INTRODUCTION

Diabetic nephropathy (DN), characterized by albuminuria, hypertension, and a progressive decline in glomerular filtration rate (GFR), develops in 10–40% of diabetic patients.1 DN is a leading cause of chronic kidney disease, a common medical problem with an estimated prevalence of 11% in the adult US population, and its annual incidence has more than doubled in the past decade to about 43% of all end-stage renal diseases (ESRDs).2 Furthermore, in Iran, it has been estimated that about 6% of diabetic patients suffer nephropathy as a consequence of diabetes.3 Therefore, developing strategies to prevent DN is one of the most favored research fields to date.

The pathogenesis of DN culminates in glomerulosclerosis (GS).4 Hyperglycemia, insulin resistance, oxidative stress, dyslipidemia, and hyperinflammatory status are among the factors that contribute to the progression of GS in DN.1,2 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase is a major rate-limiting enzyme in cholesterol biosynthesis that converts HMG-CoA to mevalonate, an early

ABSTRACT

Background: Diabetic nephropathy (DN) is characterized by albuminuria, hypertension, and a progressive decline in glomerular filtration rate. The 3-hydroxy-3-methylglutaryl coenzyme A is a well-known agent that is active in lowering total plasma and low-density lipoprotein cholesterol (LDL-C) levels in cases with hypercholesterolemia. Hence, in this study, proteinuria changes at the beginning and after the withdrawal of lovastatin in patients with type 2 DN (T2DN) were studied. Materials and Methods: Lovastatin was administered for thirty male patients with T2DN and then was withdrawn. Twenty-four hours, urine creatinine and protein levels were determined. Results: The mean levels of total cholesterol and LDL-C were reduced without any change in the triglyceride (TG) level while the high-density lipoprotein cholesterol (HDL-C) level was increased. There was a reverse linear correlation between the changes in the level of HDL-C and the changes in the level of 24 h urine protein after 90 days of lovastatin therapy (P = 0.007, r = −0.484). Conclusions: Short-term 3-month lovastatin therapy has no effect on proteinuria levels in patients with T2DN despite the antihyperlipidemic effects and reverse correlation of proteinuria with HDL-C. Key words: Diabetes type 2, nephropathy, proteinuria, statin
precursor of cholesterol. The HMG-CoA reductase inhibitors are pharmacological agents that are active in lowering total plasma and low-density lipoprotein cholesterol (LDL-C) levels in subjects with hypercholesterolemia. A recent systematic review of 27 randomized trials suggested that statins reduce the rate of kidney function loss by 1.2 ml/min/year or 76%. Another systematic review of 15 randomized studies found that statins reduce albuminuria by 47% and 48% of people with >300 mg/24 h and 30–300 mg/24 h of albumin excretion at baseline, respectively. However, statins did not significantly influence urinary albumin excretion when baseline levels were <30 mg/24 h.

Considering this controversy, we investigated the effect of lovastatin, a natural, low-cost statin, on patients with type 2 DN (T2DN) by examining renal function and proteinuria in this study.

MATERIALS AND METHODS

Patients
This study was conducted in Sheikholraees Sub-Specialized Clinic of Tabriz University of Medical Sciences (Iran) from February 2006 to March 2008. After initial clinical and laboratory evaluations, 38 males with clinically documented T2DN were enrolled in the study. To eliminate potential confounding factors, we only included patients with type 2 diabetes mellitus (DM) and proteinuria levels lower than the nephrotic range (i.e., <3.5 g/day) whose estimated GFR (eGFR) was higher than 30 mL/min/1.73 m² (as calculated by the Modification of Diet in Renal Disease formula).

All of the participants gave informed consent, and the Ethics Committee of Tabriz University of Medical Sciences reviewed and approved the study protocol, which was in compliance with the Helsinki declaration. This trial was registered with http://www.irct.ir (no. IRCT2012073010446N1).

The fasting plasma glucose (FPG) of the participants was controlled by insulin injection and/or administration of oral sulfonylurea. Blood pressure (BP) was maintained at <129/79 mmHg with treatment by angiotensin-converting enzyme inhibitors (ACEI) and/or angiotensin receptor blockers (ARB), with α-blockers and diuretics when needed. All of the patients were under their own regular restricted protein diet (≤0.8 g/kg/day) as prescribed by a nutrition consultant. Any major change in BP, protein intake, or physical activity during the study period was considered as withdrawal criteria. Exclusion criteria included the use of HMG-CoA antagonists, fibrates, aspirin, β-blockers, allopurinol, vitamins, pentoxifylline, fish oil, other antioxidant drugs consumed in the previous 3 months, active smoking, chronic inflammation (such as diabetic foot, hepatitis, and infection), active coronary artery disease in the previous 3 months (diagnosed by symptoms and electrocardiography), and poorly controlled DM (glycated hemoglobin >7.5%).

Finally, data from 30 patients with T2DN were analyzed in this study (power 0.80 and significance 0.05) while eight were excluded from the study due to the following reasons: Uncooperativeness (two patients), Vitamin C intake during the intervention period (one patient), lifestyle changes during the intervention period (one patient), smoking during the intervention period (one patient), travel to another region (one patient), change from lovastatin to atorvastatin by an endocrinologist (one patient), and development of ESRD (one patient).

Study protocol
Lovastatin (Ghazal Co, Tehran, Iran), in a dose of 20 mg/day, was administered to the patients for 90 days. At the end of the 3rd month, the patients were asked to stop lovastatin intake from the 91st day until the 120th day. To determine the trend of lipid profile and uric acid level, blood samples were obtained four times according to the following schedule: (a) Before lovastatin therapy (baseline), (b) after 45 days of lovastatin therapy (46th day), (c) after 90 days of lovastatin therapy (91st day), and (d) 30 days after the withdrawal of lovastatin therapy (121st day).

Blood sampling
The patients were asked to fast for 12 h. Blood samples were taken before the patients’ breakfast and were collected in sterile tubes, centrifuged at 3000 rpm for 10 minutes at 4°C, and then stored at −79°C until assayed.

Biochemical analyses
Serum levels of FPG, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and TG were determined using commercial reagents with an automated chemical analyzer (Abbott analyzer, Abbott Laboratories, Abbott Park, Chicago, Illinois, USA). LDL-C levels were calculated using the Friedewald equation.

Serum creatinine (Cr) and urea levels were determined by the Jaffe method and glutamate dehydrogenase, respectively. eGFR was calculated using the Modification of Diet in Renal Disease (MDRD) formula. Twenty-four hours, urine samples were collected, and Cr and protein levels assessed using colorimetric and immunoturbidimetric methods. MDRD formula has been validated in Iran.

Statistical analyses
Statistical analyses were performed using the SPSS software package version 13 (SPSS Inc., IL, USA). The results are presented as mean ± standard deviation. Distribution of variables was determined by Skewness, Kurtosis, and Kolmogorov–Smirnov Z tests. General Linear Model Repeated Measures analysis, paired sample t-test, or
Mann–Whitney U test were used to assess the differences between each of the two stages as appropriate. \( P < 0.05 \) was considered statistically significant.

**RESULTS**

The mean age of the eligible participants was 54.5 ± 6.1 years (43–66 years). The mean duration of DM was 9.7 ± 3.1 years (5–15 years). Thirteen participants (43%) had mild to moderate hypertension for 3.1 ± 3.9 years (0–11 years). The mean systolic and diastolic BPs at the beginning of the study were 124.7 ± 11.4 mmHg and 72.9 ± 5.8 mmHg, respectively.

The measured values of FPG and lipid profile are shown in Table 1. These results demonstrated that the mean values of cholesterol and LDL-C levels were significantly reduced following the 3 months of lovastatin therapy. In addition, lovastatin therapy resulted in increased HDL-C levels at the end of the 3rd month of treatment. Thirty days after the withdrawal of the lovastatin, the mean levels of cholesterol, TG, and LDL-C (but not HDL-C) were significantly increased in comparison with the levels measured on the 90th day of lovastatin therapy.

A one-way repeated-measures analysis of variance was conducted to compare serum Cr, urea, and eGFR as measured before the intervention, after 90 days of lovastatin therapy, and on the 30th day ofLovastatin withdrawal, which did not show significant change during the interventional period (for serum Cr and urea, Table 2; for eGFR, Figure 1a). A one-way repeated-measures analysis of variance was conducted to compare the 24 h urine protein level, Cr level, protein/Cr ratio, and volume as measured before the intervention, after 90 days of lovastatin therapy, and on the 30th day ofLovastatin withdrawal. The analysis did not show significant changes over the interventional period (for urine protein, Cr, and volume, Table 2; for urine protein/Cr ratio, Figure 1b). There was a reverse linear correlation between the changes in the HDL-C level after 90 days ofLovastatin therapy and the changes in the 24 h urine protein level during the same period (\( P = 0.007, r = -0.484; \) Figure 1c) while no such correlation was present during the withdrawal period (\( P = 0.288 \)).

**DISCUSSION**

In this study, other than a significant reduction in cholesterol and LDL-C, as well as a significant increase in

### Table 1: Changes in fasting blood glucose and lipid profile following 3 months lovastatin therapy and 1-month cessation

| Evaluation times               | Baseline | 45th day of therapy | 90th day of therapy | 30th day of withdrawal | \( p^1 \) | \( p^2 \) | \( p^3 \) | \( p^4 \) | \( p^5 \) |
|-------------------------------|----------|---------------------|---------------------|------------------------|----------|----------|----------|----------|----------|
| FPG (mg/dl)                   | 159.47±69.53 | 152.45±58.40 | 151.58±57.65 | 156.60±57.27 | 0.504 | 0.180 | 0.448 | 0.491 | 0.933 |
| Total cholesterol (mg/dl)     | 199.00±43.33 | 164.66±35.19 | 165.43±40.41 | 198.40±44.18 | <0.001 | <0.001 | <0.001 | <0.001 | 0.939 |
| TG (mg/dl)                    | 175.37±94.97 | 152.06±94.72 | 158.90±95.24 | 206.50±141.02 | 0.256 | 0.430 | 0.010 | 0.205 | 0.194 |
| HDL-C (mg/dl)                 | 40.00±5.30  | 42.80±5.14  | 42.47±4.38  | 40.60±4.49  | 0.005 | 0.694 | 0.071 | 0.008 | 0.615 |
| LDL-C (mg/dl)                 | 115.86±47.33 | 84.47±29.22  | 82.22±36.68  | 106.98±38.47 | <0.001 | <0.001 | <0.001 | <0.001 | 0.208 |

\*Comparison between baseline and 45th day ofLovastatin treatment; †Comparison between 45th and 90th days ofLovastatin treatment; ‡Comparison between 90th day of Lovastatin treatment and 30th day of withdrawal; §Comparison between baseline and 30th day ofLovastatin therapy and on the 30th day ofLovastatin withdrawal, the mean levels of cholesterol, TG, and LDL-C (but not HDL-C) were significantly increased in comparison with the levels measured on the 90th day ofLovastatin therapy.

### Table 2: Changes of serum creatinine and urea, and 24 h urine sample parameters following lovastatin therapy and its cessation

| Evaluation times               | Baseline | 45th day of therapy | 90th day of therapy | 30th day of withdrawal | \( p^1 \) | \( p^2 \) | \( p^3 \) | \( p^4 \) | \( p^5 \) |
|-------------------------------|----------|---------------------|---------------------|------------------------|----------|----------|----------|----------|----------|
| Serum creatinine (mg/dl)      | 1.65±0.91 | 1.61±0.85 | 1.65±0.66 | 1.61±0.92 | 0.555 | 0.498 | 0.696 | 0.990 | 0.593 |
| Urea\( ^{\text{a}} \)         | 54.53±32.05 | 51.75±25.13 | 53.36±33.92 | 51.53±30.57 | 0.199 | 0.439 | 0.572 | 0.736 | 0.205 |
| uProtein\( ^{\text{b}} \)     | 0.59±0.52 | 0.57±0.49 | 0.56±0.62 | 0.57±0.62 | 0.009 | 0.010 | 0.002 | 0.003 | 0.003 |
| uCr                            | 1210.36±309.16 | 1238.52±289.61 | 1134.22±274.27 | 1123.73±261.71 | 0.741 | 0.475 | 0.432 | 0.385 | 0.137 |
| uVolume                        | 2106.32±717.92 | 2129.31±690.98 | 2060.02±625.65 | 2106.32±717.92 | 0.479 | 0.169 | 0.458 | 0.548 | 0.781 |

Urea – Serum urea level (mg/dl); uProtein – 24 h urine protein level (mg/dl); \( ^{\text{a}} \)Comparison between baseline and 45th day oflovastatin treatment; \( ^{\text{b}} \)Comparison between baseline and 30th day ofLovastatin therapy; \( ^{\text{a}} \)Comparison between baseline and 30th day ofLovastatin therapy and 30th day of withdrawal; *Comparison between baseline and 30th day ofLovastatin therapy. Mann-Whitney U test was used
HDL-C, no other statistically meaningful change in FPG, serum Cr, serum urea, eGFR, urine Cr, urine volume, 24 h urine protein level, or urine protein/Cr ratio was observed after 90 days of lovastatin therapy. Based on these results, a reverse linear correlation between the changes of HDL-C and 24 h urine protein levels was found after 90 days of lovastatin therapy.

Considering the main target of our research, there have been conflicting results about the effects of statins on urinary protein excretion levels in different studies. We found no lowering effect of lovastatin on urinary albumin excretion levels in our patients in contrast to previous researches.\textsuperscript{13,14} In a double-blind crossover study, simvastatin therapy on a total of 19 normotensive microalbuminuric hypercholesterolemic type 2 diabetic patients had up to 25% reduced urinary albumin excretion rate compared to the basal rate;\textsuperscript{13} results of this study were similar to the present study. In a later study, treatment with cerivastatin in 60 normotensive type 2 diabetics with microalbuminuria and dyslipidemia was associated with a reduction in urinary albumin excretion;\textsuperscript{14} results of this study were similar to the present study. In a randomized, double-blind study, the effect of rosvastatin or atorvastatin on urinary albumin excretion was determined in type 2 diabetic patients with dyslipidemia for 16 weeks, yet no significant change from baseline in urinary albumin excretion was detected for either treatment group.\textsuperscript{15} Similar to previous research findings, Atthobari \textit{et al.},\textsuperscript{16} in a 4-year clinical trial using pravastatin, reported no significant reduction in urinary albumin excretion in the studied patients; in their concurrent observational study, a rise in urinary albumin excretion was found, particularly in the cases who received statins for a longer amount of time and in higher doses; results of this study were similar to the present study.

Apart from the differences among studied populations and the type of statin used in the above-mentioned works, later cellular research evaluating the possible mechanism by which statins affect the kidney function has revealed significant results. In contrast to earlier clinical findings supporting the role of statins in the reduction of urinary albumin excretion, a cellular study of human kidney
tubules proposed that statins have the potential to inhibit albumin uptake by the human proximal nephron as a result of the inhibition of HMG-CoA reductase in the proximal tubule cells. These results are similar to the results of another study using opossum kidney cells.\textsuperscript{14,17} Based on a meta-analysis of randomized trials, statins may be renoprotective.\textsuperscript{6,18} Despite the possibility of an increase in protein excretion using statins, it seems that the application of these drugs may be associated with less inflammation, endothelial dysfunction, and tubulointerstitial fibrosis. Statins may thus be associated with renal protection, in spite of increased protein excretion, and may provide an example of a class of drugs that confers renal protection despite increased proteinuria.\textsuperscript{19} In addition, the duration of statin therapy has also been proposed as a factor that may influence the proteinuria level changes; for example, in a study of 56 patients with chronic kidney disease, proteinuria was significantly reduced starting at the 6th month of atorvastatin therapy.\textsuperscript{20} This long duration of therapy is in contrast with our short-term trial.

Our results revealed that short-term lovastatin therapy in patients with T2DN has no significant influence on eGFR. Similarly, the application of simvastatin in type 2 diabetic patients for about 1 year showed no significant change in eGFR.\textsuperscript{13} Using other types of statin drugs, rosuvastatin and atorvastatin, in type 2 diabetic patients for 16 weeks had no effect on patients’ eGFR.\textsuperscript{5} In a large-scale, long-term, prospective, and post-marketing surveillance study of hypercholesterolemic patients treated with pitavastatin, an increase in eGFR was noted after 104 weeks of statin therapy.\textsuperscript{21} The baseline eGFR of patients in this study was <60 mL/min/1.73 m\textsuperscript{2}, in which compared to our research, patients’ eGFR was more than 30 mL/min/1.73 m\textsuperscript{2}. Another difference was observed between our study and a pitavastatin studies, in which eGFR was assessed using the new Japanese revised equation; in contrast, the MDRD formula was used in our research.\textsuperscript{22}The studied populations in our evaluation only included type 2 diabetic patients; however, hypercholesterolemic patients, including cases with or without DM, hypertension, heart disease, or proteinuria, were also included in the pitavastatin trial. In the pitavastatin trial, a weak correlation was observed between the change in the eGFR and that of the serum HDL-C following treatment ($P = 0.013$, $r = 0.092$). This change was attributed to the antioxidant effects of HDL-C.\textsuperscript{23} Although we neither observed any significant change in our studied patients’ proteinuria or eGFR after short-term lovastatin therapy nor any correlation between the change in the eGFR or that of serum HDL-C following statin therapy, we found a reverse linear correlation between the change in the HDL-C level and the change in the 24 h urine protein level (mg/day) after 90 days of lovastatin therapy ($P = 0.007$, $r = -0.484$). This also may be related to the antioxidant and anti-inflammatory effects of HDL-C. It is known that HDL-C has potent anti-inflammatory properties, and a reduction in the anti-inflammatory effects of HDL-C is observed in conditions such as the acute phase response, obesity, and chronic inflammatory diseases. Specifically, patients with ESRD and Alzheimer’s disease have been reported to exhibit such reduced effects of HDL-C.\textsuperscript{24,25} Serum amyloid A (SAA), a proinflammatory molecule, has been used proposed as the major culprit behind the reduced anti-inflammatory effects of HDL-C as SAA was often used to enrich HDL-C during ESRD. This is a novel finding as a similar mechanism may be responsible for patients with T2DN.\textsuperscript{24} The differences between the results of the pitavastatin therapy and the present study seem to be related to differences in the type and dosage of statin used, the treatment duration, and patients’ characteristics. Although recent data suggest that HDL-C particles dysfunction occurs in DM, and probably statin consumption improves urinary protein excretion secondary to the reduction of inflammatory factors in the serum. However, more conclusive studies are required in order for any reliable judgment to be made.\textsuperscript{26}

Thirty days after the cessation ofLovastatin in our study, patients’ mean levels of cholesterol, TG, LDL-C, and HDL-C returned to their pre-lovastatin therapy levels. This is an important clinical point indicating that statin therapy for DM type 2 patients may not be stopped unless another negative side effect on patients is observed.

Although we had fewer subjects compared with many similar studies\textsuperscript{15,21} with the exception to the Tonolo et al.\textsuperscript{13} study, we applied extremely strict criteria for patient selection. As a result, our cases had more uniform clinical characteristics at the start of the trial. As the first study of its kind in Iran, our study on the effects oflovastatin on the renal function of patients with type 2 DM showed that this low-cost statin has no negative effect on renal function, eGFR, and proteinuria. Our results may be of particular importance to the patients in developing countries with a limited budget and for whom more potent and newer products of statins are not obtainable. Although no renoprotective effect oflovastatin on proteinuria and eGFR in type 2 DM patients was observed in this research, no damaging and destructive effect on renal function was revealed either.

There was no dose titration for patients receivingLovastatin in our study; this may influence proteinuria levels as some studies have highlighted the dose titration effect on their patients.\textsuperscript{15} Based on former studies, taking ACEI or ARB drugs for BP control or renoprotection in DM type 2 cases may Influence the pure effect of statins on renal function.\textsuperscript{21} We did not differentiate our subjects in terms of who does or does not receive this class of drugs.

Furthermore, proteinuria is at least possible with all statins at some concentration but is more likely to be seen with statins that are more potent inhibitors.
of HMG-CoA reductase.\textsuperscript{27,28} As mentioned before, statin-induced proteinuria is not associated with either renal impairment or renal failure.\textsuperscript{19,27} Putting all these results together with our findings, which showed no change in proteinuria levels or eGFR after lovastatin therapy, we concluded: Although statin therapy, especially with more potent HMG-CoA inhibitors, can cause proteinuria in some studies, it seemed that statin-induced proteinuria did not cause any renal damage and is reflected in the lack of change in eGFR after starting statin therapy.

Limitations of the present study were that kidney biopsy was not done in these patients to establish the diagnosis of DN and the possibility of including a patient with non-DN/kidney disease cannot be completely ruled out.

**CONCLUSIONS**

Short-term lovastatin therapy did not show any change in proteinuria or eGFR levels in patients with T2DN although changes of proteinuria levels significantly correlated with HDL levels. In other words, lovastatin may be prescribed with safety for T2DN patients with definite indication for statin therapy and risk of renal problems.

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**Conflicts of interest**

There are no conflicts of interest.

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