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The Efficacy of *Silybum marianum* (L.) Gaertn. (Silymarin) in the Treatment of Type II Diabetes: A Randomized, Double-blind, Placebo-controlled, Clinical Trial

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Oxidative stresses are increasingly implicated in the pathogenesis of diabetic complications which may either cause direct pancreatic β-cell damage or lead to metabolic abnormalities that can induce or aggravate diabetes. The valuable effect of antioxidant nutrients on the glycemic control of diabetic patients has been reported in experimental and clinical studies. The present study was designed to investigate the effects of the herbal medicine, *Silybum marianum* seed extract (silymarin), which is known to have antioxidant properties on the glycemic profile in diabetic patients. A 4-month randomized double-blind clinical trial was conducted in 51 type II diabetic patients in two well-matched groups. The first group (n = 25) received a silymarin (200 mg) tablet 3 times a day plus conventional therapy. The second group (n = 26) received the same therapy but a placebo tablet instead of silymarin. The patients were visited monthly and glycosylated hemoglobin (HbA_1c), fasting blood glucose (FBS), insulin, total cholesterol, LDL and HDL, triglyceride, SGOT and SGPT levels were determined at the beginning and the end of the study. The results showed a significant decrease in HbA_1c, FBS, total cholesterol, LDL, triglyceride SGOT and SGPT levels in silymarin treated patients compared with placebo as well as with values at the beginning of the study in each group. In conclusion, silymarin treatment in type II diabetic patients for 4 months has a beneficial effect on improving the glycemic profile.

Keywords: silymarin; herbal medicine; antioxidant; diabetes.

INTRODUCTION

Silybum marianum (L.) Gaertn. is a member of the Asteraceae family and its seed extract contains large numbers of chemical constituents including several flavonolignans collectively known as silymarin (Pepping, 1999). Silymarin has powerful antioxidant properties and has a beneficial effect on various hepatic disorders, including hepatotoxicity secondary to acute and chronic viral hepatitis and mushroom poisoning (Sonnenbichler *et al.*, 1986; Flora *et al.*, 1998; Parish and Doering, 1986).

Diabetes mellitus is a continuously growing health problem, which causes substantial morbidity, mortality and long-term complications even in developed countries.

The favorable effect of antioxidants in the treatment of oxidative metabolic derangement in diabetes has been reported in several experimental studies (Rudich *et al.*, 1999; Packer *et al.*, 2000; Maddux *et al.*, 2001). In addition, several clinical trials, albeit of short duration, have demonstrated that treatment with antioxidants such as vitamin E, vitamin C, or glutathione improves insulin sensitivity in insulin-resistant individuals and/or patients with type II diabetes (Jacob *et al.*, 2000; Evans and Goldfine, 2000). Two placebo-controlled clinical trials have also reported that *Silybum marianum* seed extract administration to diabetic cirrhotic patients reduces insulin resistance and the need for exogenous administration of insulin (Velussi *et al.*, 1993; Velussi *et al.*, 1997). The present study was undertaken to evaluate the effects of 4 months silymarin administration on the glycemic state in type II diabetes patients.

METHODOLOGY

A total of 51 patients (19 male, 32 female) with type II diabetes from the Diabetes Clinic of Shariati Hospital were enrolled in this study. The research protocol was approved by the Ethics Committee of the Endocrinology and Metabolism Research Center of Shariati Hospital and written informed consent was obtained from each patient prior to study.

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Table 1. The demographic characteristics of patients in placebo and silymarin treated groups

Group	Silymarin (n = 25)	Placebo (n = 26)	Total
Age (year) (mean ± SD)	53.0 ± 6.6	54.1 ± 6.0	53.5 ± 6.3
Sex (male/female)	14M/11F	5M/21F	19M/32F
Duration of disease (year) (mean ± SD)	7.6 ± 4.9	11.7 ± 6.1	9.6 ± 5.9
Weight (kg) (mean ± SD)	77.2 ± 14.8	69.9 ± 10.9	73.4 ± 13.1

All the patients who participated were aged between 40 and 65 years, and had a confirmed diabetes type II diagnosis according to ADA criteria (American Diabetes Association, 2003). The patients had a fasting blood glucose level less than 250 mg/dL, the duration of diabetes was more than 2 years, and their diabetes was not controlled exclusively by diet. The exclusion criteria were insulin therapy, cardiovascular disease, infectious diseases, pregnancy and breast-feeding. The patients were then randomly allocated to two groups using a balanced randomization method.

The patients and the investigators who carried out clinical and paraclinical assessments were unaware of the treatment groups and type of medication. Silymarin (200 mg) and placebo tablets were of the same shape and kindly provided by the Institute of Medicinal Plants (Tehran, Iran). The conventional oral hypoglycemic agent (metformin and glibenclamide) treatment continued in the two groups. The compliance was assessed indirectly using a pill count method.

The first group (25 patients) received a 200 mg silymarin tablet three times a day before meals. The control group (26 patients) received a placebo tablet three times a day before meals.

The blood levels of HbA_1c and fasting blood glucose, insulin, total cholesterol, LDL and HDL, triglyceride, SGOT and SGPT were determined at the beginning and after 4 months of the study in both groups.

Blood samples were drawn after an overnight fasting (12 h). Fasting glucose levels were determined by the glucose-oxidase method using a Beckman Glucose2 Analyzer immediately after blood sampling at the Endocrine Research Center laboratory. Glycosylated hemoglobin levels were determined by a D-10 Hemoglobin testing system (Bio-Rad Laboratories, Inc.). All the other blood sample parameters were measured by an auto analyzer Hitachi 902 using commercial kits.

Patients were visited and examined every month and the efficacy of treatment was checked by determination of the fasting blood glucose level.

Statistical analysis. The statistical analysis of the recorded data at the beginning and after 4 months was performed using independent and paired Student's t-test employing SPSS statistical software for quantitative variables. A value of $p < 0.05$ was considered as statistically significant.

RESULTS

All 51 patients completed the study and there were no dropouts. The patients' demographic characteristics are summarized in Table 1.

The baseline findings of patients in the two groups (silymarin and placebo) were compared with each other regarding FBS, HbA_1c, lipid profile, insulin and liver enzymes. The two groups were completely comparable, except for the triglyceride levels that were higher in the silymarin group (Table 2).

Glucose

The average fasting blood glucose level in the silymarin group at the beginning of the study was 156 ± 46 mg/dL, which decreased significantly ($p < 0.001$) to 133 ± 39 mg/dL after 4 months of silymarin treatment. The average fasting blood glucose level in the placebo group at the beginning of the study was 167 ± 47 mg/dL, which increased significantly ($p < 0.0001$) to 188 ± 48 mg/dL after 4 months of placebo treatment.

HbA_1c

The average HbA_1c level in the silymarin group at the beginning of the study was 7.82 ± 2.01%, which decreased significantly ($p < 0.001$) to 6.78 ± 1.05% after 4 months silymarin treatment. The average HbA_1c level

Table 2. Paraclinical characteristics of the two groups at the beginning of study

	Group		
	Silymarin (mean ± SD)	Placebo (mean ± SD)	p value
FBS (mg/dL)	156 ± 46	167 ± 47	0.39
HbA_1c (%)	7.8 ± 2.0	8.3 ± 1.9	0.39
Insulin (ng/mL)	0.4 ± 0.3	0.3 ± 0.2	0.43
Cholesterol (mg/dL)	225 ± 64	211 ± 46	0.38
HDL (mg/dL)	140 ± 47	130 ± 47	0.08
LDL (mg/dL)	70 ± 33	94 ± 60	0.44
Triglyceride (mg/dL)	284 ± 206	185 ± 78	0.02
SGOT (U/L)	22 ± 5	22 ± 5	0.396
SGPT (U/L)	19 ± 9	17 ± 9	0.041

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Table 3. The average serologic parameters at the beginning and after 4 months of the study in placebo and silymarin treated groups

Group	Silymarin (mean ± SD)		*p* value	Placebo (mean ± SD)		*p* value
	Beginning	After 4 months		Beginning	After 4 months	
FBS (mg/dL)	156 ± 46	133 ± 39	0.001	167 ± 47	188 ± 48	0.0001
HbA_1c (%)	7.8 ± 2.0	6.8 ± 1.1	0.001	8.3 ± 1.9	9.5 ± 2.2	0.0001
Insulin (ng/mL)	0.4 ± 0.3	0.3 ± 0.2	0.123	0.3 ± 0.2	0.3 ± 0.2	0.396
Total cholesterol (mg/dL)	225 ± 64	198 ± 41	0.0001	211 ± 46	215 ± 50	0.565
LDL cholesterol (mg/dL)	140 ± 47	123 ± 30	0.005	130 ± 47	130 ± 44	0.933
HDL cholesterol (mg/dL)	70 ± 33	61 ± 19	0.027	94 ± 60	85 ± 91	0.392
Triglyceride (mg/dL)	284 ± 206	211 ± 136	0.004	185 ± 78	207 ± 93	0.127
SGOT (U/L)	22 ± 5	17 ± 3	0.008	22 ± 5	20 ± 5	0.039
SGPT (U/L)	19 ± 9	12 ± 6	0.0001	17 ± 9	18 ± 9	0.283

in the placebo group at the beginning of the study was 8.29 ± 1.88%, which increased significantly ($p < 0.0001$) to 9.45 ± 2.16% after 4 months of placebo treatment.

Silymarin treatment also significantly lowered blood levels of total cholesterol, LDL, triglyceride, SGOT and SGPT. The results of the clinical findings in both groups at the beginning and after 4 month of the study are summarized in Table 3.

Finally a slight but non-significant decrease in weight, systolic and diastolic blood pressure in patients on silymarin was found. In addition, no side effects of the treatment were reported during the study and there were no changes in therapy or surgical intervention in either group. At the end of the study, many of the silymarin-treated patients wished to continue the same treatment.

DISCUSSION AND CONCLUSION

The present study investigated the effect of silymarin on the glucose profile in patients with type II diabetes. The results show that although there were no statistically significant differences in the main parameters between the two groups of patients at the beginning of study (Table 2), silymarin treatment significantly lowered the HbA_1c and fasting blood glucose levels in diabetic patients at the end of the study.

The mechanism underlying the glucose lowering effect of silymarin is not clear. Silymarin is a *Silybum marianum* seed extract that contains a wide number of active constituents including flavonoids with antioxidants, that increases cellular glutathione levels and cellular membrane stabilizing properties (Flora *et al.*, 1998; Sonnenbichler *et al.*, 1986; Parish and Doering, 1986; Von Schonfeld *et al.*, 1997; Pepping, 1999). In type II diabetic patients the elevation of glucose and free fatty acid (FFA) levels leads to the generation of reactive oxygen species and oxidative stress (Brownlee, 2001; McGarry, 2002). These metabolic abnormalities not only induce late diabetic complications but also lead to insulin resistance, β-cell dysfunction and impaired insulin secretion (Boden, 1997). Silymarin, with its powerful antioxidant properties, is active against oxidative stress and may induce a positive effect on diabetic metabolic abnormalities. In support of this hypothesis, several experimental and clinical studies indicate that substances with antioxidant properties have favorable effects on oxidative metabolic derangement of hyperglycemia (Rudich *et al.*, 1999; Jacob *et al.*, 2000; Maddux *et al.*, 2001). Silymarin has been shown to increase and normalize the pancreatic levels of free radical quenching enzymes such as superoxide dismutase, glutathione peroxidase and catalase in alloxan-induced diabetic animals (Soto *et al.*, 2003). This can exert potent inhibitory effects on enhanced lipid peroxidation seen in diabetes. Two clinical studies (Velussi *et al.*, 1993; Velussi *et al.*, 1997) also reported that silymarin reduces insulin resistance and the need for exogenous administration of insulin in diabetic cirrhotic patients. In diabetic patients, aldose reductase enzyme levels increase. Silymarin, as an inhibitor of this enzyme, inhibits its deleterious effect on the nerves and red blood cells (Zhang *et al.*, 1993). It has also been reported that silymarin inhibits insulin secretion in response to glucose stimulation (Lirussi *et al.*, 2002). This effect may inhibit hyperinsulinemia and subsequent insulin resistance.

In addition, there is evidence that lipoperoxidation may negatively affect patients with diabetes (Tsuzura *et al.*, 2004). Silymarin is a powerful inhibitor of lipoperoxidation that may counteract its deleterious effect on the glucose profile in diabetic patients (Skottova *et al.*, 1999).

Silymarin also inhibits the toxic effect of alloxan and cyclosporin on pancreatic cells in experimental animals (Soto *et al.*, 1998; Soto *et al.*, 2004; Von Schonfeld *et al.*, 1997). This effect may protect pancreatic cells from harmful metabolic products in hyperglycemic patients. Furthermore, silymarin is a well-known hepatoprotective herbal medicine (Velussi *et al.*, 1993). Thus the correction of liver function following silymarin administration may positively influence lipid and glucose metabolism.

In conclusion, the results showed that silymarin treatment has a beneficial effect in reducing the glycemic state in type II diabetic patients. The use of antioxidants such as silymarin as a complementary therapy in type II diabetes patients needs further investigation in large multi-centre studies.

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