Long-Term Consequences of Diabetes

by Dr. Chris D. Meletis

Diabetes is associated with an increased risk for numerous serious complications. According to the American Diabetes Association, there are an estimated 23.6 million people in the US, approximately 8% of the population, with diabetes, which is an increase by 13.5% from 2005. It is estimated that 24%, or 5.7 million, of these people have not yet been diagnosed. Additionally, there are 57 million Americans who are prediabetic.[1] Based on 2007 data, the total annual economic cost of diabetes is estimated to be $174 billion. Medical expenditures totaled $116 billion, including $27 billion for diabetes care and $58 billion for chronic diabetes-related complications. Indirect costs are estimated at another $58 billion per year due to early mortality and loss of productivity, which does not include intangible data such as pain and suffering.[2]

Hyperglycemia causes physiological abnormalities leading to complications such as retinopathy, neuropathy, nephropathy, microvascular changes, atherosclerosis, and cognitive deficits. Specific nutrients and botanical medicines can be utilized to optimize glucose metabolism and have shown efficacy in helping decrease the risk of long-term consequences of diabetes.

Pathology of Diabetic Complications

Advanced Glycosylation End Products

Hyperglycemia increases non-enzymatic glycosylation and the formation of advanced glycosylation end products (AGEs), which are formed by sugars attaching to proteins, lipids, or nucleic acids. This reaction is irreversible, causing these products to accumulate over time. AGE formation and accumulation are greatly accelerated with increased blood sugar levels and oxidative stress.[3] Hyperglycemia increases reactive oxidative (ROS) and carbonyl intermediates, such as glyoxal and methylglyoxal, which enhance non-enzymatic glycosylation.[4] Glycosylated hemoglobin (HbA1c) is an example of an AGE and is measured to evaluate blood sugar control in diabetics. Thus HbA1c is not just a measure of recent control of blood sugar, but also a prognosticator of future of diabetes-related disease, all things being equal.

Albumin binds to the glycosylated basement membrane in capillaries, causing, in part, the thickening of the basement membrane associated with microangiopathy in diabetes. AGEs also cause cross-linking on proteins such as collagen. In blood vessels, these cross-linkages trap other proteins, such as LDL cholesterol, leading to a cascade of events resulting in increased atherogenesis. AGE accumulation is associated with cardiovascular abnormalities such as endothelial dysfunction, atherosclerosis, hypertension, and decreased vascular and cardiac elasticity.[5] Additionally, AGEs have been shown to quench nitric oxide (NO). NO is an endothelium-derived relaxing factor in smooth muscle, and decreasing levels results in impaired relaxation, which is associated with hypertension, atherosclerosis, and diabetes.[6] In diabetic individuals, AGEs have been implicated in the vascular changes found with diseases of the nerves, eyes, and kidneys.[7]

AGEs interact with specific cell receptors such as RAGE (receptor for advanced glycation end products), which are found on numerous cell types, particularly those affected in diabetes. Studies indicate that RAGE activation may cause an increase in inflammatory markers and cellular injury.[8] Research suggests that the interaction between AGEs and RAGE alters numerous physiological functions, such as gene expression, intracellular signaling, and the release of proinflammatory molecules and free radicals that contribute towards the pathology of diabetic complications.[9]

Polyol Pathway

Hyperglycemia leads to increased intracellular glucose in cells that do not require insulin for glucose transport, such as in nerves, kidneys, lens, and blood vessels. Excess glucose is metabolized by the enzyme aldose reductase to the polyol sorbitol, which is then metabolized by sorbitol dehydrogenase to fructose. Sorbitol and fructose accumulate in cells, causing osmotic water influx and cellular injury. Sorbitol is also associated with decreased myoinositol, which results in decreased Na/K ATPase activity, protein kinase C, diacylglycerol, and phosphoinositide. This pathway is believed to damage Schwann cells, causing neuropathy, and pericytes in the retinal capillaries, causing retinal microaneurysms. Researchers have shown that both enzymes of the polyol pathway contributed to hyperglycemia-induced oxidative stress in the lens, and likely cause neuronal dysfunction as well.[10] Additionally, studies indicate that aldose reductase inhibitors indirectly inhibit hydroxyl radical formation resulting from decreasing polyol levels, and these radicals are

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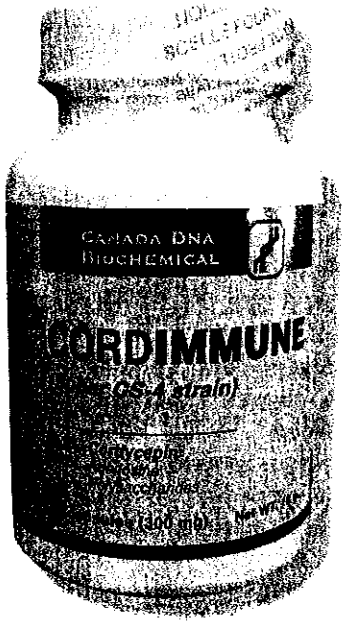

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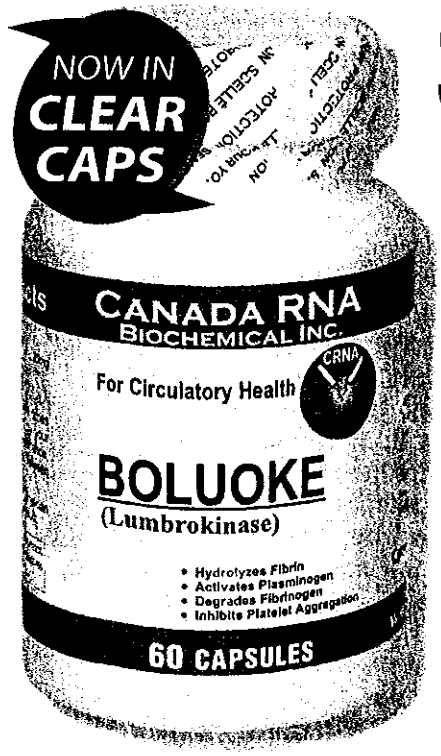

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related to the early stages of diabetic complications.[11] In addition, the polyol pathway appears to play a role in increased osteoclast activity, resulting in decreased bone mineral content in patients with type 2 diabetes.[12] This pathway is also believed to mediate myocardial ischemia-reperfusion injury in type 2 diabetes.[13]

Diabetic Complications

Neuropathy

Severe nervous system damage occurs in approximately 60% to 70% of diabetics. Impaired sensation in the feet occurs in almost 30% of diabetics over age 40, and is a major contributing factor to lower-extremity amputations.[14] Oxidative stress, AGE accumulation, and the polyol pathway are all implicated in diabetic neuropathy. Research has shown that increased markers of oxidative stress such as superoxide and peroxynitrite in diabetic patients are related to the severity of polyneuropathy, and oxygen free-radical activity in the sciatic nerve is increased in experimental diabetic neuropathy. These findings suggest that oxidative stress resulting from enhanced free-radical formation or deficient antioxidant defenses plays a role in the pathogenesis of diabetic neuropathy.[15] Additionally, research has shown that AGEs modify major axonal cytoskeletal proteins, causing axonal atrophy and degeneration and impaired axonal transport.

AGE also modifies peripheral nerve myelin, which is susceptible to phagocytosis and contributes to segmental demyelination, and glycation of extracellular matrix protein laminin causes decreased regenerative activity in diabetic neuropathy. AGE-RAGE interaction in peripheral nerves also suggests that AGEs are a significant factor in the development of neuropathy.[16] In addition, alterations in the sorbitol, hexosamine, and protein kinase C pathways are also implicated and are believed to damage Schwann cells, causing neuropathy.[17]

Microvascular changes are believed to affect mononeuropathies, whereas polyneuropathies are believed to be primarily affected by abnormal glucose metabolism. The development and progression of foot ulcers are related to the interplay among numerous diabetes-related factors such as nerve dysfunction, impaired wound healing, and microvascular and/or macrovascular disease; and AGE formation plays a role in the pathogenesis of these complications.[18]

Retinopathy

Diabetic retinopathy causes 12,000 to 24,000 new cases of blindness each year. Research indicates that keeping blood sugar levels as close to normal as possible reduces damage to the eyes by 76% in type 1 diabetics.[14] Current research suggests that oxidative stress, AGE accumulation, and increased sorbitol formation induce diabetic retinopathy. Apoptosis of retinal microvascular cells is increased in diabetic patients and indicates the progression of diabetic retinopathy. Researchers demonstrated that antioxidants and AGE inhibitors suppress this increase in apoptosis, suggesting that oxidative stress and the accumulation of AGEs appears to promote the apoptosis of retinal microvascular cells.[19] In addition, studies have shown that type 2 diabetics with diabetic retinopathy have increased activity of aldose reductase and sorbitol levels compared with type 2 diabetics without retinopathy, indicating increased polyol pathway activation in the pathology of diabetic retinopathy.[20]

Cognitive Decline

Diabetes has been associated with brain atrophy, white matter abnormalities, and cognitive impairment, and is a risk factor for dementia. The mechanism of neuronal damage likely involves both vascular changes as well as oxidative stress. Studying the hippocampus in diabetic animal models has shown that there is an increase in pro-oxidant compounds, RAGE, nuclear factor kappaB transcription factor levels, and polyol flux, suggesting that oxidative stress triggers a cascade of events that lead to neuronal damage.[21] Researchers have also shown that hyperglycemia is associated with adverse effects on the brain polyol pathway activity, neuronal structural changes, and impaired long-term spatial memory.[22] Studies indicate that individuals with diabetes have increased odds of cognitive decline and lower scores on cognitive tests, compared with nondiabetics. Also, there is a significant correlation between duration of disease and cognitive dysfunction.[23] Studies indicate that in individuals with diabetes, higher HbA1C levels are associated with lower cognitive function.[24]

One study showed that diabetic women had lower baseline scores on cognitive function tests compared with nondiabetic women, and experienced an accelerated cognitive decline. This study also showed that women with diabetes for more than 15 years had a 57% to 114% greater risk of major cognitive decline compared with nondiabetic women.[25] Additionally, other studies have shown that the risk of developing cognitive impairment among women with impaired fasting glucose or diabetes was increased by almost twofold,[26] and diabetic women had a fourfold increased risk of a major cognitive decline on the Verbal Fluency test compared with nondiabetic women.[27] Treatment to reduce fasting blood sugar has also shown benefit for improving cognitive function, and the magnitude of this effect was correlated with the degree to which fasting plasma glucose improved.[28] Thus protection and enhancement of neuron growth relative to neurites/dendrites is an essential clinical consideration for both CNS and peripheral nerve health.

Nephropathy

The kidneys are often severely damaged in patients with diabetes. In fact, diabetes is the leading cause of kidney failure, accounting for approximately 44% of new cases in

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2005.[14] It is estimated that 20% to 30% of all diabetic subjects will develop some evidence of nephropathy, ranging from microalbuminuria, to overt nephropathy or macroalbuminuria, to end-stage renal failure.[29] Some data support that diabetic nephropathy is mediated by RAGE and subsequent ROS (reactive oxygen species) generation, which damages renal structure and function.[30] AGEs accumulate in the glomerular basement membrane, mesangial cells, endothelial cells, and podocytes in patients with diabetes and/or end-stage renal failure, which are believed to cause damage by oxidative stress generation and overproduction of various growth factors and cytokines.[31] Additionally, advanced lipoxidation end-products (ALE) and AGEs are found in the glomeruli of diabetic rats, and supplementation with antioxidants protected the glomeruli from diabetes-induced enlargement, increased apoptotic rate, and decreased cell density and carboxymethyl-lysine accumulation.[32]

Vascular Changes

Diabetic adults have heart disease death rates about 2 to 4 times higher than adults without diabetes, risk for stroke is 2 to 4 times higher, and the risk of death from stroke is 2.8 times higher compared with nondiabetic adults. In addition, microvascular changes can lead to amputation, which occurs at a rate 10 times higher in individuals with diabetes than for nondiabetics.[14] Altered microvascular function leads to the development of retinopathy, neuropathy, and nephropathy, and the vascular complications associated with diabetes. Increased polyol pathway, AGE production, generation of ROS, and activation of diacylglycerol and protein kinase C isoforms are all believed to contribute to endothelial damage and dysfunction, resulting in microvascular changes.

Currently, it is believed that AGEs act through receptor-independent and dependent mechanisms increasing vascular damage, fibrosis, and inflammation associated with accelerated atherogenesis. AGEs accumulate in the heart and large blood vessels in diabetics, interacting with receptors such as RAGE to induce oxidative stress, increasing inflammation by promoting NFkappaB activation, and enhancing extracellular matrix accumulation. This leads to accelerated plaque formation, as well as increased cardiac fibrosis.[33] Research also indicates that HbA1c is independently related to carotid intima-media thickness.[34] Additionally, research suggests that NO may play a role in regulating vascular synthesis of polyols, and increasing NO synthesis or bioavailability may be beneficial in preventing diabetes-induced changes.[35]

Natural Therapies for Diabetic Complications

Antioxidants

Oxidative stress plays a role in both AGE formation and the polyol pathway. Diabetes is associated with an increased production of reactive oxygen and carbonyl species and a reduction in antioxidant defenses, which leads to oxidative stress and is, in part, responsible for diabetic complications.

Alpha lipoic acid (ALA) is a potent antioxidant and free-radical scavenger. Oral ALA supplementation has been shown to improve insulin sensitivity in patients with type 2 diabetes.[36] ALA also decreases glucose, glycated protein, glycated hemoglobin, fructosamine, and the accumulation of AGEs in high-fructose-fed rats.[37] ALA has been shown in several studies to significantly benefit both the symptoms and neurological changes seen in diabetic peripheral neuropathy.[38] One study supplemented oral ALA in doses of 600 mg, 1,200 mg, and 1,800 mg per day in individuals with symptomatic diabetic polyneuropathy. All 3 ALA dosages were effective in reducing neuropathic symptoms of diabetic polyneuropathy at 5 weeks' evaluation.[39]

ALA also benefits abnormalities associated with diabetic vascular changes. In one study, diabetic and nondiabetic rats were fed an atherogenic diet and supplemented with ALA. The results showed that ALA treatment improved several factors associated with atherosclerosis pathology, including decreased cholesterol and triglyceride levels, lowered plasma malondialdehyde (MDA), and improved endothelial function.[40] Studies using diabetic rats have also shown that supplementation with the reduced form of ALA, dihydrolipoic acid, delayed the development and progression of cataracts.[41] Animal models have shown that ALA has a protective effect against oxidative metabolites in the diabetic retina.[42]

In experimental diabetes models, tocotrienol supplementation was shown to improve various aspects of cognitive function.[43] Studies using diabetic rats have also shown that supplementation with vitamin C and vitamin E significantly decreased glycated hemoglobin, glycated LDL, and renal cortical AGEs and MDA.[44] In a human clinical trial, supplementation with vitamins C (1,000 mg) and E (800 IU) in addition to a high-fat meal showed that antioxidant supplementation minimizes meal-induced memory impairment, supporting oxidative stress as a potential contributor to diabetic cognitive dysfunction.[45]

One study using diabetic rats showed cognitive deficits and decreased cholinergic function in these animals, as well as decreased glutathione and increased lipid peroxidation. Supplementation with N-acetylcysteine significantly attenuated the cognitive deficits and oxidative stress.[46]

B Vitamins

The B vitamins are required cofactors for many of the enzymes needed for metabolizing glucose, and

research indicates that they play a significant role in the pathogenesis of diabetes.

Pyridoxine, or vitamin B6, is a cofactor involved in amino acid, lipid, and carbohydrate metabolism. It is converted into active metabolites such as pyridoxamine and pyridoxal-5-phosphate. Pyridoxamine has been shown to decrease AGE and ALE formation by inhibiting the Maillard reaction, scavenging toxic carbonyl products of sugar and lipid degradation, and inhibiting ROS.[47] Studies have also shown that pyridoxal and pyridoxal-phosphate can significantly inhibit the glycosylation of albumin.[48] Additionally, research has shown that glucose consumption is correlated with decreased levels of pyridoxal-5-phosphate and total plasma vitamin B6,[49] and diabetic patients had significantly lower levels of serum pyridoxal compared with nondiabetics.[50] Evidence also indicates that patients with diabetic neuropathy have significantly lower serum pyridoxal levels than patients with diabetes but without neuropathy.[51]

Thiamine, or vitamin B1, is frequently decreased in the plasma in patients with type 1 and type 2 diabetes.[52] Research indicates that thiamine pyrophosphate is a potent inhibitor of AGE formation.[53] Thiamine is required by the enzyme transketolase, which regulates the reductive pentosephosphate pathway. Thiamine deficiency decreases this enzymatic activity, resulting in accumulation of triosephosphates, which is associated with the development of diabetic complications. Thiamine supplementation reverses several biochemical abnormalities, including activation of protein kinase C, activation of the hexosamine pathway, and increased glycation and oxidative stress. In experimental diabetes models, thiamine has also been shown to reverse increased diuresis and glucosuria, and corrected dyslipidemia by normalizing cholesterol and triglycerides.[54] Thiamine supplementation also improves endothelium-dependent vasodilation in individuals with hyperglycemia, which may potentially decrease the risk of cardiovascular complications.[55] Interestingly, both thiamine pyrophosphate and pyridoxamine inhibited AGE formation more effectively than the AGE-inhibitor aminoguanidine.[56]

The lipid-soluble derivative of thiamine, benfotiamine, has also been shown to inhibit AGE formation and proinflammatory mediators, as well decrease diabetic complications. Benfotiamine has been shown to inhibit three major pathways of hyperglycemia-induced vascular damage: the hexosamine pathway, the AGE formation pathway, and the diacylglycerol-protein kinase C pathway. This activity has been shown to prevent experimental diabetic retinopathy.[57] Also, benfotiamine reduces inflammatory and neuropathic pain in both human and animal studies.[58,59] Human studies have also shown that benfotiamine significantly reduced serum markers of endothelial dysfunction and oxidative stress, and AGE levels increased after ingestion of a high AGE-content meal in type 2 diabetics.[60]

Research indicates that vitamin B12 is beneficial for the treatment of diabetic peripheral neuropathy. In one study, vitamin B12 was found to be more effective than nortriptyline for the treatment of symptomatic painful diabetic neuropathy.[61]

Carnitine

Acetyl-L-carnitine (ALC) is an amino acid derivative that has shown efficacy in the treatment of various diabetic complications. Supplementation with ALC has been shown to decrease pain, improve electrophysiologic factors such as nerve conduction velocities, and promote nerve regeneration in diabetic peripheral neuropathy.[62] In animal models, L-carnitine was shown to significantly reduce glycation and the accumulation of AGEs, and enhanced the utilization of glucose in high-fructose fed rats. Additionally, L-carnitine was superior to aminoguanidine at inhibiting glycation.[63] In a clinical trial, propionyl-L-carnitine supplementation in patients with non-insulin-dependant diabetes and peripheral artery disease resulted in improvements in oxidative parameters, as well as increased pain-free walking distance.[64] In addition, research has shown that the combination of acetyl carnitine and acetyl carnitine arginate can dramatically increase nerve growth factor, a molecule that promotes the survival and differentiation of sensory and sympathetic neurons.[65] This combination, in addition to uridine, may improve neuronal regrowth.[66]

Chromium

Chromium supplementation has been shown to lower the pro-inflammatory cytokines tumor necrosis factor (TNF)-alpha and interleukin-6, C-reactive protein, lipid peroxidation, glycosylatedhemoglobin, triglycerides, and cholesterol in diabetic rats.[67] According to a meta-analysis, 13 of 15 studies showed improvement in some parameter of glucose control in patients with diabetes. These studies showed substantial improvement in hyperglycemia and hyperinsulinemia, as well as improvements in cholesterol and triglycerides.[68] The mechanism of these metabolic improvements may include an increase in the number of insulin receptors in insulin-dependent cells, and an increase in phosphorylation of the insulin receptor, resulting in increased sensitivity of receptors to insulin.[69]

Fenugreek

Fenugreek (*Trigonella foenum-gracum*) has been shown to improve glycemic control, decrease insulin resistance and serum triglycerides, and increase HDL cholesterol in patients with type 2 diabetes.[70] When taken with meals, it has also been shown to decrease 24-hour urine glucose excretion by 54% in type 1 diabetics, as well as decrease total serum cholesterol, LDL, and

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VLDL cholesterol and triglycerides.[71] Fenugreek decreases sugar digestion and absorption, increases insulin action peripherally, and improves total antioxidant status.[72] Fenugreek has also shown protective activity in the liver and kidneys of diabetic rats.[73]

Bitter Melon

Bitter melon *(Momordica charantia)* has been shown to decrease both fasting and postprandial serum glucose levels in non-insulin-dependent diabetic patients.[74] Constituents of Momordica have been shown to modulate pathways and glucose receptors, improving glucose uptake into cells, as well as enhance fatty acid oxidation and glucose disposal during glucose tolerance tests in both insulin-sensitive and insulin-resistant mice.[75] Momordica was also shown to decrease blood glucose levels, restore pancreatic beta cells, and protect the liver from fatty change and necrosis in diabetic rats.[76] *Momordica charantia* seeds also have significant antioxidant activity and protective effects against lipid peroxidation by scavenging of free radicals in the liver and kidneys of diabetic rats.[77]

Cinnamon

Cinnamon (*Cinnamomum cassia*) improves insulin sensitivity[78] and significantly reduces fasting plasma glucose in type 2 diabetics.[79] One study showed that cinnamon supplementation decreased mean fasting serum glucose levels by 18% to 29%, triglycerides by 23% to 30%, LDL cholesterol by 7% to 27%, and total cholesterol by 12% to 26%.[80] In addition, constituents of cinnamon have been shown to significantly inhibit AGE formation, provide antioxidant activity, and scavenge reactive carbonyl species such as methylglyoxal.[81]

Green Tea

The constituents of green tea (*Camellia sinensis*) have been shown to decrease the reactive dicarbonyl compounds methylglyoxal and glyoxal.[82] Studies with diabetic rats have shown that green tea extract significantly reduced systolic blood pressure, blood glucose, and the level of lipid peroxides, while increasing serum glutathione and vitamin C. Green tea extract also suppressed the accumulation of aortic collagen, extent of glycation, and the formation of AGEs and cross-linking of collagen.[83] In addition, green tea extract decreased retinal superoxide production, acellular capillaries, and pericyte ghosts in the retinas of diabetic rats.[84]

Goat's Rue

Goat's rue (*Galega officinalis*) is a plant traditionally used for the treatment of diabetes. Galegine or isoamylene guanidine is the active ingredient found to lower blood glucose. Metformin, the widely prescribed biguanide, is a derivative of guanidine and shows significant efficacy in blood sugar control.[85]

Additional Therapies

Due to the immense quantity of research being conducted on therapeutic options for diabetes, there are numerous potential therapies worth mentioning.

- **Vanadium**. Supplementation with vanadyl sulfate has been shown to reduce fasting glucose and glycosylated hemoglobin.[86–88] In diabetic rats, treatment with sodium orthovanadate reversed the increased activity of polyol pathway enzymes aldose reductase and sorbitol dehydrogenase, the accumulation of sorbitol and fructose in the diabetic lens, and blood glucose and glycosylated hemoglobin levels.[89]
- **Arginine**. In diabetic mice, supplementation with L-arginine restored NO levels; prevented tissue accumulation of sorbitol; and decreased superoxide generation in the aorta, total protein kinase C activity, and plasma levels of triglycerides.[90]
- **Gymnema** (*Gymnema sylvestre*). Gymnema has been shown to decrease fasting blood glucose, glycosylated hemoglobin, and glycosylated plasma protein levels in both type 1 and type 2 diabetics.[91,92] Gymnema leaf extracts also exhibits antiperoxidative and antioxidant effects.[93,94]
- **Carnosine**. Carnosine has been shown to prevent the formation of AGEs, crosslinking, glycation, and protein carbonyl group formation.[95] Carnosine also provides antioxidant activity, thus decreasing lipid oxidation, protecting membranes from free radical damage, and chelating reactive metals.
- ***Plantago asiatica***. A methanol extract of *Plantago asiatica* has been shown to inhibit AGE formation comparable to the standard antiglycation agent aminoguanidine, and exhibits significant antioxidant activity.[96]
- ***Cyperus rotundus***. *Cyperus rotundus* extract significantly decreased the formation of AGEs and showed significant effect on preventing protein oxidation believed to form during the glycoxidation process.[97]
- **Dehydroepiandrosterone (DHEA).** DHEA has been shown to prevent AGE formation, ameliorate the oxidative imbalance induced by hyperglycemia, and downregulate the TNF-alpha/TNF-alpha receptor system in type 2 diabetic patients.[98]
- **Garlic** (*Allium sativum*). Both aged garlic extract and the constituent S-allyl cysteine inhibit the formation of glucose and methylglyoxal-derived AGEs *in vitro*.[99]
- **Turmeric** (*Curcuma longa*). Research has shown that supplementation with turmeric or curcumin significantly reduces blood sugar, glycosylated

hemoglobin, measurements of oxidative stress, and sorbitol dehydrogenase activity in diabetic rats.[100]

- **Pterocarpus** (*Pterocarpus marsupium*). Pterocarpus has been shown to improve body weight and blood glucose levels, as well as exert anticataract effects evident from decreased opacity index in diabetic rats.[101] Constituents of Pterocarpus stimulated regeneration of the beta-islet cells in diabetic rats and normalized blood glucose levels.[102]

Conclusion

Diabetes is increasing at an alarming rate, and resulting in increased complications such as retinopathy, neuropathy, nephropathy, microvascular changes, atherosclerosis, and cognitive deficits. Numerous natural products have shown efficacy in modulating the abnormal physiology associated with diabetes and related health complications. Understanding the mechanisms of this disease and its destruction of the 50 to 100 trillion cells that consitute the human frame is the first step in a true victory over diabetes.

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Notes

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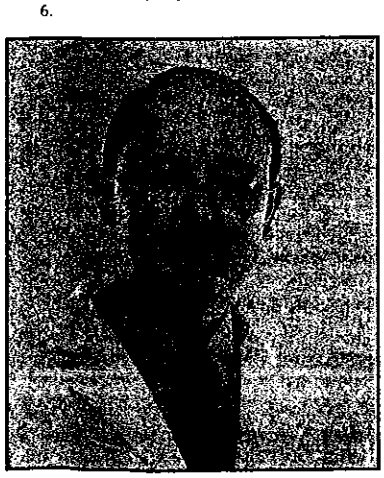

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