diet (Ubbink \textit{et al.}, 1993; Jianbo \textit{et al.}, 2011).

It is interesting to note that a cobalamin resistance may occur in diabetes, renal insufficiency and advanced age, leading to functional cobalamin deficiency despite adequate cobalamin nutrition (Solomon, 2007).

\subsection*{7.10 Vitamin B\textsubscript{3} (Niacin)}

Niacin has long been used for the treatment of lipid disorders, diabetes and cardiovascular diseases (Ganji \textit{et al.}, 2003; Kamanna and Kashyap, 2008; Kamanna \textit{et al.}, 2009). Ganji and co-workers (2003) suggested that niacin has a role beyond that of a vitamin, and could act as an important lipid lowering drug. A meta-analysis of seven trials on secondary prevention revealed that niacin was associated with a significant reduction in cardiovascular events and possible small, although non-significant, decrease in coronary and cardiovascular mortality (Duggal, \textit{et al.}, 2010).

Treatment with niacin not only induces a significant reduction in LDL cholesterol and triglyceride levels, but also increases HDL cholesterol. Niacin reduces the levels of lipoprotein A that may be atherogenic via the inhibition of fibrinolysis in the arterial wall; it also converts easily oxidized small dense LDL particles to larger, buoyant, oxidation-resistant particles (Holvoet and Collen 1995).

Niacin favourably affects apolipoprotein (Apo) B-containing lipoproteins (VLD, LDL and lipoprotein A and increases Apo A-I-containing lipoproteins (HDL) (Kamanna and Kashyap, 2008). According to Duggal and co-workers (2010), niacin raised the levels of HDL between 30\% and 35\% in patients with prior coronary diseases.

More recent findings indicate that niacin directly and noncompetitively inhibit hepatocytes diacylglycerol acyltransferase-2, a key enzyme for triglyceride synthesis, thus resulting in degradation of hepatic Apo B and a decrease in VLDL and LDL (Kamanna and Kashyap, 2008).
### Table 5: Summary of studies done on niacin and cardiovascular heart disease (Natural Standards)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Study design</th>
<th>Author, Year</th>
<th>N</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerosis (as adjunct therapy; niacin)</td>
<td>Randomized controlled trial</td>
<td>Taylor, 2004</td>
<td>167</td>
<td>Niacin only significantly reduced the rate of intima-media thickness progression in subjects without insulin resistance using statins</td>
</tr>
<tr>
<td>Atherosclerosis (as adjunct therapy; niacin)</td>
<td>Follow-up open-label study</td>
<td>Taylor, 2006</td>
<td>130</td>
<td>Niacin significantly reduced the rate of intima-media thickness progression in subjects in this 12-24 month follow-up</td>
</tr>
<tr>
<td>Cardiovascular disease (niacin)</td>
<td>Meta-analysis</td>
<td>Birjmohun, 2005</td>
<td>4,749</td>
<td>30 trials; limited data on cardiovascular event rate. 10 trials included Acipimox®</td>
</tr>
<tr>
<td>Cardiovascular disease (niacin)</td>
<td>Systematic review</td>
<td>Studer, 2005</td>
<td>67 studies (only 2 niacin trials)</td>
<td>Risk ratio for overall mortality (95% CI: 0.86-1.08), cardiac mortality and non-cardiovascular mortality indicated no benefit from niacin</td>
</tr>
<tr>
<td>Cardiovascular disease (niacin)</td>
<td>Randomized controlled trial</td>
<td>Taylor, 2004</td>
<td>167</td>
<td>Niacin only significantly reduced the rate of intima-media thickness progression in subjects without insulin resistance using statins</td>
</tr>
<tr>
<td>Cardiovascular disease (niacin)</td>
<td>Randomized controlled trial</td>
<td>Canner, 2005</td>
<td>8,341</td>
<td>Study conducted only in men; niacin found to have favourable effects on clinical outcome in patients including those with evidence of abnormal glucose metabolism or overt diabetes</td>
</tr>
<tr>
<td>Cardiovascular disease (niacin)</td>
<td>Randomized controlled trial</td>
<td>Canner, 2005</td>
<td>2,787 + 1,119</td>
<td>No statistical significance between individuals with or without metabolic syndrome</td>
</tr>
<tr>
<td>Cardiovascular disease (niacin)</td>
<td>Randomized controlled trial</td>
<td>Kuvin, 2006</td>
<td>60</td>
<td>Niacin in addition to existing medication reduced inflammatory and lipid parameters</td>
</tr>
<tr>
<td>Cardiovascular disease (niacin)</td>
<td>Randomized controlled trial</td>
<td>Chesney, 2000</td>
<td>80</td>
<td>1,500mg decreased fibrinogen by 14% and prothrombin by 60%</td>
</tr>
</tbody>
</table>

### Table 6: Summary of the functions of the vitamins and minerals effective in diabetes

<table>
<thead>
<tr>
<th>Vitamin A (µg RE)</th>
<th>Immune function as well as function to prevent diabetic complication retinopathy. Eye function support (overall); healthy skin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vitamin B₃ (mg)</td>
<td>Metabolism function; energy release; healthy nerve function (neuropathy support)</td>
</tr>
<tr>
<td>Vitamin B₅ (mg)</td>
<td>Metabolism function; energy release; healthy nerve function (neuropathy support)</td>
</tr>
<tr>
<td>Vitamin B₉ (mg)</td>
<td>Metabolism function; energy release; healthy nerve function (neuropathy support)</td>
</tr>
<tr>
<td>Pantothenic acid (mg)</td>
<td>Metabolism function; energy release; healthy nerve function (neuropathy support)</td>
</tr>
<tr>
<td>Vitamin B₁₂ (µg)</td>
<td>Metformin - the pharmaceutical agent mostly prescribed to diabetics - causes deficiency or lowering in blood serum levels. To treat deficiency 125 microgram used in studies; there are some studies showing that extreme levels over very long periods may be harmful - thus the decision to supplement only 50% of the requirement, as this is a supportive product to be used over long periods</td>
</tr>
<tr>
<td>Biotin (µg)</td>
<td>Metabolism function; energy release; healthy nerve function (neuropathy support)</td>
</tr>
<tr>
<td>Folic acid (µg)</td>
<td>Metformin - the pharmaceutical agent mostly prescribed to diabetics - causes deficiency or lowering in blood serum levels. Also important role to play in vitamin B₁₂ metabolism, cell regeneration and red blood cell formation</td>
</tr>
<tr>
<td>Vitamin C (mg)</td>
<td>Anti-oxidant function, inclusion based on the prevention of infections as infections influence glucose metabolism. Cell synthesis and healthy cell maintenance</td>
</tr>
<tr>
<td>Vitamin D (µg)</td>
<td>Vitamin D studied for prevention of retinopathy - maximum dosage included as per regulation</td>
</tr>
<tr>
<td>Vitamin E (TE)</td>
<td>Anti-oxidant function. Proposed for the improvement of abnormal sugar control, for the prevention of platelet dysfunction and atherosclerosis in diabetes. Healthy skin</td>
</tr>
<tr>
<td>Chromium (µg)</td>
<td>Glucose tolerance improvement and necessary to potentiate insulin action</td>
</tr>
<tr>
<td>Nutrient</td>
<td>Description</td>
</tr>
<tr>
<td>----------</td>
<td>-------------</td>
</tr>
<tr>
<td>Iron (mg)</td>
<td>One of the single nutrients which most people have a risk of developing a deficiency. Red blood cell production</td>
</tr>
<tr>
<td>Magnesium (mg)</td>
<td>Magnesium proven as one of the nutrients which most diabetics are deficient in</td>
</tr>
<tr>
<td>Selenium (µg)</td>
<td>Anti-oxidant, acting together with vitamin E</td>
</tr>
<tr>
<td>Zinc (mg)</td>
<td>Important in metabolic pathways. A zinc deficiency linked to poor insulin secretion. Evidence suggesting support in the retinopathy patients</td>
</tr>
</tbody>
</table>
8. References


56. NATURAL STANDARD. 2013. www.naturalstandard.com


