

Long-term (12 months) treatment with an anti-oxidant drug (silymarin) is effective on hyperinsulinemia, exogenous insulin need and malondialdehyde levels in cirrhotic diabetic patients

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Background/Aims: Several studies have demonstrated that diabetic patients with cirrhosis require insulin treatment because of insulin resistance. As chronic alcoholic liver damage is partly due to the lipoperoxidation of hepatic cell membranes, anti-oxidizing agents may be useful in treating or preventing damage due to free radicals. The aim of this study was to ascertain whether long-term treatment with silymarin is effective in reducing lipoperoxidation and insulin resistance in diabetic patients with cirrhosis.

Methods: A 12-month open, controlled study was conducted in two well-matched groups of insulin-treated diabetics with alcoholic cirrhosis. One group ($n=30$) received 600 mg silymarin per day plus standard therapy, while the control group ($n=30$) received standard therapy alone. The efficacy parameters, measured regularly during the study, included fasting blood glucose levels, mean daily blood glucose levels, daily glucosuria levels, glycosylated hemoglobin (HbA1c) and malondialdehyde levels.

Results: There was a significant decrease ($p<0.01$) in fasting blood glucose levels, mean daily blood glucose

levels, daily glucosuria and HbA1c levels already after 4 months of treatment in the silymarin group. In addition, there was a significant decrease ($p<0.01$) in fasting insulin levels and mean exogenous insulin requirements in the treated group, while the untreated group showed a significant increase ($p<0.05$) in fasting insulin levels and a stabilized insulin need. These findings are consistent with the significant decrease ($p<0.01$) in basal and glucagon-stimulated C-peptide levels in the treated group and the significant increase in both parameters in the control group. Another interesting finding was the significant decrease ($p<0.01$) in malondialdehyde/levels observed in the treated group.

Conclusions: These results show that treatment with silymarin may reduce the lipoperoxidation of cell membranes and insulin resistance, significantly decreasing endogenous insulin overproduction and the need for exogenous insulin administration.

Key words: Anti-oxidizing drug; Cirrhosis; Diabetes; Insulin resistance; Lipoperoxidation; Silymarin.

THE PRE-CLINICAL or early clinical phase of non-insulin-dependent diabetes mellitus (NIDDM) is characterized by insulin resistance in the insulin-dependent tissues (liver, muscle and body, fat) (1). About 50% of the insulin produced by the pancreas is extracted by, and degraded in, the liver. The liver also influences blood glucose levels and the related mechanisms of gluconeogenesis and glycogen synthesis (2-9).

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Insulin resistance is constantly fairly high in patients with NIDDM and hepatic cirrhosis (10-14). This metabolic disorder is partly related to increased blood glucose levels due to reduced glucose uptake by the liver. Hyperglycemia promotes hyperinsulinemia and this, together with the decreased hepatic degradation of the insulin molecule, may lead to insulin resistance in the target tissues (15-22). When dietary control and treatment with oral sulphonylurea drugs become ineffective, these patients require insulin treatment, even though they have much higher endogenous insulin levels than normal subjects (23,24). Moreover, secondary diabetes shows a wide range of variability with fre-

quent hyper- and hypoglycemic fits. Liver damage due to alcohol is related to the lipoperoxidation of hepatic cell membranes (25-30), i.e., an imbalance between lipid peroxidation and cellular antioxidant defence mechanism (31). This activity has been found to be very marked in Type I insulin-dependent diabetes mellitus (IDDM) at onset and in Type II NIDDM. Recent studies have demonstrated that increased peroxidation in diabetic patients may result in cell ageing and in long-term diabetic complications (nephropathy, macro- and micro-angiopathy). This may be due to a reduction in the antioxidant defenses of erythrocytes (mainly vitamin E), altered endothelium function and peroxide release by the glycosylated proteins (32-37).

Several studies are exploring the possibility of delaying the exhaustion of the endogenous insulin secretion with the use of some anti-oxidizing agents (such as vitamin A and E, nicotinamide). This approach is based on the hypothesis that an increase in free radicals, caused by autoimmune disease in Type I diabetes, might cause the progression of the diabetes to complete insulin dependence (38-40). Given that alcoholic diabetics with cirrhosis present high levels of peroxidation markers, such as malondialdehyde (MDA), we felt it would be interesting to perform a long-term clinical study to evaluate the efficacy of the anti-oxidizing agent silymarin (41-44) in reducing peroxidative damage.

Studies on lipoperoxidation received a great stimulus when the blood levels of MDA were shown to correlate with the level of lipoperoxidation (45-47). One endpoint in our study was the regular determination of plasma levels of MDA during treatment with silymarin. This drug has been recognized as being safe and effective in reducing the lipoperoxidation in a stable manner (48,49). Silymarin has also been shown to have an effect on the plasma membrane (increase of membrane fluidity), immunomodulation (on histamine release by mast cells) and alcohol-induced liver fibrogenesis (50-53). Moreover, pharmacokinetic data have characterized silymarin as being highly hepatotropic, with an elevated biliary secretion and high levels in enterohepatic circulation (54,55).

We also measured insulin need, fasting and mean daily blood glucose levels, glucosuria, basal and glucagon-stimulated C peptide levels. In addition, we assessed the incidence of slight and severe hypoglycemic episodes in both groups of patients during the study.

Patients and Methods

This was a randomized, open, controlled, long-term (12 months) study. Approval to conduct the study was obtained from the local Ethical Committee and all pa-

tients gave their written informed consent to participate.

A total of 60 insulin-treated diabetic patients with cirrhosis, of both sexes was recruited from the 7050 diabetic outpatients registered at our Anti-Diabetes Center.

The inclusion criteria were:

- Age 45 to 70 years
- NIDDM with alcoholic liver cirrhosis
- Body Mass Index (BMI) < 29 kg/m²
- Ascertained diabetes for a period of at least 5 years and treated with insulin only
- Undergoing stable insulin therapy for a period of at least 2 years
- Presenting raised endogenous insulin secretion
- Fasting insulin levels and basal and stimulated C-peptide levels above normal range (above 15 mU/ml for insulin; above 1 ng/ml for basal C-peptide levels and 3 ng/ml stimulated C-peptide levels)
- Negative for markers of hepatitis A, B and C
- Not addicted to alcohol for a period of at least 2 years prior to the start of the study
- No bleeding from variceal esophagus
- Liver biopsy, performed no more than 4 years prior to enrolment, demonstrating liver cirrhosis

The baseline characteristics of the two groups of patients are listed in Table 1. Both groups were homogeneous for all the parameters measured.

On inclusion into the study, the patients were randomly assigned to one of two groups: the first group (30 patients) received 600 mg silymarin (Legalon[®] from IBI Lorenzini, Milan, Italy) per day for 12 months. Patients were asked to take the drug in three separate doses (one 200 mg dose three times a day, about 2 h after each meal), by dissolving the drug in about 100 ml water. The control group (30 patients), were not treated with silymarin.

The following parameters were evaluated during the study:

- 1) Every 30 days: fasting and mean daily blood glucose levels, glucosuria, mean daily insulin requirement.
- 2) Every 60 days: HbA_{1c} levels.
- 3) Every 90 days: fasting insulin, basal and stimulated C-peptide, malondialdehyde, SCOT, SGPT, alkaline phosphatase, γ GT, bilirubin, triglycerides, total and HDL cholesterol.
- 4) Every 180 days: creatinine, microalbuminuria and hemochrome.

Blood samples were drawn after an overnight fast of no longer than 12 h for a correct determination of lipoproteins. Fasting glucose levels, mean daily blood glucose levels and glucosuria were determined by the

TABLE I

Baseline characteristics of the two groups of patients. Mean values \pm S.D.

	Untreated group	Treated group	<i>p</i> -value
Age (years)	62 \pm 3	63 \pm 4	n.s.
BMI (kg/m ²)	24.9 \pm 0.7	25.1 \pm 1.1	n.s.
Insulin need (U/day)	56 \pm 3	55 \pm 5	n.s.
Fasting insulin (mU/ml)	26.4 \pm 2.1	25.2 \pm 3.8	n.s.
Glycosylated hemoglobin (%)	8.0 \pm 0.3	7.9 \pm 0.2	n.s.
Basal C peptide (ng/ml)	1.6 \pm 0.2	1.56 \pm 0.26	n.s.
Stimulated C peptide (ng/ml)	4.2 \pm 0.9	4.12 \pm 1.1	n.s.
Fasting blood glucose (mg/dl)	193 \pm 17	190 \pm 14	n.s.
Mean daily blood glucose (mg/dl)	205 \pm 13	202 \pm 19	n.s.
Total daily glucosuria (g/day)	37 \pm 8	37 \pm 12	n.s.
Malondialdehyde (μ mol/ml)	2.2 \pm 0.2	2.2 \pm 0.25	n.s.
SGOT (U/l)	35 \pm 5	34 \pm 7	n.s.
SGPT (U/l)	44.0 \pm 3	42.5 \pm 3	n.s.
γ GT (U/l)	20 \pm 2	19 \pm 2	n.s.
Alkaline phosphatase (U/l)	55 \pm 4	52 \pm 2	n.s.
Bilirubin (mg/dl)	1.1 \pm 0.2	1.0 \pm 0.3	n.s.
Creatinine (mg/dl)	1.0 \pm 0.15	0.9 \pm 0.1	n.s.
Microalbuminuria (mg/day)	16 \pm 1	19 \pm 4	n.s.
Total cholesterol (mg/dl)	162 \pm 9	155 \pm 8	n.s.
Triglycerides (mg/dl)	139 \pm 22	139 \pm 36	n.s.
HDL cholesterol (mg/dl)	34 \pm 5	35 \pm 9	n.s.
Systolic BP (mmHg)	144 \pm 6	145 \pm 4	n.s.
Diastolic BP (mmHg)	83 \pm 6	80 \pm 5	n.s.

glucose-oxidase method using a Beckman Glucose 2 Analyzer immediately after blood sampling in our Anti-diabetes Center. All the other blood samples were immediately analyzed by the Central Analysis Laboratory using standard methods. To determine the mean daily blood glucose levels, further blood samples were taken 2 h after breakfast, immediately before and 2 h after dinner. Stimulated C-peptide levels were measured 6 min after the i.v. injection of 1 mg glucagon (Glucagon Novo). HbA1c was determined by HPLC (High Pressure Liquid Chromatography) using an automatic analyzer (Menarini, Florence, Italy).

Malondialdehyde levels were also determined in a homogeneous group of healthy volunteers. These subjects were comparable with the study population for age, sex and BMI. In addition, they were negative for hepatitis A, B, and C markers, and were not previously alcohol addicted.

Statistical analysis

The statistical analysis of the recorded data (Software Cadplus3, a db3plus clipper compiled data base by the DIAINF Study Group, Florence, Italy), was performed using a biomedical statistical analysis program running on an IBM compatible 486 PC (56). The analysis of the variance test and Student's two-tailed *t*-

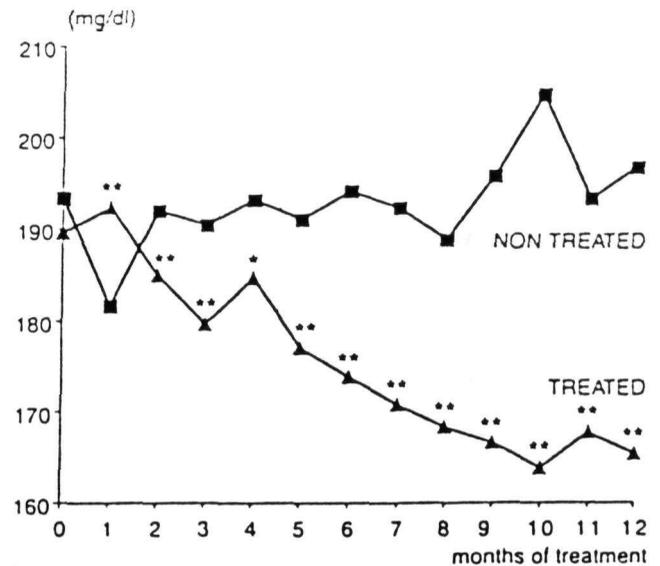


Fig. 1. Mean fasting blood glucose in the two groups of patients. Treated group (Δ — Δ) vs non-treated group (\blacksquare — \blacksquare): **p*<0.05; ***p*<0.01.

test were used in these analyses with the significance limit being fixed at *p*=0.05.

Results

After a temporary increase at T₁ fasting blood glucose levels in the silymarin-treated group showed a progressive and statistically significant reduction from 190 \pm 14 mg/dl at baseline to 174 \pm 7 mg/dl at T₆ (*p*<0.01). This parameter further improved during the study, giving a final value of 165 \pm 1 mg/dl at T₁₂ (*p*<0.01 compared to T₀). In contrast, with the exception of an unexpected glycaemic peak at T₁₀, stable fasting blood glucose levels were observed throughout the study in the untreated patients. There were significant differences between groups in favor of the treated group (Fig. 1).

A much more evident reduction was observed in the treated group for mean daily blood glucose values, which decreased from 202 \pm 19 mg/dl at T₀ to 175 \pm 14 mg/dl at T₆ (*p*<0.01 compared to baseline) and to 172 \pm 14 mg/dl at T₁₂ (*p*<0.01 compared to baseline). There were no significant changes in mean daily blood glucose levels in the untreated patients. Significant differences were observed between groups in favor of the treated group (Fig. 2).

The improvement in mean daily blood glucose levels in the silymarin-treated group did not increase the number of slight or severe hypoglycemic episodes (2.16 episodes/patient/year), which were similar (2.2 episodes/patient/year; n.s.) during an equivalent period prior to the start of the study. Only a slight and non-

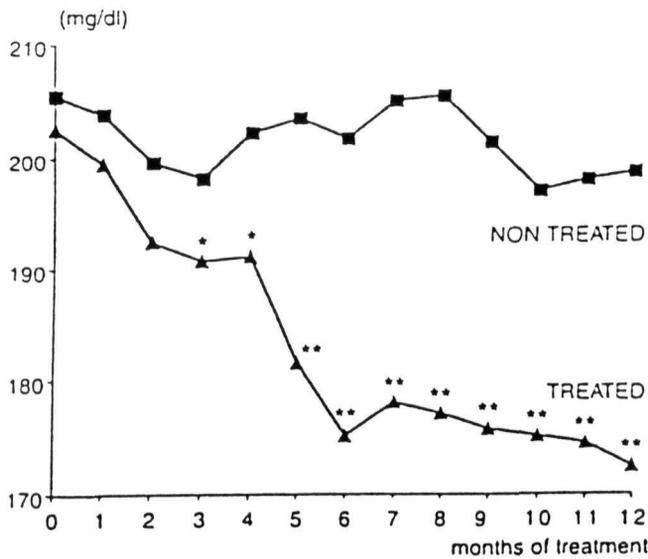


Fig. 2. Mean daily blood glucose in the two groups of patients. Treated group (Δ — Δ) vs non-treated group (\blacksquare — \blacksquare): * $p < 0.05$; ** $p < 0.01$.

significant variation was recorded in the untreated group (2.3 episodes/patient/year).

Total daily glucosuria decreased significantly from 37 ± 12 g/day at T_0 to 26 ± 6 g/day at T_6 ($p < 0.01$ compared to baseline) and to 22 ± 7 g/day at T_{12} ($p < 0.01$ compared to baseline). In contrast, a significant increase ($p < 0.01$) in this parameter was observed in the untreated group, indicating a worsening glucose homeostasis. There were significant differences between groups in favor of the treated group (Fig. 3).

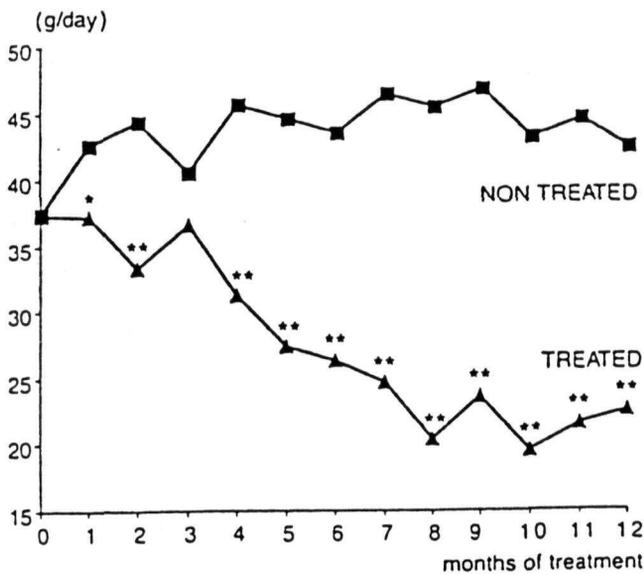


Fig. 3. Mean daily glucosuria in the two groups of patients. Treated group (Δ — Δ) vs non-treated group (\blacksquare — \blacksquare): * $p < 0.05$; ** $p < 0.01$.

TABLE 2

Glycosylated hemoglobin in the treated group

Time	Mean value \pm S.D. (%)	Significance vs baseline values
T_0	7.9 ± 0.3	
T_2	7.8 ± 0.3	$p < 0.01$
T_4	7.7 ± 0.3	$p < 0.01$
T_6	7.5 ± 0.2	$P < 0.01$
T_8	7.3 ± 0.2	$p < 0.01$
T_{10}	7.2 ± 0.2	$p < 0.01$
T_{12}	7.2 ± 0.2	$p < 0.01$

These three parameters (fasting glucose levels, mean daily blood glucose levels and glucosuria) showed a slow decrease in the silymarin-treated group monthly, particularly during the second period of the study.

Glycosylated hemoglobin levels decreased progressively throughout the study in the treated group, and the differences were significant, compared to baseline ($p < 0.01$), at all evaluation time points (Table 2 and Fig. 4). On the other hand, HbA1c levels did not change in the untreated group.

The mean daily insulin requirement in the silymarin-treated group decreased significantly and constantly throughout the study, from 55 ± 5 IU/day at T_0 to 45 ± 3 IU/day at T_6 ($p < 0.01$), and to 42 ± 2 IU/day at T_{12} ($p < 0.01$ compared to baseline). There were no changes in mean daily insulin requirement in the untreated group, the differences between groups being statisti-

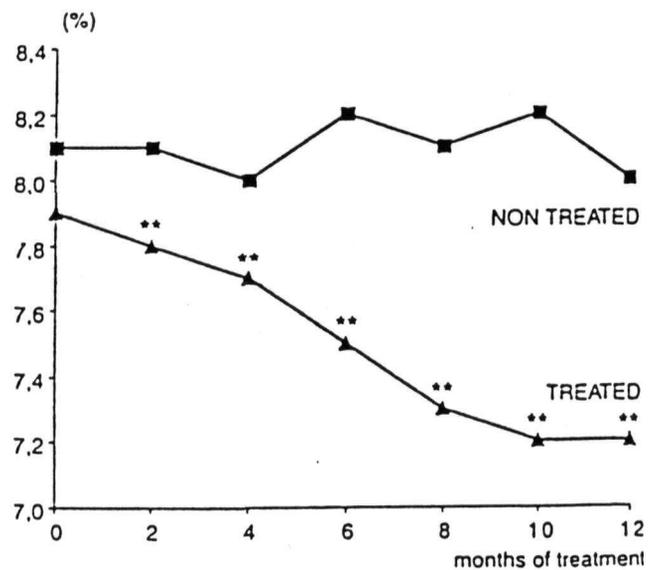


Fig. 4. Glycosylated hemoglobin in the two groups of patients. Treated group (Δ — Δ) vs non-treated group (\blacksquare — \blacksquare): ** $p < 0.01$.

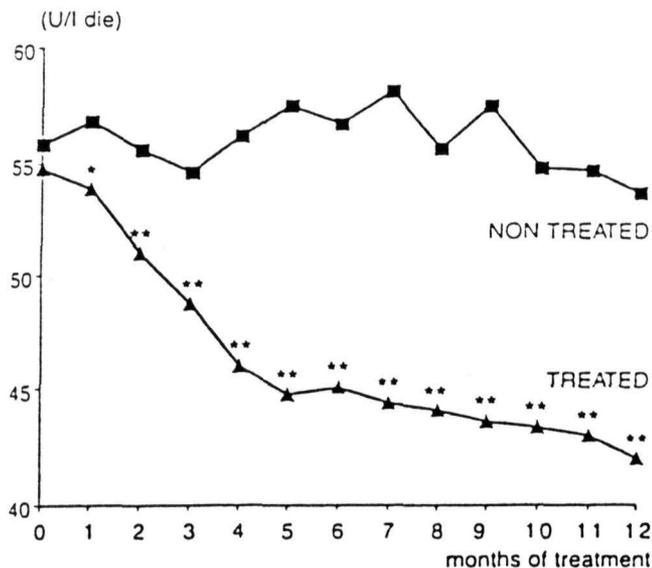


Fig. 5. Mean insulin need per day in the two groups of patients. Treated group: (△—△) vs non-treated group (■—■): * $p<0.05$; ** $p<0.01$.

cally significant ($p<0.01$) in favor of the silymarin-treated group at all times during the study (Fig. 5).

Moreover a statistically significant decrease in fasting insulin values was recorded for silymarin-treated patients, as shown in Table 3. In contrast, there was an increase in fasting insulin values in the untreated group. The difference between the two groups was again statistically significant ($p<0.01$) in favor of the silymarin-treated group (Fig. 6).

Mean blood levels of malondialdehyde decreased significantly in the silymarin-treated group during the study (Table 4). The final value at T_{12} (1.55 ± 0.11 $\mu\text{mol/ml}$) did not differ significantly from the upper value of normal range (1.5 $\mu\text{mol/ml}$) in our Central Analysis Laboratory. In contrast, the untreated patients showed a slight but non-significant increase in this parameter. The difference between the two groups was significant ($p<0.01$) in favor of the silymarin-treated group (Fig. 7).

Mean values for basal C-peptide demonstrated a

TABLE 3

Fasting insulin values in the treated group

Time	Mean value \pm S.D. (mU/ml)	Significance vs baseline values
T_0	25.2 ± 3.8	
T_3	18.4 ± 1.8	$p<0.01$
T_6	16.4 ± 1.9	$p<0.01$
T_9	15.2 ± 1.7	$p<0.01$
T_{12}	15.3 ± 2.1	$p<0.01$

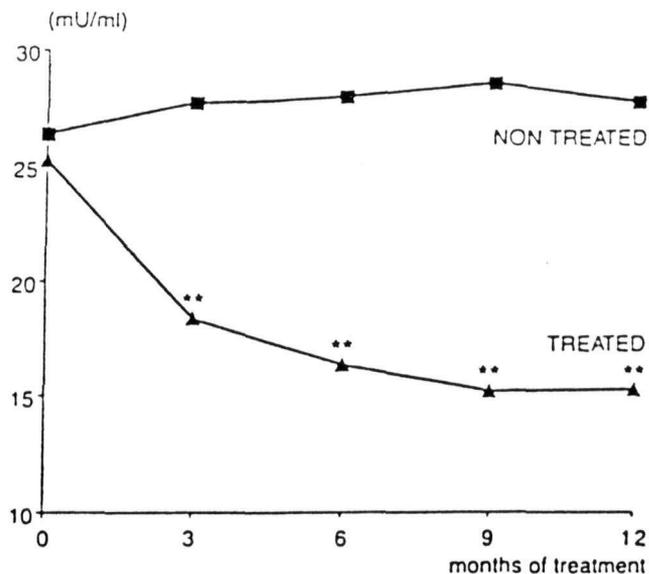


Fig. 6. Fasting insulinemia in the two groups of patients. Treated group (△—△) vs non-treated group (■—■): ** $p<0.01$.

slow but regular decrease in the silymarin-treated group, from 1.56 ± 0.26 ng/ml at T_0 to 1.33 ± 0.17 ng/ml at T_6 ($p<0.01$) and to 1.15 ± 0.14 ng/ml at T_{12} ($p<0.01$). The mean value of stimulated C-peptide showed a similar statistically significant decrease at each of the time points (Table 5).

It is important to stress that the untreated group showed a significant increase in mean basal and stimulated C-peptide values. Mean basal C-peptide values

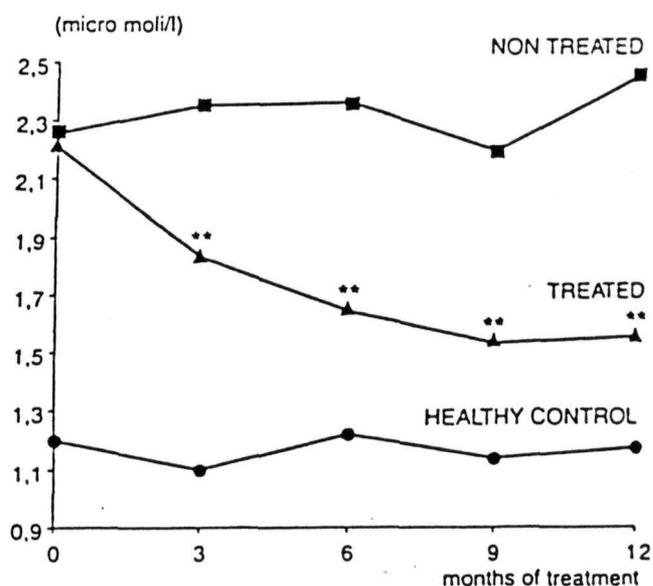


Fig. 7. Mean malondialdehyde blood levels in the two groups of patients and in healthy controls. Treated group (△—△) vs non-treated group (■—■): ** $p<0.01$. Healthy control group: (●—●).

TABLE 4

Mean blood levels of malondialdehyde in the treated group

Time	Mean value \pm S.D. ($\mu\text{mol/l}$)	Significance versus baseline values
T ₀	2.2 \pm 0.3	
T ₃	1.8 \pm 0.1	<i>p</i> < 0.01
T ₆	1.6 \pm 0.1	<i>p</i> < 0.01
T ₉	1.53 \pm 0.08	<i>p</i> < 0.01
T ₁₂	1.55 \pm 0.11	<i>p</i> < 0.01

TABLE 5

Mean values of stimulated C-peptide in the treated group

Time	Mean value \pm S.D. (ng/ml)	Significance vs baseline values
T ₀	4.12 \pm 1.08	
T ₃	3.81 \pm 0.75	<i>p</i> < 0.05
T ₆	3.51 \pm 0.68	<i>p</i> < 0.01
T ₁₂	3.41 \pm 0.53	<i>p</i> < 0.01

increased from 1.6 \pm 0.2 ng/ml at T₀ to 1.74 \pm 0.28 ng/ml at T₆ (*p* < 0.05) and to 1.75 \pm 0.24 ng/ml at T₁₂ (*p* < 0.05). The mean values of stimulated C-peptide increased from 4.2 \pm 0.84 ng/ml at T₀ to 4.7 \pm 0.75 ng/ml at T₆ (*p* < 0.01). Although the mean values decreased to 4.53 \pm 0.5 ng/ml at T₁₂, the difference, compared to baseline values, was still statistically significant (*p* < 0.01). The difference between the two groups was statistically significant (*p* < 0.01) in favor of the silymarin-treated group at each of the time points (Fig. 8 and 9).

No statistically significant variations were recorded for γ GT, alkaline phosphatase, creatinine, bilirubin, microalbuminuria and hemochrome in the two groups of patients. There was a slow and continuous decrease in SGOT and SGPT values in the silymarin-treated group. SGOT decreased from 34 \pm 6.7 U/l at T₀ to 32 \pm 6.1 U/l at T₆ (*p* < 0.05) and 30 \pm 3.5 U/l at T₁₂ (*p* < 0.01); SGPT decreased from 42.5 \pm 2.7 U/l at T₀ to 39.3 \pm 3.1 U/l at T₆ (*p* < 0.01) and 32.2 \pm 3.6 U/l at T₁₂ (*p* < 0.01). Total cholesterol values showed a slight, but non-significant increase from 155 \pm 8 mg/dl at T₀ to 162 \pm 9 mg/dl at T₆ in the silymarin-treated group. However, this value increased to 167 \pm 9 mg/dl at T₁₂, with a highly significant difference compared to baseline values (*p* < 0.01). The untreated patients showed a slight, but non-significant decrease in total cholesterol values (162 \pm 9 at T₀ to 150 \pm 5 mg/dl at T₆). The HDL cholesterol levels increased significantly from 34.7 \pm 9.4 mg/dl at T₀ to 38.3 \pm 6.7 mg/dl at T₁₂ (*p* < 0.01) in silymarin-treated patients, with a significant difference in

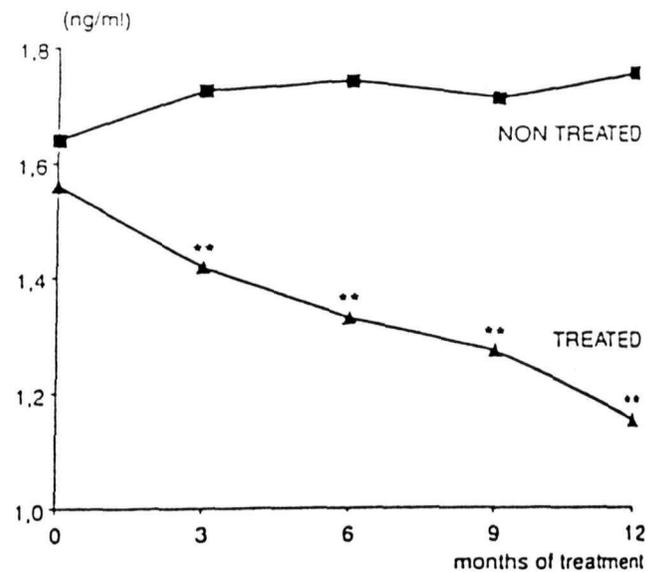


Fig. 8. Mean basal C-peptide levels in the two groups of patients. Treated group (Δ — Δ) vs non-treated group (\blacksquare — \blacksquare). ** *p* < 0.01.

favor of the silymarin-treated group. Triglycerides increased significantly from 139 \pm 36 mg/dl at T₀ to 154 \pm 26 mg/dl at T₁₂ (*p* < 0.01) in the treated group, while in controls there was a significant decrease from 139 \pm 22 mg/dl at T₀ to 128 \pm 19 mg/dl at T₁₂ (*p* < 0.01). No clinical variations in liver volume and abdomen size were observed during the trial. No side effects to treatment were reported during the study and no medical or surgical interventions were necessary in either group. Finally we recorded a slight but non-significant variation in BMI (a 2.5% decrease was found at the end of the study compared with baseline values) in the silymarin-treated group of patients. This group of patients also experienced a slight variation in systolic and diastolic blood pressures (a 1.5% decrease was found at the end of the study compared with baseline values). No patient dropped out of the study. Compliance in the silymarin-treated group was about 95%. After the 12-month study period had ended, all the silymarin-treated patients chose to continue the treatment.

Discussion

The aim of our study was to evaluate the efficacy and tolerability of long-term (12 months) anti-oxidant treatment with silymarin in comparison with no treatment in patients affected by alcoholic liver cirrhosis and NIDDM. These patients were receiving rather high doses of insulin (0.7 \pm 0.05 IU/kg body weight per day), although they had high endogenous insulin secretion. This particular cohort of patients presented several factors:

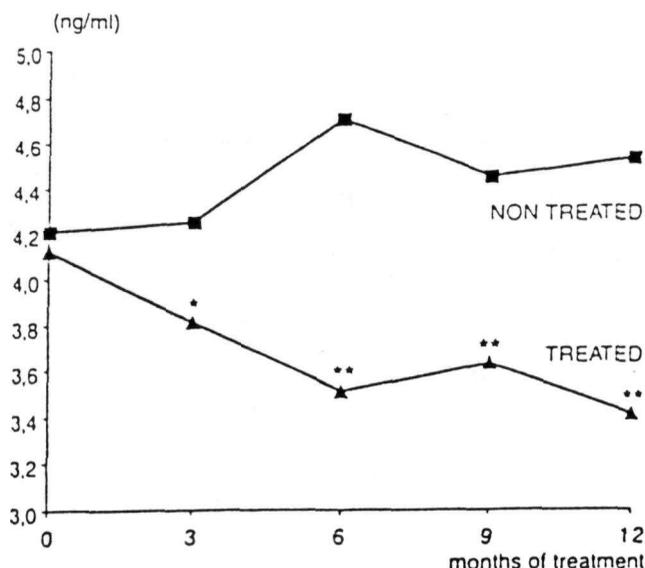


Fig. 9. Mean stimulated C-peptide levels in the two groups of patients. Treated group (Δ — Δ) vs non-treated group (\blacksquare — \blacksquare): * $p < 0.05$; ** $p < 0.01$.

- 1) Hepatic cell membrane damage due to excessive alcohol consumption;
- 2) Insulin resistance;
- 3) Overproduction of insulin by the pancreas and exogenous insulin administration, in order to overcome the insulin resistance in the target tissues.

Insulin resistance in hepatopathic patients seems to be of a particular type involving receptor and post-receptor mechanisms (57-59). We suggest that this disturbance depends on a malfunction of liver cells both at the membrane level, with the insulin receptor involvement, and inside the liver cell with the damage to energy storage (glycogen and triglycerides) due to prior alcohol addition. An active and effective therapy is therefore necessary to restore the normal membrane and intracellular activity of the hepatocyte.

On the basis of the current literature, we postulated that lipoperoxidation could represent a serious problem at the hepatocyte level in this group of diabetic patients, and that the restoration of normal MDA levels using an antioxidant agent would be an important and interesting therapeutic goal. We therefore carried out a clinical study in 60 well-matched patients, who were randomly divided into two comparable groups; the only difference between the two groups was that one was treated with silymarin plus the standard therapy, while the other group received standard therapy alone.

Results showed that there were statistically significant differences between the two groups of patients for almost all the parameters assessed. The most interest-

ing finding was that the levels of MDA in the silymarin-treated group decreased continuously, until the end of the study when they reached a level which was close to those found in a healthy population (Fig. 7). This demonstrated that silymarin was effective in neutralizing excess superoxides and hence limiting cellular damage. The reduction in lipoperoxidative damage resulted in a significant decrease in mean fasting and daily blood glucose levels and total daily glucosuria levels. However, the most important result from the clinical point of view was the reduction in the total daily exogenous insulin requirements in the silymarin-treated group due to improvements in insulin utilization by the target tissues. It is also important to note that the slight decrease in systolic and diastolic blood pressures and in BMI observed in this group may be related to the drop in exogenous insulin administration.

The significant decrease in fasting insulin levels observed in the silymarin-treated group, in contrast with the increase recorded in the untreated patients, indicates that the activity of endogenous and exogenous insulin had improved. This is confirmed by the significant reduction in the basal and stimulated C-peptide levels observed in the silymarin-treated group at the end of the study and implies that the pancreas was less stimulated by insulin overproduction because of increased sensitivity of the target tissues to insulin action.

It is interesting to note that SGOT and SGPT values decreased significantly ($p < 0.01$) only in the silymarin-treated patients, which confirms that silymarin is able to restore normal liver membrane permeability by reducing enzyme dispersion in the extracellular medium. There was a significant increase in total cholesterol levels in silymarin-treated patients, compared to the slight decrease observed in the untreated group. This can be explained by an improvement in liver cell metabolism following anti-oxidant therapy, if we consider that no other variations were recorded between the two groups of patients regarding diet, eating behavior and physical activity, and that no therapy other than silymarin was administered during the 12-month study. Hence the results of this study point to the efficacy of silymarin in the treatment of cirrhotic patients with NIDDM.

In conclusion, long-term treatment with silymarin was shown to be effective in reducing insulin resistance and in maintaining a better metabolic compensation of glucose metabolism in diabetic patients with cirrhosis.

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