ORIGINAL ARTICLE

Effects of atorvastatin on proteinuria of type 2 diabetic nephropathy in patients with history of gestational diabetes mellitus: A clinical study

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ABSTRACT

Background: Gestational diabetes is known as one of the diseases through pregnancy. In the present study, changes in proteinuria after atorvastatin administration among patients with history of gestational diabetes were studied. **Materials and Methods:** In this randomized clinical trial, 42 patients were included in the study. Atorvastatin was administered for 21 patients, and 21 patients were designated as control group. Lipid profile, protein, and 24 h urine creatinine (uCr) levels were determined in the beginning and 3 months after intervention. $P < 0.05$ was considered statistically significant. **Results:** Lipid profile in intervention group was enhanced; low-density lipoprotein (LDL) had decreased while triglyceride had not changed and high-density lipoprotein had been increased. There was no statistically significant change in serum Cr, serum urea, estimated glomerular filtration rate, uCr, urine volume, 24-h urine protein level, or urine protein/Cr ratio on both groups during the study; also, there was no statistically significant difference between groups. **Conclusions:** Although LDL level decreased after atorvastatin therapy, atorvastatin therapy had no effect on the level of proteinuria or other parameters related to kidney function.

Key words: Atorvastatin, gestational diabetes, nephropathy, proteinuria

INTRODUCTION

Gestational diabetes, which is defined as impaired tolerance to glucose, is a known risk factor for type 2 diabetes mellitus (DM) and always gynecologists and endocrinologists have tried to control it. Although most of the gestational diabetes cases undergo a remission after delivery, some patients do not. Nephropathy in diabetic patients is defined by hypertension, albuminuria, and a decline in glomerular filtration rate (GFR).[1] This is induced by prolonged glomerular hyperfiltration accompanying progressive increase in protein excretion induced by diabetic state. Leading cause of end-stage renal disease in many countries is diabetes.[2-4] Estimated prevalence of diabetes in the world is about 6.5% and also it has been declared that there will be a 69% increase in numbers of people with diabetes in developing countries and a 20% increase in developed countries.[5,6] Hence, preventing diabetic nephropathy has always been a field of interest for clinicians and researchers.

Glomerulosclerosis is the main event in the pathogenesis of diabetic nephropathy.[7] Dyslipidemia and hyperinflammatory status and increased oxidative stress are of the factors contributed to the progression of glomerulosclerosis.[8-10] Dyslipidemia as a contributing

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factor contributing in diabetic nephropathy is present in many patients with type 2 diabetes, and it has been a goal of therapy to subside progression of glumerosclerosis.[11-14]

3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor agents (statins) are one of the most common and used medications for dyslipidemia.[15] In addition, it has been already shown that statins reduce both total mortality and cardiovascular mortality in patients without end-stage renal diseases.[16] In a study, it was shown that statins do not affect renal function as measured by creatinine (Cr) clearance but reduces protein excretion in urine among patients with chronic renal diseases; meanwhile, statins are proved to be safe among these patients.[17-19] In another study, systematic review of 27 randomized trials suggested that statins reduce the rate of kidney function loss by 1.2 ml/min/year.[20] Another study had concluded that statins reduce albuminuria by 47% in people with >300 mg/24 h of albumin excretion at baseline. However, statins did not significantly influence urinary albumin excretion when baseline levels were <30 mg/24 h.[21]

Considering this issue, in the present study, effect of atorvastatin as a well-known statin was investigated in patients with diabetic nephropathy with history of gestational diabetes by examining proteinuria and renal function.

MATERIALS AND METHODS

Patients and settings

The current study was conducted in Educational-Medical Centers of Tabriz University of Medical Sciences (Tabriz, Iran) from January 2014 to January 2016. After primary laboratory and clinical evaluations, 50 women with documented type 2 diabetic nephropathy and history of gestational diabetes were included in the study. Then, patients who were 20–65 years old with type 2 DM and proteinuria levels lower than <3 g/d (nephrotic range) and estimated GFR (eGFR) >30 mL/min/1.73 m^2 (as calculated by the Modification of Diet in Renal Disease [MDRD] formula) were also included in the study.[22] Informed consent was filled by participants, which was approved by the Tabriz University of Medical Sciences Ethics Committee; also, this consent was in compliance with the Helsinki Declaration. This study was registered in Iranian Registry of Clinical Trials(IRCT2016100918946N4).

Diabetic states of patients were controlled using insulin injection or oral anti-diabetic agents. Blood pressure was controlled using angiotensin receptor blockers and/or angiotensin-converting enzyme inhibitors and diuretics when needed, and blood pressure was kept <130/90 mmHg. All participants were under provision of a nutrition consultant and maintained a regular low-protein diet. Exclusion criteria included the use of fibrates, statins antagonists, aspirin, allopurinol, β-blockers, pentoxifylline, fish oil, other antioxidant drugs consumption in the past 6 months, active smoking, active coronary artery disease in the previous 6 months, diabetic foot, hepatitis, and poorly controlled diabetes (HbA1c >7.5%).

Finally, data from 50 patients with type 2 diabetic nephropathy and history of gestational diabetes were analyzed in this study (power 0.80 and significance 0.05), while eight were excluded from the study due to the uncooperativeness (four patients), Vitamin C intake during the intervention period (one patient), smoking during the intervention period (one patient), and development of end-stage renal disease (two patients). Using RandList software (version 1.2, DatInf GmbH, Tubingen, Germany), patients were divided into two groups randomly: one group receiving atorvastatin and the other group receiving placebo.

Study protocol

Atorvastatin 10 mg (Atorva©, NJ, USA) per day was administered to the patients in intervention group for 90 days. At the end of the 3rd month, the patients were asked to stop atorvastatin intake for a month. Meanwhile, for control group, exact protocol was administered using placebo instead of atorvastatin. Laboratory tests including lipid profile and uric acid level were performed in two stages: before intervention (baseline) and 90 days after intervention (91st day).

Blood sampling

Blood samples were obtained after 8 h of fasting in the morning before breakfast in sterile tubes. Then, they were centrifuged at 3000 rpm for 10 min at 4°C and then stored at −79°C until assayed.

Laboratory analysis

Serum levels of fasting blood sugar (FBS), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and triglyceride were determined using an automated chemical analyzer (Abbott analyzer, Abbott Laboratories, Abbott Park, Chicago, IL, USA). Then, low-density lipoprotein cholesterol (LDL-C) levels were calculated using the Friedewald equation.[23]

Jaffe method and glutamate dehydrogenase were used to calculate serum Cr (sCr) and urea levels, respectively.[24,25] Twenty-four hour urine samples were collected, and Cr and protein levels were assessed using colorimetric and immunoturbidimetric methods. eGFR was calculated using the MDRD formula.[22]

Statistical analyses

Statistical analyses were performed using the SPSS software package version 16 (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 was 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 participants was 57.64 ± 7.33 years in intervention group (45–68 years) and 58.88 ± 6.39 years in control group (45–68 years). The mean duration of DM was 9.76 ± 3.11 years (5–15 years) in intervention group and 8.89 ± 4.21 years in control group. The mean systolic and diastolic blood pressures at the beginning of the study were 121.68 ± 10.12 mmHg and 77.86 ± 4.12 mmHg in intervention group and 125.66 ± 12.52 mmHg and 75.65 ± 5.49 mmHg, in control group, respectively. These differences between two groups were not statistically significant.

Measured FBS and lipid profile in both groups are shown in Table 1; TC and LDL-C levels were reduced in intervention group statistically significant, and HDL-C after the intervention was increased statistically significant; also, this difference was statistically significant when it was compared to control group. These changes in control group were not seen. A comparison of baseline sCr, urea, eGFR, 24-h urine protein level, urine Cr (uCr), and protein/Cr ratio and values in 90th day is shown in Table 2. Subsequent analysis did not show any significant change during this period in both groups.

DISCUSSION

In the present study, although there was a significant reduction in TC and LDL-C, as well as a statistically significant increase in HDL-C, no other statistically significant changes in FPG, sCr, serum Urea, eGFR, uCr, urine volume, 24-h urine protein level, or urine protein/Cr ratio were detected after atorvastatin therapy period.

Based on the present study, there is a controversy in results about urinary protein excretion levels and statin therapy in different studies. In the present study, there is no effect of atorvastatin therapy on urinary albumin excretion levels, in contrast to previous researches.

In a study by Nakamura *et al*., normotensive type 2 DM with microalbuminuria and dyslipidemia were treated with cerivastatin therapy which was associated with a significant reduction in urinary albumin excretion.[26] In another study by Tonolo *et al*., administering simvastatin therapy on normotensive microalbuminuric hypercholesterolemic type 2 diabetic patients, urinary albumin excretion rate compared to the basal rate had decreased about 25%.[27] Interestingly, in a study by Atthobari *et al*., pravastatin was reported not only to have no significant reduction in urinary albumin excretion but also to rise in urinary albumin excretion, particularly in the patients who received statins for a longer amount of time and in higher doses.[28] In contrast to mentioned clinical findings supporting the role of statins reducing the urinary albumin excretion, a study by Campese *et al*. concluded that statins have the potential

Table 1: Changes in fasting blood glucose and lipid profile; a comparison between baseline and 90th day values in both groups

	Baseline			90th day			*P*	
	Intervention group	Control group	*P*	Intervention group	Control group	*P*	Intervention group	Control group
FBS (mg/dl)	169.12±55.62	174.18±53.25	0.76	158.12±42.33	170.48±48.87	0.38	0.47	0.81
TC (mg/dl)	210.11±52.23	206.58±72.82	0.85	152.45±62.69	195.77±72.57	0.04	0.002	0.63
LDL-C (mg/dl)	119.86±42.08	125.91±38.69	0.63	79.87±24.88	110.31±38.86	0.004	0.0006	0.19
HDL-C (mg/dl)	36.25±15.89	41.09±18.12	0.36	45.49±10.15	38.20±17.84	0.11	0.03	0.60
TG (mg/dl)	188.56±68.41	192.25±70.31	0.86	140.28±42.91	181.64±65.11	0.019	0.009	0.91

FBS – Fasting blood sugar; TC – Total cholesterol; TG – Triglyceride; HDL-C – High-density lipoprotein-cholesterol; LDL-C – Low-density lipoprotein-cholesterol

Table 2: Changes in serum creatinine, serum urea, estimated glomerular filtration rate, urine creatinine, urine volume, 24-h urine protein level, and urine protein/creatinine ratio; a comparison between baseline and 90th day values in both groups

	Baseline			90th day			*P*	
	Intervention group	Control group	*P*	Intervention group	Control group	*P*	Intervention group	Control group
sCr (mg/dl)	1.78±0.91	1.75±0.86	0.91	1.73±1.05	1.77±0.95	0.89	0.86	0.94
Urea (mg/dl)	59.22±25.58	61.57±29.54	0.78	53.81±19.89	59.32±33.58	0.52	0.44	0.81
uProtein (mg/day)	936.29±448.95	786.59±569.56	0.34	882.71±598.53	812.36±602.89	0.7	0.74	0.88
uVolume (ml/day)	2215.84±865.52	1996.65±975.58	0.44	2308.25±1012.55	2015.89±982.57	0.34	0.75	0.94
uCr (mg/day)	1128.29±368.36	1289.75±401.59	0.18	1236.89±528.75	1349.64±485.54	0.47	0.71	0.66
Protein/Cr ratio	0.83±0.29	0.79±0.35	0.68	0.78±0.38	0.81±0.22	0.75	0.63	0.82
eGFR	72.41±34.59	71.85±36.89	0.95	70.85±39.73	72.93±37.82	0.86	0.89	0.92

sCr – Serum creatinine; Urea – Serum urea level; uProtein – 24 h urine protein level; uCr – 24 h urine creatinine level; uVolume – 24 h urine volume; eGFR – Estimated glomerular filtration rate; Cr – Creatinine

to inhibit albumin uptake by the human proximal nephron, as a result of the inhibition of HMG-CoA reductase in the proximal tubule cells.[29]

Although statin use is associated with an increase in protein excretion, it has been proved that the application of statins may lead to decreased inflammation, improved endothelial dysfunction, and inhibition of tubulointerstitial fibrosis.[20,30,31] In addition, duration of statin therapy is proposed as a factor that may influence the proteinuria level changes; in a study by D'Amico on patients with chronic kidney disease, following atorvastatin therapy, proteinuria was significantly reduced starting at the 6th month.[32] In the present study, atorvastatin therapy was used in a short-term method.

According to results of the present study, short-term atorvastatin therapy in patients with type 2 diabetes with history of gestational diabetes has no significant influence on eGFR. Similarly, in a study by Tonolo *et al*., simvastatin therapy in type 2 diabetic patients for 1 year showed no significant change in eGFR.[27] In a large-scale, long-term, prospective postmarketing surveillance study of hypercholesterolemic patients treated with pitavastatin, an increase in eGFR was noted after 104 weeks of statin therapy.[33] In the present study, we did not observe any significant change in our studied patients' proteinuria or eGFR after short-term atorvastatin therapy.

In the present study, extremely strict criteria for patient selection were designated. Hence, our patients at the start of the study had uniform clinical characteristics. As the first study of its kind in Iran, our study on the effects of lovastatin 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 of lovastatin on proteinuria and eGFR in type 2 diabetic patients with history of gestational diabetes was observed in this research, no damaging and destructive effect on renal function was revealed either.

Unfortunately, in the present study, dose titration for patients receiving atorvastatin was not performed; this may lead to proteinuria levels as some studies have highlighted the dose titration effect on their patients.[34] Based on former studies, taking angiotensin-converting enzyme inhibitor or angiotensin receptor blocker drugs for blood pressure control or renoprotection in type 2 DM cases may influence the pure effect of statins on renal function.[33] No differentiation of patients in terms of who does or does not receive this class of drugs was performed.

Finally, although proteinuria is at possible with all inhibitors of HMG-CoA reductase at some concentration, it is more likely to be seen with statins that are more potent inhibitors of HMG-CoA reductase.[35,36]

CONCLUSIONS

Short-term atorvastatin therapy did not show any change in proteinuria or eGFR levels in patients with type 2 diabetes with history of gestational diabetes. In other words, atorvastatin may be prescribed with safety for patients with type 2 diabetes with a history of gestational diabetes with the risk of renal problems and definite indication for statin therapy.

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Conflicts of interest

There are no conflicts of interest.

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