Dietary Aloe Vera Supplementation and Glycemic Control in Diabetes

By Ken Jones
Townsend Letter for Doctors and Patients
May, 2007

Diabetes is a deficiency or absence of the hormone insulin, which is the main hormone responsible for the control of sugar in the blood. According to the National Health Interview Survey, (1) conducted by the Center for Health Statistics at the Center for Disease Control (CDC) in 2005, nearly 20.8 million adults and children in the United States, or about seven percent of the population, suffered from diabetes. Of this group, only about 15.6 million have been formally diagnosed with diabetes; another 6.2 million people remain unaware that they have the disease. Diabetes is currently the fifth-leading cause of death in the United States, but health policy experts believe that mortality attributed to diabetes is vastly under-reported. Diabetes is associated with a number of serious complications that increase the risk of death, including heart disease and stroke, obesity, cancer, high blood pressure, kidney failure, neurological diseases, traumatic amputations, and metabolic imbalances.

Only 35% to 40% of decedents with diabetes have it listed anywhere on the death certificate, and only about ten percent to 15% have diabetes listed as the underlying cause of death. The overall risk of death for diabetics is about twice that for non-diabetics of comparable age. Heart disease and stroke account for about 65% of deaths for people with diabetes. Adult diabetics' risk factors for stroke and death from heart disease are two to four times that of non-diabetic adults. Additionally, diabetes is associated with a number of co-morbid conditions that adversely affect quality of life, including blindness and other vision problems, mouth and gum diseases, loss of extremities due to amputation, impaired circulation, loss of mobility, and osteoporosis. (2)

Diabetes has been linked to factors associated with a Western lifestyle, but the reality is that diabetes is one of the leading causes of death worldwide. There are two main types of diabetes. Type 1 is caused by an absolute deficiency of insulin, and because it usually manifests before the age of 25, type 1 is sometimes called insulin-dependent or juvenile-onset diabetes. Management of the disease requires insulin supplementation, usually administered by injection or via metered infusion pumps. Type 2, or non-insulin-dependent, diabetes usually manifests after age 40 and is due to a combination of relative deficiency of insulin (insufficient quantities are made in the body) and insulin resistance, meaning that the body is unable to efficiently utilize the reduced amount of insulin it does produce. Type 2 diabetes sometimes requires supplementary insulin, but, more commonly, it can be managed through diet and exercise, often in combination with oral hypoglycemic medications. There is a strong correlation between being overweight or obese and the development of type 2 diabetes. (3) The American Diabetes Association website (http://www.diabetes.org/home.jsp) offers information on weight loss and a brochure titled "Weight Loss Matters" to provide advice on how to start losing weight and become more active. (4)

Although the management of type 1 diabetes requires insulin supplementation, type 2 diabetes can often be managed solely by getting sufficient exercise and eating a healthy diet. In some cases, oral medications can be added to the treatment regimen to stimulate the pancreas to produce more insulin, decrease the amount of glucose made by the liver, slow the absorption of starches in the diet, or control blood sugar. But the management of diabetes without any side effects is still a challenge and has increased the demand for research on natural products with antidiabetic activity.

An abundance of evidence has implicated oxidative stress in the pathogenesis of diabetes (see Kaneto et al. (5) for a recent review). Infiltration of pancreatic tissues by various immune cells triggers inflammatory processes that lead to destruction of [beta]-cells. In type 2 diabetes, [beta]-cell dysfunction results in hyperglycemia and insulin resistance, a process known as "glucose toxicity." Under these conditions, oxidative stress is provoked, and the JNK kinase pathway* is activated. JNK activation together with oxidative stress is involved in the progression of atherosclerosis, which is often associated with diabetes. It is likely that activation of the JNK pathway and oxidative stress are involved in the pathogenesis of both type 1 and type 2 diabetes. (6)

A growing body of preclinical and clinical research shows that the gel** of the Aloe vera plant, administered as a juice or in dried form, has significant antidiabetic activity. Not surprisingly, studies using animal models outnumber clinical trials, but animal studies provide supporting evidence and often provide insights into mechanisms of action.

The control of blood sugar is critical in the management of diabetes. Research has shown that elevated blood sugar leads to increased oxidative

stress and risk of cardiovascular disease, and evidence of oxidative damage has been demonstrated in arterial samples from human diabetic subjects. (7) Patients with diabetes have decreased antioxidant defenses with lower levels of antioxidants such as vitamins C and E, or reduced activities of antioxidant enzymes such as catalase (CAT), superoxide dismutase (SOD), and glutathione peroxidase (GPx). Singh et al. conducted an extensive study, (8) showing that oral dosing with aloe induced the Phase II enzyme system (including SOD, catalase, and glutathione peroxidase) of mice and significantly reduced lipid peroxidation. Supplementation with Aloe vera gel has also been found to markedly enhance the bioavailability and half-life of the antioxidant vitamins, ascorbate (vitamin C), and tocopherol (vitamin E). (9)

n the studies reported here, oral treatment with Aloe vera gel has been shown to aid in the normalization of blood sugar and to stimulate the body's own antioxidant defenses. These studies indicate that Aloe vera gel has a beneficial effect on the liver, as a hypoglycemic agent, and in cardiovascular disease by reducing oxidative stress.

Support for this hypothesis may be found in two studies from Thailand (10,11) that investigated the effect of Aloe vera gel on oxidative stress in streptozotocin-diabetic rats.*** In the first study, investigators examined the effect of orally administered Aloe vera ethanolic extract (300 mg/kg, 1X/day, 21 days) on various measures of oxidative stress in streptozotocin-diabetic rats. The Aloe-treated group was compared to normal control rats (not streptozotocin-diabetic), a control group of streptozotocin-diabetic rats, and a third treatment group of streptozotocin-diabetic rats given a reference drug, the oral hypoglycemic glibenclamide (600 [micro]g/kg/day x 21 days). Both the Aloe-treated group and the glibenclamide-treated groups showed similar ameliorative effects on oxidative stress in comparison to the diabetic control group. These included significantly reduced levels of plasma glucose and significantly elevated levels of insulin. Thiobarbituric acid reactive substances (TBARS) in plasma (a measure of lipid peroxidation), hydroperoxides, and alpha-tocopherol were all significantly reduced in the Aloe-and glibenclamide-treated groups, while reduced glutathione in plasma and pancreas, and vitamin C were all significantly elevated. Pancreatic activities of the oxygen-radical scavenging enzyme SOD and the peroxide-reducing enzymes CAT and GPx were all significantly reduced compared to the diabetic controls. Increased activity of these enzymes in diabetic rats is considered an adaptive response to oxidative stress, and therefore their reduction by Aloe vera is indicative of modulation of oxidative stress.

These results indicated that Aloe vera gel treatment effectively normalized many of the measures of oxidative stress that may be responsible for many diabetes complications. The investigators noted that preliminary phytochemical investigations had indicated the presence of phenolic compounds in the Aloe vera gel extract and speculated that those compounds could be responsible for the observed activity. Indeed, while phenolics with antidiabetic activity have not yet been isolated, a separate group of investigators recently reported on the isolation of five phytosterols from Aloe vera gel that markedly reduced blood glucose levels in a mouse model of type 2 diabetes. (12)

The second study by Rajasekaran's group (11) was designed similarly to the first, in that, again, four groups of animals were used: normal controls, streptozotocin-diabetic controls, and two groups of streptozotocin-diabetic rats, treated with either Aloe vera gel extract (300 mg/kg/d x 21 days) or glibenclamide (600 [micro]g/kg/d X 21 days). Similar results were noted: lipid peroxides and TBARS were significantly reduced compared to the untreated diabetic controls; liver and kidney reduced glutathione (GSH) was significantly elevated. Plasma glucose and glycosylated hemoglobin were significantly reduced in the Aloe and glibenclamide groups. Anomalously, however, in this study, the activities of SOD, CAT, GPx, and glutathione-S-transferase (GST) were all lower in the untreated diabetic control group than in the non-diabetic controls or the Aloe-and glibenclamide-treated groups. The authors rationalized these results by noting that decreased activity of SOD, CAT, and GPx in the untreated diabetic animals may have been due to glycation of the enzymes, and reduced activity of GST may be due to inactivation by reactive oxygen species. They postulated that in the Aloe-treated group, the administered extract may have reduced blood glucose levels and thus prevented the glycation of enzymes and their subsequent inactivation. They did not, however, reconcile this explanation with the results of their previous study in which the opposite results were seen.

A third and more recent study by this group (13) focused more specifically on changes in blood lipid profiles of streptozotocin-diabetic rats treated with Aloe vera gel extract. The study was designed similarly to the previous studies, with two control and two treatment groups. As in the previous studies, both the Aloe treatment and the glibenclamide treatment significantly lowered plasma glucose and elevated

insulin levels, suggesting a possible insulinogenic effect associated with the activation of [beta]-cells. Aloe-and glibenclamide-treated groups both displayed "normalized" lipid profiles after 21 days, including significant reductions in plasma cholesterol, triglycerides, free fatty acids, and phospholipids, and significant reductions in low-density lipoprotein (LDL) and very low density lipoprotein (VLDL), and a concomitant increase in high density lipoprotein (HDL). Diabetic nephropathy is another chronic condition associated with the disease and abnormal lipid metabolism, and the renal accumulation of lipids has been proposed to play a role in its pathogenesis. The finding that treatment of the diabetic rats with Aloe extract was able to essentially normalize lipid profiles provided further evidence for the application of Aloe vera gel in the treatment of diabetes.

Supporting evidence for the antidiabetic activity of Aloe vera was also reported from an animal study by Korean investigators. (14) Lim et al. studied lifelong dietary Aloe vera supplementation in aged rats (from six weeks to 16 months). Rats fed various freeze-dried Aloe preparations at a level of one percent of the diet (per weight) over this period displayed reduced levels of hepatic lipid peroxidation (measured as phosphatidylcholine hydroperoxide), elevated activity of SOD and CAT, and a 30% lower level of hepatic cholesterol compared to the control group in 16-month-old animals, but not in four-month-old animals. Can et al. (15) examined oxidative stress markers in the livers of neonatal streptozotocin-induced type 2 diabetic rats given various Aloe preparations by gavage (1x/day x 15 d). Glutathione (GSH), non-enzymatic glycosylation (NEG), and lipid peroxidation (LPO) were determined in liver tissue; biochemical markers for liver function (serum alkaline phosphatase [ALP]; alanine transaminase [ALT]) were also evaluated. All parameters were compared to control non-diabetic rats and to an untreated diabetic control group. In this group, degenerative changes in liver tissue were evident, while liver damage in diabetic rats given Aloe gel, pulp, or glibenclamide was decreased. GSH was increased, and NEG and LPO were significantly decreased. ALP and ALT activities were also decreased. All these results were consistent with the hypothesis that Aloe vera gel extract protects against diabetes-related hepatotoxicity in a manner that is comparable to glibenclamide when used in the treatment of type 2 diabetes.

Human clinical trials on the antidiabetic actions of Aloe vera are relatively few, but the results reported are consistent with those of the animal studies. One early clinical study (16) focused primarily on the beneficial effects of a combination product containing Aloe vera gel and "husk of Isabgol" (the Indian term for Psyllium seed husks) on various parameters related to cardiovascular health, including serum cholesterol and triglycerides, fasting and postprandial blood sugar, total lipids, and increases in HDL. Additionally, frequency of angina attacks and intake of cardiac drugs were monitored. The study's relevance to diabetes was based on the fact that of the 5000 individuals in the study, 3167 were diabetics displaying symptoms of heart disease often associated with diabetes (angina, atherosclerosis, hypertension). Patients consumed 100 g of Aloe vera gel 20 g of "husk of Isabgol" mixed with wheat flour and baked into bread. This "medication" was consumed at lunch and dinner, but the paper does not specify whether the amounts consumed as described above were a total daily intake, or whether this amount was consumed at each meal. The study also notes that the patients were monitored for a period of five years, but does not specify the actual length of the treatment regimen. Smoking and alcohol consumption during the treatment was prohibited, but patients with pre-existing medication regimens maintained them. These included [beta]-blockers, verapamil, nifedipine, isosorbide dinitrate, sulphonylureas, digoxin, and diuretics and B-complex.

The following key findings were noted:

- ☑ Feelings of well-being and decreased symptoms of angina appeared in many patients by the second week of therapy. From three months to one year, all but 348 patients had normal ECG profiles even after treadmill exercise.|

- ☑ Lipid profiles improved in most patients after three months of therapy. None of the patients suffered new myocardial infarctions during the course of the study.

- ☑ After three months treatment, 4652 patients displayed normal levels of HDL cholesterol. Total blood lipids and serum triglycerides were similarly within normal ranges for over 90% of patients.

- ☑ Among the 3167 diabetic patients, fasting blood glucose levels had fallen to normal values in 94% of patients after two months of treatment. All oral hypoglycemic medications had to be withdrawn after two months of treatment.

Although this study is marred by serious metho-dological and design flaws, it is noteworthy as it is one of the earliest clinical trials to address the potential anti-diabetic activity of Aloe vera gel.

More recent (and better-designed) clinical studies have focused specifically on the antidiabetic activity of Aloe vera gel in diabetic patients. In a human clinical trial (17) conducted at the Mahidol University of Bangkok, Thailand, patients with high fasting blood sugar and typical diabetic curves of glucose tolerance, who had never been treated with hypoglycemic drugs, were treated with 80% Aloe vera juice (1 tbsp/2x/day x 42 days). Thirty-six patients received the Aloe juice, while a control group of 36 received a similarly flavored carminative mixture. Blood samples were taken weekly for measurement of fasting blood glucose levels and every two weeks for triglyceride and cholesterol analyses. Before treatment, the patients in the control and treated groups showed no significant differences in blood markers. After two weeks of treatment, blood sugar in the treatment group had been significantly reduced compared to their initial values (17%), and by day 42 of the treatment, these levels were further reduced to 43% of the initial values. Blood triglycerides were significantly reduced to 70% compared to initial values after 28 days and to 45% of initial values by day 42 of treatment. Cholesterol levels were unchanged throughout the treatment. In control groups, no changes in any of these parameters were observed over the course of treatment (Figure 1). No adverse side effects were reported due to Aloe vera supplementation, and there was no difference in weight or appetite in the treatment group.

At Mahidol University, a second trial (18) with Aloe vera was conducted to determine the effect of Aloe treatment in patients unresponsive to glibenclamide, an antidiabetic medication used to lower blood sugar levels by stimulating the production and release of insulin from the pancreas. In this study, levels of fasting blood glucose, cholesterol, and triglycerides were unchanged when glibenclamide was used alone. Results for the Aloe treatment group were similar to the first study with a 49% decrease in blood sugar levels and a 52% decrease in triglycerides at day 42, and no change in cholesterol. A control group of patients receiving glibenclamide alone showed no changes in any of these parameters. The results of treatment with glibenclamide and Aloe in combination were the same as treatment with Aloe juice alone (as determined in the previous study (17)). The authors note that even though blood sugar levels had dropped significantly after 42 days, they had still not reached normal values and suggested that the dose may not have been high enough. This may also account for the lack of effect on cholesterol seen in this and the previous Mahidol study.

No dosing study has been conducted to establish the optimum daily intake of Aloe vera as a functional food in conjunction with the studies cited here. General recommendations for Aloe vera as a supplement range from one to two ounces of single strength juice or 150 to 300 milligrams of 200:1 gel powder twice a day, in the morning and before bed. Single-strength Aloe vera gel is typically standardized to 0.5 percent solids, and gel powders are commonly referred to as a 200X or 200:1 concentration. Whole leaf Aloe vera products are usually standardized to one-percent solids, and the powders are a 100X concentration.

Conclusion

Diabetes is the fifth-leading cause of death in the United States, and health policy experts believe that mortality attributed to diabetes is vastly under-reported. The overall risk of death for diabetics is about twice that for non-diabetics, and diabetes is associated with a number of complications that increase the risk of death, including heart disease and stroke, obesity, cancer, high blood pressure, kidney failure, neurological diseases, traumatic amputations, and metabolic imbalances. Elevated blood sugar, indicative of diabetes, leads to increased oxidative stress, which is associated with the pathogenesis of diabetes. Oxidative damage has been demonstrated in arterial samples from human diabetic subjects, and patients with diabetes have decreased antioxidant defenses.

Although type 2 diabetes can often be managed solely by exercise and a healthy diet, oral medications may be required to control blood sugar. But the management of diabetes without side effects, such as weight gain and increased risk of chronic disease, drives further research for alternatives, such as natural products with antidiabetic activity and protection from the damaging effects of oxidative stress.

Preclinical and clinical research shows that Aloe vera has significant antidiabetic activity including normalization of blood glucose and protection from oxidative stress. Aloe vera has been shown in human clinical trials to be as effective as glibenclamide in controlling blood glucose, and in one study, Aloe supplementation was shown effective in patients unresponsive to glibenclamide. In animal studies, Aloe supplementation showed significant reductions in blood triglycerides, free fatty acids, and phospholipids, and significant reductions in LDL and VLDL, while increasing HDL without weight gain normally associated with conventional medications.

Patients with diabetes have decreased antioxidant defenses and lower levels of antioxidants such as vitamins C and E, as well as reduced activities of Phase II antioxidant enzymes such as CAT, SOD, and

GPx. Oral supplementation with Aloe vera has been shown to naturally stimulate production of these Phase II enzymes and, in human clinical studies, increase the bioavailability and half-life of vitamins C and E in the blood. Additional studies show that Aloe supplementation can increase GSH, decrease NEG, LPO, ALP, and ALT, suggesting that Aloe vera may also protect against diabetes-related hepatotoxicity.

While it is clear that more and better-designed human clinical studies are required to fully understand the activities of Aloe vera in blood glucose control and its protective effects against hepatotoxicity and oxidative stress, an abundance of research supports a role for Aloe vera supplementation in the management of type 2 diabetes. Aloe vera is not recommended as a replacement for conventional treatments for diabetes, and a health care professional should always be consulted before making any dietary changes that may affect your health.

Notes

1. Centers for Disease Control, National Center for Health Statistics. National Health Interview Survey. Available at:http://www.cdc.gov/nchs/nhis.htm. Accessed January 26, 2007.

2. Centers for Disease Control. Publications and Products. National Diabetes Fact Sheet Available at:http://www.cdc.gov/diabetes/pubs/estimates05.htm #deaths Accessed January 26, 2007.

3. Harris Ml, Flegal KM, Cowie CC, Eberhardt MS, Goldstein DE, Little RR, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in U.S. adults. The Third National Health and Nutrition Examination Survey, 1988-1994. Diabetes Care. 1998;21:518-24.

4. American Diabetes Association, Weight Loss Matters. Available at:http://www.diabetes.org/weightloss-and-exercise/weightloss.jsp. Accessed January 26, 2007.

5. Kaneto H, Katakami N, Kawamori D, Miyatsuka T, et al. Involvement of oxidative sress in the pathogenesis of diabetes. Antioxid Redox Signal. 2007;[epub ahead of print].

6. Kaneto H. The JNK pathway as a therapeutic target for diabetes. Expert Opin Ther Targets. 2005:9:581-592.

7. Haidara MA, Yassin HZ, Rateb M, Ammar H, Zorkana MA. Role of oxidative stress in development of cardiovascular complications in diabetes mellitus. Curr Vasc Pharmacol. 2006;4:215-227.

8. Singh RP Dhanalakshmi S, Rao AR. Chemomodulatory action of aloe vera on the profiles of enzymes associated with carcinogen metabolism and antioxidant status regulation in mice. Phytomedicine. 2000: 7:209-219.

9. Vinson JA, Al Kharrat H, Andreoli L. Effect of aloe vera preparations on the human bioavailability of vitamins C and E. Phytomedicine. 2005; 12:760-765.

10. Rajasekaran, S, Sivagnanam K, Subramanian S. Modulatory effects of aloe vera leaf gel extract on oxidative stress in rats treated with streptozotocin. Journal of Pharmacy and Pharmacology. 2005;31:241-246.

11. Rajasekaran, S. Sivagnanam K, Subramanian S. Antioxidant effect of aloe vera gel extract in streptozotocin-induced diabetes in rats. Pharmacological Reports. 2005;57:90-96.

12. Tanaka T, Misawa E, Ito Y, Habara N, et al. Identification of five phytosterols from aloe vera gel as anti-diabetic compounds. Biol Pharm Bull. 2006;29:1418-1422.

13. Rajasekaran S, Kasiappan R, Sivagnanam K, Subramanian S. Beneficial effects of aloe vera leaf gel extract on lipid profile status in rats with streptotozotocin diabetes. Clin Exp. Pharmacol Physiol. 2006;33:232-237.

14. Lim OB, Choue RW, Kim JD, Yu BP, et. al. Efficacy of dietary aloe vera supplementation in hepatic cholesterol and oxidative status in aged rats. J Nutritional Science & Vitaminology. 2003; 49:292-296.

15. Can A, Akev N, Ozsoay N, Bolkent S, et al. Effect of aloe vera leaf gel pulp on the liver in type-IJ diabetic rats. Biol Pharm Bull. 2004: 27:694-698.

16. Agarwal 0. P. Prevention of Atheromatous Heart Disease. Angiology. 1985;36: 485-92.

17. Yongchaiyudha S, Rungpitarangsi V, Bunyapraphatsara N, Chokechaijaroenporn O. Antidiabetic activity of aloe vera L. juice. I. Clinical trial in new cases of diabetes mellitus. Phytomedicine. 1996; 3:241-244.

18. Bunyapraphatsara N, Yongchaiyudha S, Rungpitarangsi V, Chokechaijaroenporn O. Antidiabetic activity of aloe vera L. juice 11. Clinical trial in diabetes mellitus patients in combination with glibenclamide. Phytomedicine. 1996;3:245-248.

---

* The c-Jun N-terminal kinase (JNK) signaling pathway is a major mediator of stress responses in cells. Activation of the JNK pathway interferes with insulin action and reduces insulin biosynthesis and is thought to play a central role in the etiology of diabetes.

** The “gel” of the Aloe vera plant refers to the colorless, mucilaginous pulp from the inner part of the succulent leaves, obtained after the epidermis has been removed.

*** Streptozotocin is a glucosyl-nitrosourea compound that is selectively toxic to the insulin-producing cells of the pancreas. It is used in research to produce an animal model for type 1 diabetes.

http://www.townsendletter.com