



Potential Effect of Silymarin Supplementation on Metabolic Complications and Graft Function in Kidney Transplant Recipients—A Pilot, Monocentric Study

Matej Vnučák^{1,2} · Karol Graňák^{1,2} · Patrícia Kleinová^{1,2} · Tímea Blichová^{1,2} · Andrej Kollár^{1,2} · Ivana Dedinská^{1,2}

Received: 9 December 2024 / Revised: 25 February 2025 / Accepted: 8 March 2025 / Published online: 26 March 2025
 © The Author(s) 2025

Abstract

Introduction Silymarin is an extract of the plant *Silybum marianum*, which is used as a complementary treatment for liver diseases. However, it significantly interferes with lipid metabolism, and also affects glucose metabolism—in animal models, its administration led to a significant rise in plasma glutathione, while in in vivo models it decreased podocyte damage with nephroprotection in diabetic nephropathy.

Material and methodology We performed a pilot, monocentric, analysis of patients transplanted at the Transplantation-Nephrology Department of UNM in patients with insulin resistance defined by HOMA-IR index > 2 with subsequent supplementation of 450 mg of silymarin per day for 180 days with monitoring of metabolic parameters, graft function and level immunosuppressants.

Results Our study was a prospective study including 28 patients after primary kidney transplantation, 71.4% men ($n=21$). The average age of patients at the time of initiation of silymarin supplementation was 52.6 ± 10.2 years, 42.8% of patients ($n=12$) had a glucose metabolism disorder. We did not observe statistically significant changes in the monitored parameters during the silymarin supplementation in the time horizon of three and six months. We did not observe statistically significant differences in the observed parameters in the group of patients without a disorder of carbohydrate metabolism. In patients with impaired glucose tolerance or non-insulin-dependent diabetes mellitus, we recorded a statistically significant decrease in LDL-cholesterol during the observed period ($P=0.0170$).

Conclusion In our study, we did not confirm a significant effect of silymarin supplementation on insulin resistance and carbohydrate metabolism, graft function, but the effect on lipid metabolism and reduction of plasma LDL-cholesterol concentrations in patients with diabetes mellitus or prediabetes may be promising.

Keywords Silymarin · Kidney transplantation · Insulin resistance · Diabetes mellitus · Dyslipidemia

Abbreviations

ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BMI	Body mass index
CKD-EPI	Chronic kidney disease epidemiology collaboration

CNI	Calcineurin inhibitors
DM	Diabetes mellitus
eGFR	Estimated glomerular filtration rate
GGT	Gamma-glutamyl transferase
HDL	High density lipoprotein
HOMA-IR	Homeostatic model assessment for insulin resistance
IRI	Immunoreactive insulin
KT	Kidney transplatnation
LDL	Low density lipoprotein
M	Month
TAC	Tacrolimus
T2DM	Type 2 diabetes mellitus
UACR	Urinary albumin to creatinine ratio

✉ Karol Graňák
granak.k@gmail.com

¹ Transplant-Nephrology Department, University Hospital Martin, Kollárova 2, 03601 Martin, Slovakia

² Clinic of Internal Medicine I., University Hospital Martin and Jessenius Faculty of Medicine in Martin, Comenius University in Bratislava, Martin, Slovakia

1 Introduction

Milk thistle, also known as *Silybum marianum*, contains an active component called silymarin, which has recently been recognised as a potentially useful therapeutic agent for a variety of medical disorders. The multifaceted therapeutic properties and favourable safety profile of this substance make it a promising candidate for use in kidney transplant patients [1]. Silymarin have potential nephroprotective effect against drug induced nephropathy, can have protective benefit in the onset and progression of diabetic nephropathy and protective effect against oxidative stress in kidney tissue [2, 3]. It can also effect cholesterol levels and progression of atherosclerosis and also improvement of glycemic control in type 2 diabetes mellitus (T2DM), reduce insulin resistance and diabetic complications through antioxidant mechanism [4, 5]. In patients after kidney transplantation (KT) can silymarin be useful in reduction oxidative stress with enhancing mitochondrial function [6]. It can also decrease risk of kidney injury by its anti-inflammatory effect and reducing interleukin 6 (IL-6) and tumor necrosis alpha (TNF- α) [7].

This pilot study aims to evaluate the effects of silymarin supplementation on metabolic parameters and graft function in kidney transplant recipients, considering its established therapeutic properties and potential benefits in transplant medicine.

2 Materials and Methods

Our prospective study consisted of patients after primary kidney transplantation in the Transplant-nephrology department. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) scores greater than 2 and more than one year after KT were used as inclusion criteria. The study excluded patients who had received lipid-lowering therapy, inhibitors of the renin angiotensin aldosterone system, and inhibitors of sodium glucose transport protein 2 in less than 12 months prior to the study, severe infection, or biopsy-proven acute rejection during follow-up or 12 months prior to KT. We included patients who met the inclusion criteria in the study and supplemented them with three tablets of silymarin, divided into three daily doses, for 180 days. One coated tablet contained 240 mg of dry extract from the milk thistle (*Cardui mariae fructus extractum siccum*), which converted 150 mg of silymarin to silybinin. The tablet is a coated white, biconvex coated tablet with a homogeneous smooth surface. Patients underwent check-ups at the Transplantation Nephrology Clinic in the third and sixth months after the start of the study.

In assessing patient compliance, we utilised two complementary techniques to evaluate adherence to the silymarin supplementation regimen over the study period. Initially, we adopted a pill counting method in which patients were directed to bring their remaining medication to follow-up appointments at 3 and 6 months. The research team subsequently computed compliance rates by contrasting the quantity of tablets ingested with the anticipated intake according to the specified thrice-daily dosage regimen.

Furthermore, we used systematic patient self-reporting at these follow-up appointments, wherein patients were requested to delineate their adherence patterns, including any missed doses and justifications for non-compliance when relevant. This dual methodology enabled us to cross-verify compliance data and discern any possible obstacles to adherence. Patients exhibiting less than 80% adherence as determined by pill counts received supplementary counselling regarding the significance of consistent medication intake for the validity of the trial.

The baseline information collected included age at time of the study, weight, height, body mass index (BMI), gender, number of KT, time since KT to start of a study (in months), history of hepatopathy defined either by imaging methods or laboratory parameters, history of diabetes mellitus or prediabetes, including impaired fasting glycaemia (fasting blood glucose between 5.6 and 6.9 mmol/l) or abnormal glucose tolerance test (glycaemia after two hours from 7.8 to 10.9 mmol/l), and history of abnormal lipid metabolism (dyslipoproteinemia) defined either as an elevated plasma levels of total cholesterol, triglycerides, low density lipoprotein or decreased plasma concentrations of high density lipoproteins. We also recorded the patients' medication, which included oral antihyperglycemics, insulin therapy, treatment with statins, ezetimibe, fibrate, the average daily dose of prednisone in milligrams, and the use of calcineurin inhibitors (CNI) in their treatment regimen.

At the beginning of the study, in the third and sixth months, we recorded the following parameters: fasting blood sugar, fasting immunoreactive insulin (IRI) and C-peptide, total cholesterol, triglycerides, high density lipoprotein (HDL-) and low density lipoprotein (LDL-) cholesterol, hepatic enzymes: GGT (gamma-glutamyl transferase), AST (aspartate aminotransferase), ALT (alanine aminotransferase), ALP (alkaline phosphatase), serum creatinine and urea levels, urinary albumine creatine ratio (UACR), serum tacrolimus (TAC) levels, and weight.

The aims of the study were to determine whether silymarin supplementation would have an effect on insulin resistance reflected by the level of IRI, C-peptide, and calculated HOMA-IR, the effect on lipid metabolism, graft function reflected by plasmatic concentrations of creatinine and

UACR, hepatic enzymes, weight, and levels of TAC in the monitored intervals.

A certified statistical tool, MedCalc Software (VAT registration number BE 0809 344,640; Member of the International Association of Statistical Computing, Ostend, Belgium), was utilised for statistical analysis. Categorical variables were expressed as weighted percentages and frequencies. Parametric (t-test) or non-parametric (Mann–Whitney) tests were employed to compare continuous variables across groups. We employed the χ^2 test and Fisher's exact test to examine the relationships between categorical variables. A p-value of less than 0.05 was deemed statistically significant.

2.1 Ethical Permission

In accordance with the ethical requirements of the institutional ethical committee (University Hospital Martin), all procedures involving human volunteers received approval. All written informed consents were preserved for a minimum of 20 years post-research completion and received approval from the university hospital's ethical committee. The clinical and scientific activities reported adhered to the principles of the Declaration of Istanbul regarding organ trafficking and transplant tourism.

3 Results

28 patients were included in the study, 20 males (71.4%), average age 52.6 ± 10.2 years; all of the study subjects were after primary KT with an average time of 105 ± 64.5 months after KT. Only one patient (3.6%) received treatment with oral antihyperglycemics (metformin); none received insulin; 67.9% received statins; 10.7% received fibrates; and 3.6% received additional ezetimibe. Average daily dose of prednisone was 6.2 ± 2.1 mg, and all patients were treated with CNI. Table 1 shows the basic characteristics of the participants.

In our study, we did not observe statistically significant changes in glucose metabolism, lipid profile, graft function, or other monitored parameters. However, we observed a decrease in LDL-C in Month 3 without statistical significance. Table 2 shows the course of monitored parameters during follow-up.

In the next step, we divided patients into two groups: with and without type 2 diabetes mellitus (T2DM) or prediabetes. There were no statistically significant differences in compared groups from the point of view of basic characteristics (Table 3).

In our study, we observed a statistically significantly higher FBS in all monitored intervals in patients with T2DM or prediabetes (P 0.0015; 0.0005 and 0.0026,

Table 1 Basic characteristics of a study

n = 28 Basic characteristics of the patients (baseline)

Gender—males (%)	71.4 (<i>n</i> = 20)
Primary kidney transplantation (%)	100 (<i>n</i> = 28)
Time since kidney transplantation to the treatment (months)	105 ± 64.5
Age at the time of the treatment (years)	52.6 ± 10.2
BMI (kg/m ²)	30.7 ± 4.7
Weight (kg)	93.1 ± 15.1
Hepatopathy in anamnesis (%)	10.7 (<i>n</i> = 3)
Type 2 diabetes mellitus in anamnesis (%)	21.4 (<i>n</i> = 6)
Prediabetes in anamnesis (%)	21.4 (<i>n</i> = 6)
Dyslipoproteinemia in anamnesis (%)	78.6 (<i>n</i> = 22)
Treatment (baseline)	
Oral antihyperglycemics (%)	3.6 (<i>n</i> = 1)
Insulin treatment (%)	<i>n</i> = 0
Statin (%)	67.9 (<i>n</i> = 19)
Ezetimibe (%)	3.6 (<i>n</i> = 1)
Fibrate (%)	10.7 (<i>n</i> = 3)
Average dose of prednisone (mg/day)	6.2 ± 2.1
Calcineurin inhibitor – tacrolimus (%)	100 (<i>n</i> = 28)

BMI body mass index

Table 2 Development of monitored parameters

	Baseline	M3	M6
Fasting blood sugar (mmol/l)	6 ± 1.3	5.9 ± 1.2	6.1 ± 1.8
IRI (mU/l)	12 ± 5	10.8 ± 5	10.6 ± 4.6
C-peptide (μg/l)	4.3 ± 1.3	4.1 ± 1.6	4.2 ± 1.5
HOMA-IR	3.2 ± 2	2.9 ± 1.8	2.8 ± 2.2
Cholesterol (mmol/l)	4.4 ± 0.9	4.4 ± 1	4.5 ± 1
Triglycerides (mmol/l)	2.2 ± 1	2.1 ± 0.8	2.2 ± 1.1
HDL-cholesterol (mmol/l)	1.2 ± 0.4	1.2 ± 0.4	1.2 ± 0.4
LDL-cholesterol (mmol/l)	2.7 ± 0.9	2.2 ± 0.7	2.2 ± 0.7
GGT (μkat/l)	0.6 ± 0.3	0.6 ± 0.4	0.7 ± 0.4
AST (μkat/l)	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.2
ALT (μkat/l)	0.5 ± 0.2	0.5 ± 0.2	0.5 ± 0.2
ALP (μkat/l)	1.2 ± 0.3	1.2 ± 0.3	1.2 ± 0.3
Creatinine (μmol/l)	122 ± 43	124 ± 42	118.6 ± 39.9
Urea (mmol/l)	8.1 ± 2.5	7.9 ± 2.5	7.6 ± 3
eGFR (CKD-EPI) (ml/min)	59.1 ± 15.3	58.6 ± 17.4	60.7 ± 16.7
UACR (g/mol)	4.8 ± 8.6	4 ± 7.7	6.9 ± 14
Tacrolimus level (μg/l)	5.1 ± 1.5	5.5 ± 1.7	5.5 ± 2.1
Weight (kg)	93.1 ± 15.1	93.7 ± 14.9	94.4 ± 15.6

IRI immunoreactive insulin, *HOMA-IR* Homeostatic Model Assessment for Insulin Resistance, *HDL* high density lipoprotein, *LDL* low density lipoprotein, *GGT* Gamma-glutamyl transferase, *AST* aspartate aminotransferase, *ALT* alanine aminotransferase, *ALP* alkaline phosphatase, *eGFR* estimated glomerular filtration rate, *UACR* urinary albumin to creatinine ratio, *M* month

Table 3 Comparison of groups in basic characteristics

<i>n</i> = 28	No DM <i>n</i> = 16	DM or prediabetes <i>n</i> = 12	P value
Basic characteristics of a study (baseline)			
Gender–males (%)	62.5 (<i>n</i> = 10)	83.3 (<i>n</i> = 10)	0.3078
Primary kidney transplantation (%)	100 (<i>n</i> = 16)	100 (<i>n</i> = 12)	–
Time since kidney transplantation to the treatment (months)	112 ± 68.8	95.6 ± 60.1	0.5163
Age at the time of the treatment (years)	52.2 ± 10.8	53.3 ± 9.8	0.7838
BMI (kg/m ²)	30.8 ± 4.8	30.6 ± 4.8	0.9140
weight (kg)	91.9 ± 14	94.8 ± 16.9	0.6237
Hepatopathy in medical history (%)	12.5 (<i>n</i> = 2)	8.3 (<i>n</i> = 1)	0.9290
Type 2 diabetes mellitus in medical history (%)	–	50 (<i>n</i> = 6)	–
Prediabetes in anamnesis (%)	–	50 (<i>n</i> = 6)	–
Dyslipoproteinemia in anamnesis (%)	81.3 (<i>n</i> = 13)	75 (<i>n</i> = 9)	0.7451
Treatment (baseline)			
Oral antihyperglycemics (%)	–	8.3 (<i>n</i> = 1)	–
Insulin treatment (%)	–	–	–
Statin (%)	62.5 (<i>n</i> = 10)	75 (<i>n</i> = 9)	0.4913
Ezetimibe (%)	6.3 (<i>n</i> = 1)	<i>n</i> = 0	0.3845
Fibrate (%)	18.8 (<i>n</i> = 3)	<i>n</i> = 0	0.1185
Average dose of prednisone (mg/day)	6.25 ± 2.2	6 ± 2	0.7597
Calcineurin inhibitor–tacrolimus (%)	100 (<i>n</i> = 16)	<i>n</i> = 12 (100)	–

DM diabetes mellitus, BMI body mass index

respectively) compared to the other group. Logically, we observed differences in HOMA-IR in the observed group at the beginning of the study, which were at the limit of significance ($P = 0.0510$). The differences became statistically significant in the 6th month ($P = 0.0059$). While we did not observe statistically significant differences in LDL-C between the compared groups at baseline, in the third month the differences in plasma LDL-C values were significantly lower in patients with an abnormal glucose metabolism ($P = 0.0504$) at the border of statistical significance. In the 6th month the differences were not significant, but in the group of patients with T2DM or prediabetes, numerically lower LDL-C values persisted without significant differences in the patient's weight between the compared groups (Table 4).

In patients without T2DM or prediabetes, we observed a decrease in HOMA-IR at the edge of significance ($P = 0.0516$) (Fig. 1). In patients with T2DM or diabetes we observed statistical significant decrease of LDL-C (Fig. 2).

Supplementation of silymarin for 6 months did not have an effect on graft function reflected by serum levels of creatinine and UACR, as well as on the level of TAC, liver functions, and weight in the whole study group, neither in patients with or without T2DM or prediabetes.

4 Discussion

Silymarin has a stable use in the treatment of liver diseases. However, due to its pluripotent anti-inflammatory, anti-fibrotic, and other effects, its use is significantly wider. It not only affects liver metabolism but also influences the metabolism of lipids and sugars. Furthermore, it has potential use in diseases of the gastrointestinal tract, cardiovascular diseases, and the prevention of atherosclerosis progression. Therefore, silymarin also serves as a supplementary treatment for diseases of the pancreas or metabolic disorders [8].

The potential effect of silymarin on lipid metabolism lies in several mechanisms. The research by Krecman et al. (1998) confirms that silymarin may be able to stop HMG-CoA reductase, which is the main enzyme involved in making cholesterol [9]. Another possible effect of silymarin is to raise the expression of LDL-cholesterol receptors, which leads to more LDL-C being taken in. Silymarin also acts as a potent antioxidant, reducing oxidative stress and inflammation associated with dyslipidaemia and atherosclerosis [10]. By an indirect mechanism of affecting bile acid synthesis, silymarin can affect fat metabolism [11]. Patients with impaired glucose metabolism, particularly

Table 4 Comparison of individual monitored parameters: patients without diabetes mellitus versus patients with prediabetes and diabetes mellitus

	non DM <i>n</i> = 16	DM or prediabetes <i>n</i> = 12	P value
Baseline			
Fasting blood sugar (mmol/l)	5.3 ± 0.5	6.8 ± 1.6	0.0015
IRI (mU/l)	11.1 ± 3.2	13.1 ± 6.8	0.3090
C-peptide (µg/l)	4.3 ± 1.3	4.2 ± 1.4	0.8469
HOMA-IR	2.6 ± 0.8	4.1 ± 2.8	0.0510
Cholesterol (mmol/l)	4.6 ± 0.9	4.2 ± 0.8	0.2337
Triglycerides (mmol/l)	2.1 ± 1	2.2 ± 1.1	0.8038
HDL-cholesterol (mmol/l)	1.2 ± 0.3	1.1 ± 0.6	0.5673
LDL-cholesterol (mmol/l)	3 ± 1	2.4 ± 0.6	0.0772
GGT (µkat/l)	0.6 ± 0.3	0.6 ± 0.3	1.0000
AST (µkat/l)	0.4 ± 0.1	0.5 ± 0.3	0.2222
ALT (µkat/l)	0.5 ± 0.2	0.5 ± 0.2	1.0000
ALP (µkat/l)	1.1 ± 0.3	1.3 ± 0.3	0.0927
Creatinine (µmol/l)	116.8 ± 37.9	128.4 ± 49.8	0.4896
Urea (mmol/l)	8 ± 2	8.2 ± 3.2	0.8405
eGFR (ml/min)	59.7 ± 14.8	58.3 ± 16.6	0.8159
UACR (g/mol)	3.7 ± 6.1	6.2 ± 11.3	0.4579
Tacrolimus levels (µg/l)	5.1 ± 1.6	5 ± 1.2	0.8575
Weight (kg)	91.9 ± 14	94.8 ± 16.9	0.6237
M3			
Fasting blood sugar (mmol/l)	5.3 ± 0.5	6.7 ± 1.3	0.0005
IRI (mU/l)	9.7 ± 4	12.2 ± 5.9	0.1927
C-peptide (µg/l)	4 ± 1.6	4.2 ± 1.8	0.7588
HOMA-IR	2.3 ± 1.1	3.7 ± 2.3	0.5614
Cholesterol (mmol/l)	4.5 ± 1	4.3 ± 1.1	0.6200
Triglycerides (mmol/l)	2.2 ± 0.8	2 ± 0.9	0.5402
HDL-cholesterol (mmol/l)	1.2 ± 0.3	1.2 ± 0.6	1.0000
LDL-cholesterol (mmol/l)	2.4 ± 0.8	1.9 ± 0.3	0.0504
GGT (µkat/l)	0.6 ± 0.4	0.6 ± 0.4	1.0000
AST (µkat/l)	0.4 ± 0.1	0.5 ± 0.3	0.2222
ALT (µkat/l)	0.4 ± 0.2	0.5 ± 0.2	0.2019
ALP (µkat/l)	1.1 ± 0.3	1.2 ± 0.4	0.4558
Creatinine (µmol/l)	124.2 ± 47.3	123.8 ± 34.7	0.9810
Urea (mmol/l)	8.2 ± 2.6	7.4 ± 2.4	0.4129
eGFR (ml/min)	58.4 ± 19.2	58.9 ± 15.6	0.9418
UACR (g/mol)	2.7 ± 5.3	5.7 ± 10.1	0.3173
Tacrolimus levels (µg/l)	5.9 ± 1.7	4.9 ± 1.5	0.1177
Weight (kg)	92.4 ± 13.4	95.3 ± 17	0.6176
M6			
Fasting blood sugar (mmol/l)	5.2 ± 1.1	7.1 ± 1.9	0.0026
IRI (mU/l)	9 ± 3.5	12.3 ± 5.2	0.0551
C-peptide (µg/l)	4 ± 1.1	4.3 ± 1.9	0.6029

Table 4 (continued)

	non DM <i>n</i> = 16	DM or prediabetes <i>n</i> = 12	P value
HOMA-IR	1.9 ± 1.2	4.1 ± 2.6	0.0059
Cholesterol (mmol/l)	4.7 ± 1	4.2 ± 0.9	0.1838
Triglycerides (mmol/l)	2.3 ± 1.2	2 ± 0.9	0.4748
HDL-cholesterol (mmol/l)	1.2 ± 0.3	1.1 ± 0.4	0.4558
LDL-cholesterol (mmol/l)	2.4 ± 0.8	2 ± 0.6	0.1589
GGT (µkat/l)	0.8 ± 0.5	0.6 ± 0.3	0.2310
AST (µkat/l)	0.4 ± 0.1	0.5 ± 0.3	0.2222
ALT (µkat/l)	0.5 ± 0.2	0.5 ± 0.2	1.0000
ALP (µkat/l)	1.1 ± 0.2	1.3 ± 0.3	0.0639
Creatinine (µmol/l)	111.7 ± 36.9	127.2 ± 43.4	0.3170
Urea (mmol/l)	7.5 ± 2.3	7.8 ± 3.8	0.7973
eGFR (ml/min)	63 ± 17.6	57.8 ± 15.7	0.4256
UACR (g/mol)	6.2 ± 14.8	7.7 ± 13.7	0.7864
Tacrolimus levels (µg/l)	4.8 ± 1.7	6.5 ± 2.5	0.0516
Weight (kg)	93 ± 14.3	96 ± 17.6	0.6228

DM diabetes mellitus, IRI immunoreactive insulin, HOMA-IR Homeostatic Model Assessment for Insulin Resistance, HDL high density lipoprotein, LDL low density lipoprotein, GGT Gamma-glutamyl transferase, AST aspartate aminotransferase, ALT alanine aminotransferase, ALP alkaline phosphatase, eGFR estimated glomerular filtration rate, UACR urinary albumin to creatinine ratio, M month

those with T2DM, exhibit altered lipid metabolism compared to the non-diabetic population. This is due to increased lipolysis of adipose tissue, increased hepatic lipogenesis, impaired fatty acid oxidation, and reduced antilipolytic effect of insulin due to insulin resistance [12]. In our study, we confirmed a significant decrease in LDL-C already in the 3rd month after the initiation of silymarin supplementation in patients with T2DM or prediabetes.

In animal models, after the administration of silymarin, there was a significant increase in pancreatic and plasma glutathione with the prevention of lipoperoxidation. At the same time, after the administration of streptozocin to mice, the antioxidant activity of renal structures increased with the reduction of superoxide production by podocytes in hyperglycaemic animal models and in vivo in the kidney cortex [13]. In experimental models, the anti-inflammatory effect of silymarin was proven with the regulation of several inflammatory mediators, TNF-α, and several antagonists of interleukin receptors (IL-1β, IL-6, IL-1). In addition, silymarin reduces the synthesis of leukotrienes and prostaglandins along with inhibition of cyclooxygenase II [14]. Meta-analysis by Hadi et al. (2018) concluded that silymarin supplementation in patients with T2DM can lead to a decrease in FBS, glycated haemoglobin, LDL-C, malondialdehyde, and insulin and can potentially increase HDL-C [15].

Fig. 1 Development of fasting blood glucose, IRI, C-peptide and HOMA-IR in non-DM patients

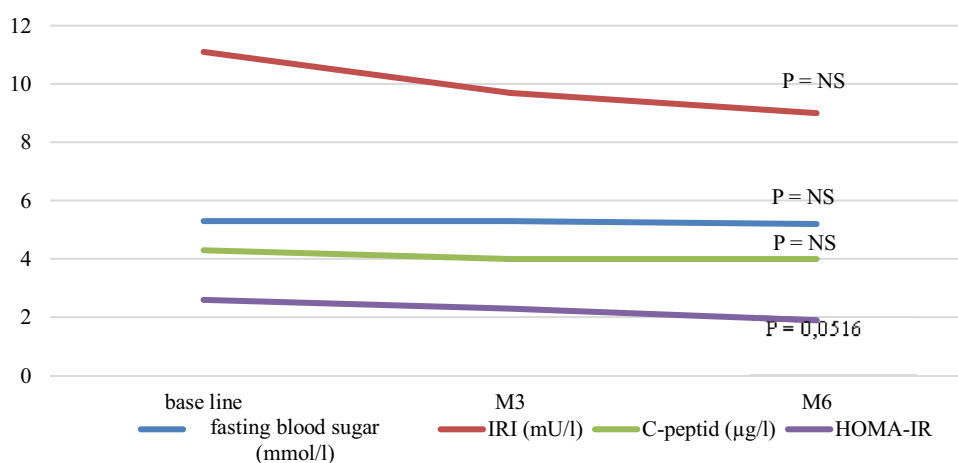
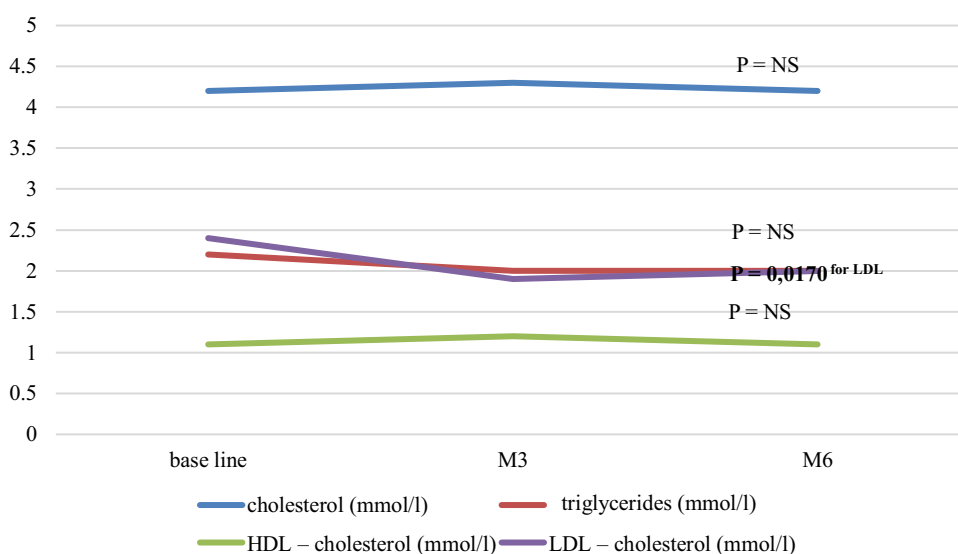


Fig. 2 Development of cholesterol, triglycerides, LDL- and HDL-cholesterol in patients with T2DM or prediabetes



In a small randomized study by Fallahzadeh et al. (2012) involving 60 patients with T2DM, there was a significant reduction in UACR and urinary TNF- α after silymarin supplementation compared to a placebo [16]. In our study, we did not notice a significant decrease in UACR in the entire group of patients, regardless of the presence of a carbohydrate metabolism disorder. It should be noted that the baseline value of UACR in our group was relatively low due to our inability to prove the potential antiproteinuric effect of silymarin, as the reported work by Fallahzadeh et al. included patients with T2DM and significant albuminuria (> 300 mg albumin in urine/day). It is also important to say that nowadays we have extensive possibilities of renoprotection from SGLT2i, finerenone, and glucagon-like peptide 1 receptor agonists in patients with T2DM (as well as without), while at the time of the mentioned study there were no such possibilities.

Hepatic dysfunction can significantly increase TAC plasma levels in KTR with subsequent CNI toxicity. In liver

transplant patients with pre-existing kidney dysfunction, tacrolimus administration had to be discontinued in 31.6% of cases due to deterioration of renal functions, which indicates a two-way link between the liver and kidneys [17]. The metaanalysis of Mohammadi et al. (2024). The aggregated findings demonstrated that silymarin supplementation resulted in a significant decrease in blood levels of ALP, ALT, creatinine, and AST, alongside a notable increase in serum glutathione in the silymarin-treated group relative to the untreated group. Furthermore, there was an insignificant reduction in serum concentrations of GGT malondialdehyde, total bilirubin, albumin and blood urea nitrogen. Our investigation did not reveal statistically significant differences in subjects administered silymarin [18]. The results of the animal study of Terzi and Ciftci (2022) indicate potential nephroprotective effect of silymarine in tacrolimus-induced nephro- and hepatotoxicity in rats [19]. Given that tacrolimus experiences significant hepatic metabolism primarily through the cytochrome P450 system and is prone to

several drug-drug interactions, it is reasonable to conclude that probable liver dysfunction may result in increased tacrolimus plasma concentrations, hence causing TAC-induced nephrotoxicity. Tacrolimus treatment is linked to mild to moderate increases in serum aminotransferase levels in 5 to 10% of patients. These elevations are typically moderate, asymptomatic, and self-limiting; nevertheless, they may occasionally be chronic and necessitate dose adjustment [20].

In our study, we did not observe significant differences in TAC levels after silymarin supplementation, and we did not confirm the hypothesis that silymarin supplementation leads to better liver metabolism with a potential improvement in TAC metabolism, which would lead to a decrease in its effective plasma concentrations.

This study possesses numerous significant limitations that must be acknowledged when interpreting our findings. The restricted sample size ($n=28$) considerably hampered our statistical power, especially for the subgroup analyses contrasting individuals with and without diabetes mellitus. The restricted sample size of 16 patients in the non-DM group and 12 in the DM/prediabetes group constrained our capacity to identify significant differences, hence heightening the likelihood of type II errors and the possibility for overinterpretation of marginally significant findings.

The lack of a placebo-controlled design constitutes a significant methodological constraint. In the absence of a control group, we cannot conclusively ascribe any observed alterations to silymarin supplementation instead of natural illness progression, regression to the mean, or other confounding variables. Our fundamental hypothesis posited that untreated patients would exhibit a deterioration in metabolic markers and no enhancement in graft function; however, this remains unverified in the absence of a good control group.

Third, our pragmatic methodology for sample size determination, influenced by the constrained eligible population at our singular centre rather than by formal power analyses, further limits the robustness of our conclusions. The post-hoc power analysis indicated that our study lacked sufficient power to identify clinically significant changes in our primary objectives.

The very low baseline values of some parameters, such as UACR, in our sample may have induced a floor effect, constraining our capacity to identify prospective enhancements. Moreover, the dependence on pill counting and self-reporting for evaluating compliance creates possible measurement bias.

The particular formulation properties of the silymarin preparation utilised may influence bioavailability and efficacy, thus restricting generalisability to different silymarin products. To mitigate these constraints, we recommend conducting a multicenter, placebo-controlled, randomised trial with a sufficient sample size determined by rigorous

power calculations. This forthcoming investigation ought to encompass a wider patient demographic, incorporating individuals with more pronounced baseline abnormalities (such as substantial albuminuria), even post comprehensive supportive antiproteinuric therapy, and should utilise more rigorous methodologies to guarantee and evaluate treatment adherence.

Our research offers significant preliminary data supporting silymarin as a viable supplementary treatment for kidney transplant recipients experiencing metabolic problems, especially in individuals with disrupted glucose metabolism. The most significant findings are the subgroup analysis, which demonstrated a statistically significant reduction in LDL-C levels after the third month of silymarin supplementation, particularly in patients with T2DM or prediabetes. Considering that kidney transplant recipients experience heightened cardiovascular risk, especially those with concurrent diabetes, your discovery that silymarin may diminish LDL-C carries significant therapeutic ramifications. This impact may aid in reducing cardiovascular risk in this susceptible population, particularly as numerous patients would be unable to endure full-dose statin medication following transplantation. Our research indicates that silymarin may function as an adjunct to conventional lipid-lowering treatments. Sixty-seven point nine percent of individuals in your cohort who were previously on statins exhibited a reduction in LDL-C with silymarin supplementation, indicating potential additive benefits. The marginally significant reduction in HOMA-IR among non-diabetic patients indicates possible metabolic advantages beyond lipid metabolism, aligning with silymarin's documented anti-inflammatory and antioxidative characteristics. Our study offers initial safety data about silymarin supplementation in kidney transplant recipients, indicating no detrimental effects on tacrolimus levels or graft function.

5 Conclusion

Silymarin is a substance used mainly as supportive therapy in various liver diseases, but its pluripotent effects predestine it for potential use in kidney, metabolic, and other diseases. In our study, we confirmed a positive effect on lowering LDL-C in patients with abnormal glucose metabolism, which may pave the way for its use, particularly in patients with hepatic dysfunction and limited use of other hypolipemic therapies that may have hepatotoxic effects. It is important to carry out further large studies that will confirm its potential benefit mentioned above.

Author Contributions M.V. participated in performing the research design, data analysis, and writing the paper. K.G. participated in data

analysis. P.K. and T.B. participated in writing the paper. A.K. participated in data analysis. I.D. participated in data analysis. All authors have read and agreed to the published version of the manuscript.

Funding Open access funding provided by The Ministry of Education, Science, Research and Sport of the Slovak Republic in cooperation with Centre for Scientific and Technical Information of the Slovak Republic. Funded by the EU NextGenerationEU through the Recovery and Resilience Plan for Slovakia under the project No. 09I03-03-V04-00211.

Data Availability The data that support the findings of this study are available on request from the corresponding author, G.K.

Declarations

Conflict of interest The authors declare no competing interests.

Institutional review board statement The study was conducted in accordance with the Declaration of Helsinki, and approved by Ethics Committee of University Hospital Martin (EK 33/2024).

Informed consent statement Informed consent was obtained from all subjects involved in the study.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

1. Saller R, Melzer J, Reichling J, Brignoli R, Meier R. An updated systematic review of the pharmacology of silymarin. *Forsch Komplementmed*. 2007;14(2):70–80.
2. Sedighifard Z, Roghani F, Bidram P, Harandi SA, Molavi S. Silymarin for the prevention of contrast-induced nephropathy: a placebo-controlled clinical trial. *Int J Prev Med*. 2016;22(7):23.
3. Rafieian-Kopaei M, Nasri H. Silymarin and diabetic nephropathy. *J Renal Inj Prev*. 2012;1(1):3–5.
4. Voroneanu L, Nistor I, Dumea R, Apetrii M, Covic A. Silymarin in type 2 diabetes mellitus: a systematic review and meta-analysis of randomized controlled trials. *J Diabetes Res*. 2016;2016:5147468.
5. Kadoglou NPE, Panayiotou C, Vardas M, Balaskas N, Kostomit-sopoulos NG, Tsaroucha AK, Valsami G. A comprehensive review of the cardiovascular protective properties of silibinin/silymarin: a new kid on the block. *Pharmaceuticals (Basel)*. 2022;15(5):538.
6. Ommati MM, Farshad O, Azarpira N, et al. Silymarin mitigates bile duct obstruction-induced cholemic nephropathy. *Naunyn Schmiedeberg Arch Pharmacol*. 2021;394(6):1301–14.
7. Al-Kadi A, Al-Shaimaa F, Ahmed N, et al. (2020). Silymarin protects against sepsis-induced acute liver and kidney injury via anti-inflammatory and antioxidant mechanisms in the rat. 3(4):190–197.
8. Federico A, Dallio M, Loguercio C. Silymarin/silybin and chronic liver disease: a marriage of many years. *Molecules*. 2017;22(2):191.
9. Krecman V, Skottová N, Walterová D, Ulrichová J, Simánek V. Silymarin inhibits the development of diet-induced hypercholesterolemia in rats. *Planta Med*. 1998;64(2):138–42.
10. Surai PF. Silymarin as a natural antioxidant: an overview of the current evidence and perspectives. *Antioxidants (Basel)*. 2015;4(1):204–47.
11. Crocenzi FA, Roma MG. Silymarin as a new hepatoprotective agent in experimental cholestasis: new possibilities for an ancient medication. *Curr Med Chem*. 2006;13(9):1055–74.
12. Sanders FW, Griffin JL. De novo lipogenesis in the liver in health and disease: more than just a shunting yard for glucose. *Biol Rev Camb Philos Soc*. 2016;91(2):452–68.
13. Khazim K, Gorin Y, Cavaglieri RC, Abboud HE, Fanti P. The antioxidant silybin prevents high glucose-induced oxidative stress and podocyte injury in vitro and in vivo. *Am J Physiol Renal Physiol*. 2013;305(5):F691–700.
14. Malihi F, Hosseini-Tabatabaei A, Esmaily H, Khorasani R, Baeri M, Abdollahi M. Improvement of inflammatory and toxic stress biomarkers by silymarin in a murine model of type one diabetes mellitus. *Open Life Sci*. 2009;4(3):369–80.
15. Hadi A, Pourmasoumi M, Mohammadi H, Symonds M, Miraghajani M. The effects of silymarin supplementation on metabolic status and oxidative stress in patients with type 2 diabetes mellitus: a systematic review and meta-analysis of clinical trials. *Complement Ther Med*. 2018;41:311–9.
16. Fallahzadeh MK, Dormanesh B, Sagheb MM, et al. Effect of addition of silymarin to renin-angiotensin system inhibitors on proteinuria in type 2 diabetic patients with overt nephropathy: a randomized, double-blind, placebo-controlled trial. *Am J Kidney Dis*. 2012;60(6):896–903.
17. Gastaca M, Prieto M, Palomares I, et al. Long-term outcomes of liver transplantation in patients with pretransplant renal dysfunction treated with induction therapy and delayed reduced de novo once-daily tacrolimus. *Transplant Proc*. 2020;52(5):1489–92.
18. Mohammadi S, Ashtary-Larky D, Asbaghi O, Farrokhi V, Jadidi Y, Mofidi F, Mohammadian M, Afrisham R. Effects of silymarin supplementation on liver and kidney functions: a systematic review and dose-response meta-analysis. *Phytother Res*. 2024;38(5):2572–93.
19. Terzi F, Ciftci MK. Protective effect of silymarin on tacrolimus-induced kidney and liver toxicity. *BMC Complement Med Ther*. 2022;22(1):331.
20. Kaplowitz N. Drug-induced liver injury. *Clin Infect Dis*. 2004;1(38 Suppl 2):S44–8.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.