



ORIGINAL ARTICLE

Silymarin improves glycemic control through reduction of insulin resistance in newly diagnosed patients of type 2 diabetes mellitus.

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ABSTRACT... Objective: To study, analyse and compare the effects of Silymarin on glycemic control and insulin resistance in newly diagnosed type 2 diabetes mellitus (T2DM) subjects. **Study Design:** Observational study. **Setting:** Suleman Roshan Medical College Hospital. **Period:** March 2019 to February 2020. **Material & Methods:** A sample of 200 newly diagnosed cases of T2DM were recruited according to inclusion criteria selected by non-probability convenient sampling. Subjects were divided into 2 groups; OHA- oral hypoglycemia agent and OHA+ Silymarin (200 mg). Baseline fasting (FBG) and random blood glucose (RBG), glycated HbA1 (A1C), fasting insulin (FI) and insulin resistance (HOMA-IR) were detected. Silymarin therapy was continued for 3 months. Study variables were analysed after 3 months. Data was analyzed on SPSS (ver.19) at 95% confidence interval ($P \leq 0.05$) considered statistically significant. **Results:** Age of diabetics taking oral hypoglycemic agents (OHA) and diabetic taking OHA+ Silymarin supplementation was noted as 50.3 ± 13.3 and 49.9 ± 14.5 years ($P=0.91$). 3 months Silymarin supplementation improves the fasting blood glucose, random blood glucose, glycated hemoglobin A1 (A1C), fasting insulin and insulin resistance (HOMA-IR) ($P=0.0001$). **Conclusion:** Silymarin improves blood glucose levels in type 2 diabetics that is mediated through reduction of insulin resistance.

Key words: Glycemic Control, Insulin Resistance, Silymarin, Type 2 Diabetics.

INTRODUCTION

The incidence and prevalence of type 2 diabetes mellitus (T2DM) is seriously increasing throughout the World. DM is a glucose metabolic disorder of chronic hyperglycemia caused by insulin deficiency. This insulin deficiency may be absolute or relative. Absolute insulin deficiency is observed in the type 1 DM while relative deficiency is seen T2DM. Relative insulin deficiency is caused by receptor insensitivity or post receptor signalling defects. T2DM is characterized by chronic hyperglycemia that damages various tissues and organs especially in insulin independent cells such as the retina, nerve fibers, kidneys, etc. Hence, the long term complications of DM affect the eyes, nerves, blood vessels, heart and kidneys frequently.^{1,2} World prevalence of DM was 382 million in 2013 as reported by the International Diabetes Federation

(IDF), this accounts 8.3% of total World's population. Prevalence of DM will increase to 592 millions by the 2035 that means 3 new cases each 10 seconds.^{1,2} The hallmark of T2DM is a progressive decline of β -cell function of pancreas and reduced insulin sensitivity of target organs. This eventually results in chronic hyperglycemia, a hallmark feature of T2DM. Insulin resistance is aggravated by the oxidative stress, inflammation and inflammatory mediators.^{3,4} Cardiovascular system is the most often affected system in DM due to severe dyslipidemia. Hyperlipidemia and dyslipidemia result from metabolic defects caused by insulin deficiency. Lipid peroxidation increases the risk of cardiovascular diseases. Current care of DM includes the pharmacological and non-pharmacological interventions. Caloric restrictions and physical exercise are the life style modifications helpful for glycemic control.

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Pharmacological interventions include the; oral hypoglycemic agents and the insulin therapy. Despite much efficacy of current drug therapy of DM, the adverse drug reactions (ADRs) is problematic, hence natural remedies have been analyzed of their anti – diabetic efficacy.^{3,4} Natural remedies have been reported of their beneficial antioxidants effects that neutralize the oxidative stress of chronic hyperglycemia. Silymarin^{5,6} is one of the vastly researched herbal agents that are currently reported for various diseases. Silymarin is derived from milk thistle plant (*Silybum marianum* (L.)). It is rich in polyphenolic flavonolignan that show potential of anti-oxidant properties. Silymarin includes the 4 flavonolignan isomers and one flavonoid. Flavonolignans include the; iso-silybin, silybin, silychristin and silydianin and flavonoid include the taxifolin.^{5,6} Silymarin is known of its hypolipidemic, hypoglycemic, anti-atherosclerosis, anti-osteoporosis, renoprotective and anti-cancer activities. Silymarin has been used in sepsis, burn therapy and Alzheimer disease.^{5,6}

The present study was planned to analyse and compare the blood glucose regulating efficacy and anti-insulin resistance properties of Silymarin in type 2 diabetic subjects presenting at our tertiary care hospital.

MATERIAL & METHODS

The present observational study was conducted at the Department of Medicine and Pharmacology, Suleman Roshan Medical College Hospital from March 2019 to February 2020. Study protocol was presented and was approved by the research ethics committee. Participants were interviewed of the purpose of study and were educated to adhere to the drug therapy. Participants were handled in conformation to the Declaration of Helsinki (1975).

A sample of 200 newly diagnosed cases of T2DM were recruited according to inclusion criteria selected by non-probability convenient sampling. Subjects were divided into 2 groups; oral hypoglycemia agent (OHA) (glimepride+metformin) and OHA (glimepride+metformin) + Silymarin (200 mg

bid). DM was diagnosed according to the criteria of ADA (American Diabetes Association). Newly diagnosed DM, age 40 – 60 years with suboptimal glycemic control were included. Diet and physical exercise were continued. Exclusion criteria were; chronic liver disease, ischemic heart disease, renal insufficiency (SCr > 2 mg/dl), severe heart dysfunction (NYHA class III or more), cerebral stroke, psychiatric disease, smoking, steroid use and severe infections. Patients taking multi-vitamin, multi-mineral pills were also excluded. Pregnancy and breastfeeding female were strictly excluded. Verbal consent was taken from the participants. The subjects were informed the inclusion to study protocol is on voluntary basis, it will cause no harm or monetary expenses and they can leave at any time if feeling worried or without telling the reason and this will not affect their diabetic therapy. At baseline, all patients underwent thorough history taking and clinical examination. Blood samples were collected to measure the following parameters at baseline and at end of treatment and used to evaluate the treatment outcomes, baseline fasting (FBG) and random blood glucose (RBG), glycated HbA1 (A1C), fasting insulin (FI) and insulin resistance (HOMA-IR) were detected. Silymarin therapy was continued for 3 months. Fasting (FBG) and random blood glucose (RBG), glycated HbA1 (A1C), fasting insulin (FI) and insulin resistance (HOMA-IR) were repeated after 3rd month drug therapy.

Blood glucose was estimated by hexokinase method, A1C by TINIA – colorimetric method, and fasting insulin (FI) by ELISA assay kit. Homeostasis Model Assessment – Insulin Resistance (HOMA-IR) was calculated from FBG and FI by formula as; $HOMA-IR = \frac{\text{Fasting Blood Glucose (mg/dL)} \times \text{Fasting Insulin } (\mu\text{U/m})}{405}$.⁷ Baseline and 3rd month laboratory findings were noted in a pre – structured proforma. Data was entered in a Microsoft Excel Sheet (ver. 13.0). Data was kept in lockers to maintain the confidentiality of personal patient records. Data was copied to the SPSS (version 19.0). Data was analysed by Student t – test (Paired sample t – test). 95% confidence interval (CI) was taken statistically significant ($P \leq 0.05$).

RESULTS

Age of Diabetics taking oral hypoglycemic agents (OHA) and diabetic taking OHA+ Silymarin supplementation (SS) was noted as 50.3 ± 13.3 49.9 ± 14.5 years ($P=0.91$). Baseline fasting blood glucose (FBG), random blood glucose (RBG), glycated hemoglobin A1 (A1C), fasting insulin (FI) and insulin resistance (HOMA-IR) were noted at baseline (Table-I to V). After 3 months Silymarin supplementation (SS) the FBG, RBG, A1C, FI and HOMA-IR were rechecked and found improved as shown in Table-I to V. Differences were found statistically significant ($P=0.0001$).

DISCUSSION

The present observational study was conducted at tertiary hospital of Suleman Roshan Medical College Hospital Tando Adam. Age of Diabetics taking oral hypoglycemic agents (OHA) and diabetic taking OHA+ Silymarin supplementation (SS) was noted as 50.3 ± 13.3 49.9 ± 14.5 years ($P=0.91$). The findings are in agreement with previous studies.^{8,9} We found 3 months Silymarin supplementation (SS) reduced the FBG, RBG, A1C, FI and HOMA-IR ($P=0.0001$). The findings are concordant with previous studies.^{9,10}

	Mean	Std. Deviation	P-Value
Baseline - Diabetic (OHA)	319.70	23.43	0.91
Baseline - Diabetic (OHA+Silymarin)	315.40	30.72	
3 month - Diabetic (OHA)	243.25	41.28	0.0001
3 months Diabetic (OHA+Silymarin)	188.95	55.36	

Table-I. Fasting blood glucose (mg/dl) in study groups.

	Mean	Std. Deviation	P-Value
Baseline - Diabetic (OHA)	319.70	23.43	0.91
Baseline - Diabetic (OHA+Silymarin)	315.40	30.72	
3 month - Diabetic (OHA)	243.25	41.28	0.0001
3 months Diabetic (OHA+Silymarin)	188.95	55.36	

Table-II. Random blood glucose (mg/dl) in study groups.

	Mean	Std. Deviation	P-Value
Baseline - Diabetic (OHA)	8.66	0.72	0.91
Baseline - Diabetic (OHA+Silymarin)	8.50	0.67	
3 month - Diabetic (OHA)	7.09	0.78	0.0001
3 months Diabetic (OHA+Silymarin)	6.49	0.50	

Table-III. A1C (%) in study groups.

	Mean	Std. Deviation	P-Value
Baseline - Diabetic (OHA)	16.28	1.07	0.91
Baseline - Diabetic (OHA+Silymarin)	16.06	1.20	
3 month - Diabetic (OHA)	14.32	1.14	0.0001
3 months Diabetic (OHA+Silymarin)	13.71	0.86	

Table-IV. Fasting insulin (μ U/L) in study groups.

	Mean	Std. Deviation	P-Value
Baseline - Diabetic (OHA)	4.58	1.05	0.91
Baseline - Diabetic (OHA+Silymarin)	4.06	0.96	
3 month - Diabetic (OHA)	1.82	0.71	0.0001
3 months Diabetic (OHA+Silymarin)	1.35	0.21	

Table-V. Insulin resistance (HOMA-IR) in study groups.

Silymarin proved an excellent glucose regulator by decreasing the insulin resistance. Several mechanisms of anti-diabetic activity of Silymarin have been proposed hence it has attracted the researchers for the diabetic therapy and its complications.⁸ Previous studies¹⁰⁻¹² have documented the therapeutic potential of Silymarin and its derivatives in both in-vivo and in-vitro studies. Silymarin shows anti-oxidant, anti-inflammatory, anti-gluconeogenesis and membrane stabilizing potential. Insulin gene expression and β -cell proliferation is documented. Silymarin exerts the peroxisome proliferator-activated receptor- γ (PPAR γ) agonist like activity. Above findings¹⁰⁻¹² make silymarin ideal of its anti-diabetic potential. Positive effect on glycemic control and insulin resistance reducing potential of silymarin is documented in our present study and the findings are in line with above studies.^{13,14}

In present study, the silymarin significantly decreased FBG, RBG, A1C, FI and HOMA-IR compared to control group. The findings of present study are of clinical significance as the burden of DM is increasing in the country and silymarin is herbal agent with less side effects that may be exploited of its anti-diabetic activity. Anti-diabetic potential of Silymarin is supported by another previous study¹⁵ that supplemented 200 mg dose thrice daily for T2DM subjects for 120 days along with glibenclamide and reported optimal glycemic control. A1C was found low compared to baseline by that study, and finding is highly concordant to the present study. Another previous study¹⁶ used 600 mg silymarin daily in diabetics with alcoholic cirrhosis, and found reduction in FBG, A1C and Fasting Insulin (FI). It has been reported that the polyphenolic compounds of silymarin also modify the glycemic and lipid profile of type 2 diabetics.^{15,17} Anti diabetic activity of silymarin has been reported by another previous study¹⁸ that used 140 mg silymarin three times a day for 45 days in type 2 diabetics and found positive effects on glycemic and lipid profile. Mitigation of insulin resistance is consistent with other previous studies.¹⁸⁻²⁰ Reduction of insulin resistance (HOMA-IR) and fasting insulin (FI) are findings of great clinical significance. The findings of present study are supported by above reviewed literature

however further studies are warranted with large sample size in indigenous population to reach to a stronger conclusion. Silymarin shows positive effect on the glycemic control and insulin resistance that needs further elaboration in large prospective studies in future.

CONCLUSION

Silymarin has potential of improving blood glucose levels in type 2 diabetics that is mediated through reduction of insulin resistance. As the insulin resistance is major problem in type 2 diabetics hence silymarin may be prescribed as a natural remedy to overcome this problem.






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AUTHORSHIP AND CONTRIBUTION DECLARATION

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2	Shomail Saeed Siddiqui	Concept, Drug arrangement, Performa.	
3	Muhammad Atif Ata	Study setting, arrangement pt data.	
4	Kashif Rasheed Shaikh	Pt counseling and blood sample Procedure.	
5	Umair Ali Soomro	Hemotological examination of blood sample.	
6	Shumaila Shaikh	Manuscript writing, Data analysis, Proof reading.	