ORIGINAL ARTICLE

Effect of sitagliptin on proteinuria in patients with type 2 diabetes – A renoprotective effect of sitagliptin

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Background: Diabetic nephropathy, the leading cause of chronic renal failure, is related to diabetes poor control. Some antihyperglycemic drugs like dipeptidyl peptidase-4 inhibitors have shown to prevent diabetic nephropathy. This study endeavors to assess the effect of sitagliptin on proteinuria in Iranian type 2 diabetics. **Materials and Methods**: A total of 90 type 2 diabetic patients aged between 30 and 80 years with glycated hemoglobin (HbA1C) <8.5 and normotensive under treatment of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers were randomly assigned into two groups. One group received 50 mg sitagliptin per day and the other group received placebo. The two groups were evaluated for albumin–creatinine ratio (ACR) and estimated glomerular filtration rate (eGFR) at baseline and 3 months later. **Results:** Eighty-four patients, 38 (45%) males and 46 (55%) females, were enrolled in this study. The mean age was 58.47 ± 7.33. The two groups did not differ in baseline characteristics. After 3 months, in the sitagliptin group, HbA1C (7.89 ± 0.39 to 7.37 ± 0.61, $P < 0.001$), fasting blood sugar (FBS) (136.86 ± 22.51 to 130.53, $P = 0.04$), systolic blood pressure (BP) (124.39 ± 9.70 mmHg to 119.32 ± 9 mmHg), diastolic BP (76.44 ± 6.53 to 73.13 ± 5.34 mmHg, $P < 0.001$), and ACR (314.40 ± 414.64 to 293.49 ± 400.71, $P < 0.001$) were significantly decreased and eGFR was significantly increased (73.35 ± 10.73 to 76.86 ± 10.59, $P < 0.001$) at 3 months compared to the placebo group. ACR reduction was higher in macroalbuminuric (Ma) patients compared to microalbuminuric (Mi) patients in the sitagliptin group (−30.25 ± 35.57 vs. −11.12 ± 14.01, $P = 0.02$). No significant difference was observed between the Ma and Mi subgroups regarding changes in eGFR. Univariate analysis showed that changes in ACR correlated with FBS ($r = 0.68$, $P < 0.0001$), insulin ($r = 0.44$, $P = 0.03$), and homeostatic model assessment for insulin resistance ($r = 0.69$, $P < 0.0001$) and did not correlate with eGFR and BP. **Conclusion:** In conclusion, sitagliptin is a well-tolerated drug that improves glycemic control, lowers BP, and reduces urinary albumin excretion, especially in Ma type 2 diabetic patients.

Key words: Nephropathy, sitagliptin, type 2 diabetes

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INTRODUCTION

Incidence and prevalence of diabetes mellitus (DM) has dramatically risen in both developed and developing countries. It is estimated to be 4.4% by 2030 for all age groups worldwide.[1]

Due to its high prevalence, diabetes and its complications impose a huge financial burden on the society. It is well established that diabetic nephropathy is the leading cause of end-stage renal disease, and a risk factor for cardiovascular mortality in diabetic patients; thus, it increases the risk of mortality in these patients.[2-5] A great majority of the patients diagnosed with diabetes have already been affected on average, up to 10 years prior to diagnosis, and approximately 7% of the patients diagnosed with type 2 diabetic already suffer from albuminuria.[6] Diabetic renal disease, one of

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the most disabling complications of the disease, is strongly associated with poor diabetic control.[7] Studies reported that in patients with type 2 diabetes, the annual mortality rate was 45.7/1000 in microalbuminuric (Mi) patients and 80.8/1000 among those with microalbuminuria.[8] In other words, macroalbuminuria was associated with a 2.2-fold increased risk of cardiovascular death. Hyperglycemia induces microvascular adverse effects through diverting multiple metabolic pathways including: (1) activating protein kinase-c pathway, (2) overproducing reactive oxygen species, (3) increasing production of advanced glycation end products, (4) increasing polyol pathway activity, and (5) enhancing hexosamine biosynthesis pathway that leads to mesangial expansion.[9] In tandem, all of these reactions ultimately lead to glomerular sclerosis and diabetic nephropathy.

Blood pressure (BP) and glycemic control represent the major cornerstones for preventing and treating diabetic nephropathy.[10,11] The United Kingdom Prospective Diabetes Study demonstrated that good diabetic control, which decreases glycated hemoglobin (HbA1C) from 7.9 to 7, has a key role in prevention of diabetic nephropathy.[12] In a similar study, decreasing HbA1C to 6.5 was associated with slower progression of microalbuminuria and renal adverse events.[13] Although many studies support the role of glycemic control in prevention of renal adverse events, the choice of antihyperglycemic agents to achieve these goals remains controversial.

Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, is a rather new and well-tolerated drug for treatment of type 2 DM. DPP-4 inhibitors hinder rapid degradation of circulating glucagon-like peptide-1 (GLP-1), and consequently increase plasma concentration of endogenous GLP-1, which leads to enhancing its incretin effect.[14,15]

The main target of GLP-1 is the pancreatic β-cell where it promotes insulin secretion in the absence of hypoglycemia or weight gain, and inhibits glucagon secretion.[16] GLP-1 receptors are also expressed in glomerular endothelial cells in kidney.[17] Based on animal models, DPP-4 inhibitors have been effective for management of diabetic renal disease through inactivation of DPP-4.[18,19] Some studies have demonstrated the effect of DPP-4 inhibitors on albuminuria in type 2 DM patients, but their efficacy has not yet been proven in humans.

Recent studies have also demonstrated that the therapeutic effect of DPP-4 inhibitors may not solely be mediated by direct action of endogenous GLP-1. Other neuropeptides, incretin hormones, and also other pathways such as the gut-brain and brain-periphery axes might contribute to glucose-lowering effect of DPP-4I.[20-22]

A pioneering study conducted by Hattori is the first one that assessed the effects of GLP-1 (sitagliptin) on human renal endothelial cells.[23] This study revealed that sitagliptin is able to diminish albuminuria by lowering blood glucose, and controlling BP without reducing glomerular filtration rate (GFR). Similar studies showed that sitagliptin could reduce urine albumin-to-creatinine ratio (ACR), and also decrease HbA1C, body mass index (BMI), and BP.[24-26] The present study is a randomized controlled double-blind clinical trial that aims to assess the effect of sitagliptin on albuminuria in Iranian population with type 2 diabetes.

MATERIALS AND METHODS

The present study was a double-blind randomized controlled trial performed on type 2 diabetic patients in Isfahan Endocrine and Metabolism Research Center. This study was approved by the Ethics Committee of the Medical University of Isfahan, and it was registered in Iranian Registry of Clinical Trials (IRCT20201028049174N1). Ninety patients who met the study's inclusion criteria (age, between 30 and 80 years, 7.5< HbA1C <8.5, GFR >60, BP <140/90 under treatment with angiotensin-converting enzyme inhibitors or angiotensin receptor blocker (ARB) antihypertensive drugs for at least 6 months) were selected using convenience sampling method and signed written informed consent for participating in the study. The patients who were pregnant, had a history of malignancy, severe liver disease, psychosis, urinary tract infection, uncontrolled BP, heart failure, and DPP4 intolerance were excluded from the study. The participants were randomly divided into two groups: the treatment group who were treated with 50 mg sitagliptin per day for 3 months and the control group who received placebo.

Patients of both the groups were assessed for weight, systolic BP (SBP), diastolic BP, fasting blood sugar (FBS), HbA1C, blood urea nitrogen, creatinine, estimated glomerular filtration rate (eGFR), triglyceride (TG), cholesterol (CHOL), low-density lipoprotein (LDL), high-density lipoprotein (HDL), insulin, aspartate aminotransferase, alanine aminotransferase, uric acid, ACR, and homeostatic model assessment for insulin resistance (HOMA-IR) at the beginning of the study and at 3 months thereafter. Avoiding possible influences on BP, lipid, and glucose metabolism, no changes were made to the type and dose of glucose-lowering drugs, angiotensin--converting enzyme inhibitors, and ARBs during the study period.

Data were analyzed both descriptively and inferentially using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). Numerical variables were compared between the two groups using paired sample *t*-test for normally distributed

variables, and Wilcoxon signed-rank test for variables that were not normally distributed. To compare variables before and after treatment in each group, we used independent *t*-test or ANCOVA test when data were normally distributed, and Mann–Whitney test when they were not normally distributed. Categorized variables were compared using Chi-square or Fisher's exact test. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 84 patients were enrolled consecutively in our study. Thirty-eight (45%) were male and 46 (55%) were female, and the mean age of patients was 58.47 ± 7.33 years. There was no significant difference between the two groups regarding sex and age ($P = 0.81$ for sex and $P = 0.59$ for age). The mean duration of diabetes was 14.65 ± 3.2 years. The average of HbA1C in the treatment and control groups was 7.89 ± 0.39 and 7.79 ± 0.30, respectively. The mean FBS was 136.86 ± 22.51 mg/dl in the treatment group and 142.60 ± 17.60 mg/dl in the control group. Furthermore, the mean BMI was 27.98 ± 3.57 in the treatment group, and 28.76 ± 4.67 in the control group ($P = 0.38$).

Table 1 shows a comparison of baseline characteristics between the two groups. The two groups were similar regarding age, sex, duration of diabetes, body weight, FBS, HbA1C, lipid profile, BP, eGFR, ACR, and HOMA-IR at baseline. No significant differences were observed between the two groups regarding the body weight, TG, and CHOL 3 months after treatment [Table 2]; however, LDL CHOL was significantly higher in the control group ($P = 0.013$), and HDL was decreased significantly in the control group ($P = 0.001$). Other variables were significantly different between the two groups after 3 months. The control group had higher FBS ($P = 0.016$) and HbA1C ($P < 0.001$) compared to the sitagliptin group. Both SBP and diastolic BP were also significantly higher in the control group than the sitagliptin group ($P = 0.005$ and $P < 0.001$, respectively). ACR decreased more in the sitagliptin group compared to the control group ($P = 0.001$).

The control group showed no change in body weight, FBS, HbA1C, TG, LDL, BP, eGFR, and HOMA-IR after 3 months, but a significant reduction was observed in CHOL (from 176.87 ± 30.50 at baseline to 163.95 ± 34.75 at 3 months, $P = 0.03$) and HDL (from 44.22 ± 8.28 to 41.63 ± 7.41, $P = 0.01$) and significant increase in ACR (from 298.73 ± 427.42 to 299.96 ± 425.70). Conversely, at 3 months after treatment, the changes in BP, FBS, HbA1C, GFR, CHOL, LDL, ACR, and HOMA-IR level were significant in the sitagliptin group. SBP fell from 124.39 ± 9.70 mmHg at baseline to 119.32 ± 9 mmHg at 3 months and diastolic BP level fell from 76.44 ± 6.53 to 73.13 ± 5.34 mmHg ($P < 0.001$). In addition, FBS was decreased from 136.86 ± 22.51 to 130.53 ± 26.83 ($P = 0.04$), and HbA1C declined from 7.89 ± 0.39 to7.37 ± 0.61 ($P < 0.001$). eGFR significantly increased from 73.35 ± 10.73 at baseline to 76.86 ± 10.59 at 3 months ($P < 0.001$). Moreover, ACR decreased from 314.40 ± 414.64 to 293.49 ± 400.71 ($P < 0.001$) and HOMA-IR declined from 4.06 ± 2.14 to 3.28 ± 2.15 ($P < 0.001$). We found no significant changes in body weight, TG, and HDL in the sitagliptin group 3 months after the treatment [Table 2].

We also divided each group into two subgroups of microalbuminuria (30–299 mg) and macroalbuminuria (≥300 mg) according to the baseline urinary albumin excretion level. The significant decrease in ACR level occurred in both the subgroups of the sitagliptin group (in the macroalbuminuria group from 527.01 ± 491.28 at baseline to 496.76 ± 477.77 at 3 months, $P = 0.001$, and in the microalbuminuria group from 91.67 ± 70.51 to 80.54 ± 66.81, $P = 0.002$, Table 3. Moreover, urinary albumin excretion

Table 1: Demographic and baseline characteristics of two groups. BMI, body mass index; SYS BP, systolic blood pressure; DIA BP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen; Cr, creatinine; HOMA-IR, homeostasis assessment model of insulin resistance; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; ACR, Albumin creatinine ratio.

	sitagliptin	control	*P*
Sex (male/female)	20/23	18/23	0.81
Age (years)	58.04±7.27	58.90±7.40	0.59
Weight (kg)	71.24±7.07	73.00±8.48	0.30
BMI (kg/m2)	27.98±3.57	28.76±4.67	0.38
Duration (years)	14.39±3.59	14.91±2.76	0.45
SYS BP (mmHg)	124.39±9.70	128.92±7.85	0.13
DIA BP (mmHg)	76.44±6.53	78.04±5.63	0.22
FBS (mg/dl)	136.86±22.51	142.60±17.60	0.47
HbA1C(%)	7.89±0.39	7.79±0.30	0.14
BUN (mg/dl)	31.00±6.98	32.20±5.57	0.67
Cr (mg/dl)	1.01±0.13	1.01±0.15	0.72
eGFR	73.35±10.73	72.66±7.75	0.59
TG (mgldl)	132.76±4036	140.65±32.88	0.38
CHOL (mg/dl)	177.62±31.87	176.87±30.50	0.74
LDL (mg/dl)	92.31±21.99	88.94±17.28	0.51
HDL (mg/dl)	44.32±8.68	44.22±8.28	0.85
INSULIN	12.21±6.00	12.10±4.77	0.97
AST	20.81±9.00	21.14±9.23	0.56
ALT	23.74±11.02	25.82±13.77	0.98
URICACID	4.61±0.99	4.93±0.89	0.81
ACR	314.40±414.64	298.73±427.42	0.98
HOMA-IR	4.06±2.14	4.35±2.29	0.56

was significantly reduced in the macroalbuminuria subgroup in comparison to the microalbuminuria subgroup (−30.25 ± 35.57 vs. −11.12 ± 14.01, $P = 0.02$). No significant changes were observed in ACR of the two subgroups of the control group (microalbuminuria group: $P = 0.11$ and macroalbuminuria group: $P = 0.88$) at

Table 2: Comparison of body weight, glucose, lipid profile, and renal function in each group and between the two groups at baseline and after three months of sitagliptin consumption. SYS BP, systolic blood pressure; DIA BP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen; Cr, creatinine; HOMA-IR, homeostasis assessment model of insulin resistance; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; ACR, Albumin creatinine ratio

	Sitagliptin			Control			*P*
	Before	After	*P*	Before	After	*P*	
Weight	71.24±7.07	71.30±6.92	0.69	73.00±8.48	72.93±8.52	0.65	0.3
SYSBP	124.39±9.70	119.32±9.10	<0.001	128.92±7.85	127.31±10.13	0.18	0.005
DIABP	76.44±6.53	73.13±5.34	<0.001	78.04±5.63	78.29±7.71	0.75	<0.001
FBS	136.86±22.51	130.53±26.83	0.04	142.60±17.60	148.17±30.59	0.23	<0.016
HbA1C	7.89±0.39	7.37±0.61	<0.001	7.79±0.30	7.80±0.67	0.87	<0.001
BUN	31.00±6.98	30.00±5.62	0.16	32.20±5.57	33.49±8.26	0.17	0.025
Cr	1.01±0.13	0.96±0.12	<0.001	1.01±0.15	0.97±0.16	0.04	0.49
eGFR	73.35±10.73	76.86±10.59	<0.001	72.66±7.75	73.52±9.24	0.31	0.01
TG	132.76±4036	128.83±46.67	0.37	140.65±32.88	140.65±45.47	1	0.45
CHOL	177.62±31.87	159.62±29.94	0.05	176.87±30.50	163.95±34.75	0.03	0.25
LDL	92.31±21.99	82.55±14.72	<0.001	88.94±17.28	86.49±16.94	0.23	0.013
HDL	44.32±8.68	44.51±7.15	0.77	44.22±8.28	41.63±741	0.01	0.001
INSULIN	12.21±6.00	9.88±5.24	<0.001	12.10±4.77	12.10±4.70	1	<0.001
AST	20.81±9.00	20.74±7.14	0.23	21.14±9.23	20.48±8.41	0.20	0.89
ALT	23.74±11.02	20.12±9.49	<0.001	25.82±13.77	25.63±12.56	0.21	0.02
URICACID	4.61±0.99	3.99±0.81	<0.001	4.93±0.89	4.74±0.90	0.02	<0.001
ACR	314.40±414.64	293.49±400.71	<0.001	298.73±427.42	299.96±425.7	0.02	<0.001
HOMA-IR	4.06±2.14	3.28±2.15	<0.001	4.35±2.29	4.52±2.24	0.53	<0.001

Table 3: Comparison of body weight, glucose, and lipid profile, and renal function in each subgroup and between the two subgroups of microalbuminuric patients three months after treatment. SYS BP, systolic blood pressure; DIA BP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen; Cr, creatinine; HOMA-IR, homeostasis assessment model of insulin resistance; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; ACR, Albumin creatinine ratio

	Sitagliptin			control			*P*
	Before	After	*P*	Before	After	*P*	
Weight	71.80±6.66	71.57±6.42	0.29	72.95±9.89	72.97±9.96	0.90	0.78
SYSBP	125.47±9.34	119.90±8.55	0.004	127.09±8.54	127.50±11.92	0.78	0.08
DIABP	75.52±6.76	72.85±5.14	0.03	77.04±5.71	77.50±8.12	0.64	0.02
FBS	136.00±24.41	130.28±21.36	0.11	143.36±19.86	148.36±37.57	0.75	0.12
HbA1C	7.81±0.32	7.39±0.52	<0.001	7.79±0.30	7.75±0.69	0.53	0.014
BUN	30.84±7.76	30.21±5.61	0.58	30.87±4.86	33.10±9.66	0.16	0.14
Cr	1.01±0.11	0.95±0.09	0.001	0.99±0.14	0.93±0.16	0.04	0.90
eGFR	72.59±11.14	76.01±10.00	0.001	73.99±7.74	75.69±9.50	0.20	0.33
TG	121.19±38.35	112.23±31.04	0.007	137.59±36.31	134.90±46.16	0.68	0.24
CHOL	177.95±31.12	158.00±27.43	0.001	176.77 32.32	156.23±33.77	0.04	0.78
LDL	91.83±19.78	82.92±12.49	0.002	86.79±20.06	81.41±17.19	0.11	0.69
HDL	45.57±8.26	44.95 6.31	0.58	45.90±8.73	42.00±7.52	0.005	0.027
INSULIN	11.49±5.13	9.56±4.53	<0.001	11.22±3.80	11.06±3.86	0.62	<0.001
AST	19.90±6.43	18.90±5.33	0.39	19.27±7.37	19.13±7.29	0.80	0.79
ALT	20.42 8.14	17.90 7.79	0.045	23.22 10.44	22.54 9.73	0.61	0.137
URICACID	4.60 0.82	3.92±0.66	<0.001	4.96±0.88	4.73±0.95	0.05	<0.02
ACR	91.67±70.51	80.54±66.81	0.002	79.31 57.36	81.97±62.04	0.11	0.001
HOMA-IR	3.80±1.84	3.11 1.72	<0.001	3.92±1.37	4.15±2.37	0.53	0.025

3 months [Table 4]. There were no significant differences between the two subgroups of the control group regarding changes in ACR levels [Table 5].

A significant rise was found in eGFR in both the micro- and macroalbuminuric (Ma) subgroups of the sitagliptin group 3 months after the initiation of treatment (from 72.59 ± 11.14 to 76.01 ± 10.00, $P = 0.001$, in micro- and from 74.08 ± 10.54 to 77.67 ± 11.30 in the macroalbuminuria subgroup) [Tables 3 and 4]. There were no significant differences between the two subgroups of both the sitagliptin and control groups regarding changes in eGFR levels [Table 5].

Univariate regression analysis of the Ma group showed that the change in ACR correlated significantly with the change in FBS ($r = 0.68$, $P < 0.0001$), insulin ($r = 0.44$, $P = 0.03$), HbA1C ($r = 0.36$, $P = 0.09$), and TG ($r = 0.39$, $P = 0.06$). However, the change in ACR did not correlate with change in eGFR and SBP (data not shown).

DISCUSSION

In this study, the effect of treatment with sitagliptin on FBS, HbA1C, BP, ACR, and eGFR was investigated in a group of Iranian adults with type 2 diabetes.

The obtained results indicated that sitagliptin significantly reduced FBS and HbA1C. FBS decreased 6.33 mg (from 136.86 ± 22.51 to 130.53 ± 26.83) and HbA1C decreased 0.52 (from 7.89 ± 0.39 to 7.37 ± 0.61) after 3 months of treatment without changes in body weight. These results corroborated the results of previous studies that evaluated the effects of DPP-4 inhibitors on glycemic control in these patients. As we mentioned earlier, another important factor in development and progression of diabetic nephropathy is hypertension. Several studies revealed that sitagliptin decreased SBP and diastolic BP in diabetic patients. In concordance with results of similar studies, we found that SBP and diastolic BP fell 5.07 mmHg and 3.31 mmHg after 3 months of treatment, respectively, in the sitagliptin group.

Table 4: Comparison of body weight, glucose, lipid profile and renal function in each subgroup and between the two subgroups of macroalbuminuric patients three months after three months. SYS BP, systolic blood pressure; DIA BP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FBS, fasting blood sugar; HbA1c, hemoglobin A1c; BUN, blood urea nitrogen; Cr, creatinine; HOMA-IR, homeostasis assessment model of insulin resistance; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; AST, Aspartate Aminotransferase; ALT, Alanine Aminotransferase; ACR, Albumin creatinine ratio

	Sitagliptin			control			*P*
	Before	After	*P*	Before	After	*P*	
Weight	70.70±7.56	71.04±7.51	0.78	73.05±6.76	72.89±6.74	0.42	0.68
SYSBP	123.36±10.14	118.77±9.77	0.007	131.05±6.57	127.10±7.87	0.04	0.171
DIABP	77.31±6.31	73.40±5.64	<0.001	79.21±5.48	79.21±7.31	1	0.007
FBS	137.68±21.06	130.77±31.70	0.18	141.73±15.06	147.94±20.82	0.19	0.04
HbA1C	7.97±0.37	7.36±0.70	<0.001	7.78±0.30	7.86±0.66	0.54	<0.001
BUN	31.15±6.34	29.79±5.75	0.15	33.74±6.07	33.94±6.51	0.82	0.34
Cr	1.01±0.15	0.97±0.14	0.005	1.03±0.16	1.02±0.16	0.56	0.192
eGFR	74.08±10.54	77.67±11.30	<0.001	71.11±7.67	71.00±8.48	0.91	0.009
TG	143.81±39.94	144.68±53.84	0.91	144.21±44.40	147.31±44.95	0.69	0.83
CHOL	177.31±33.30	160.31±32.80	<0.001	177.00±29.12	172.94±34.54	0.37	0.03
LDL	92.77±24.38	82.20±16.91	0.004	91.43±13.49	92.36±15.01	0.65	0.002
HDL	44.13±9.08	44.09±7.99	0.19	42.42±7.51	42.21±7.46	0.78	0.89
INSULIN	12.90±6.78	10.19 5.93	<0.001	13.13±5.62	13.31±5.38	0.65	<0.001
AST	22.50±10.80	22.00±8.47	0.28	23.31±10.80	22.05±15.12	0.17	0.11
ALT	26.90±12.59	22.36±10.58	0.004	28.84±16.62	27.05±15.12	0.20	0.08
URICACID	4.61±1.16	4.06±0.96	<0.001	4.90±0.93	4.76±0.87	0.24	0.001
ACR	527.01±491.28	496.76±477.77	0.001	552.80±524.55	552.38±522.39	0.88	0.001
HOMA-IR	4.32±2.42	3.44±2.54	<0.001	4.85±3.00	4.94±2.06	0.82	0.004

Table 5: comparison of changes in eGFR and ACR in micro and macroalbuminuria subgroups of control and sitagliptin groups. eGFR, estimated glomerular filtration rate; ACR, Albumin creatinine ratio

	Sitagliptin		*P*	Control		*P*
	microalbuminuria	macroalbuminuria		microalbuminuria	macroalbuminuria	
DIF eGFR	3.41±4.01	3.58±3.88	0.88	1.64±6.04	-0.16±4.53	0.29
DIF ACR	-11.12±14.01	-30.25±35.57	0.02	2.56±7.57	-0.42±12.47	0.33

The beneficial effect of DPP4 inhibitors on improvement of lipid metabolism has been shown in numerous studies. In this study, sitagliptin reduced total CHOL-LDL-C and TG level in Mi patients, but TG and HDL-c did not change significantly in the Ma subgroups. In a meta-analysis of 11 randomized controlled clinical trials assessing the effect of sitagliptin on lipid metabolism, Minhua *et al*.[27] reported that sitagliptin therapy significantly improved serum TG and HDL-C with no significant reduction in LDL-c and total CHOL in 2338 type 2 diabetic patients. However, another meta-analysis by Monami *et al*.[28] revealed that treatment with DPP-4 inhibitors is associated with significant reduction in total CHOL in diabetic patients. Kubota also showed that total CHOL decreased within 12-week treatment with sitagliptin.[29]

The main purpose of this study was to assess the influence of sitagliptin therapy on urinary albumin excretion. Our findings indicated that ACR decreased, and eGFR increased significantly in the sitagliptin group 3 months after treatment. Although several studies have shown a decrease in urinary albumin excretion with sitagliptin consumption, most of the previous studies were nonrandomized, and had no control group. In the study performed by Kawasaki *et al*.,[26] a no-randomized uncontrolled study, sitagliptin reduced ACR and eGFR in patients with diabetic albuminuria. They argued that eGFR reduction might improve renal tissues and lead to reduction of ACR and concluded that sitagliptin reduced ACR via decreasing BP and eGFR levels toward lowering HbA1C. In contrast with the results obtained by Kawasaki *et al*.[26] and the results of this study, Mori *et al*. study[25] showed that sitagliptin reduced albuminuria in patients with type 2 diabetes through glycemic control, lowering BP, and amelioration of inflammation without reducing eGFR. In Mori's study, sitagliptin decreased urinary albumin excretion more in normo- and Mi subjects. In contrast, we found that the fall of ACR was more significant in Ma patients compared with those with microalbuminuria. These results suggest that the beneficial effect of sitagliptin in reducing urinary albumin excretion becomes even more profound with progression of nephropathy.

Our study showed that sitagliptin consumption lowered BP and increased eGFR. However, in regression analysis, no significant relationship was found between the changes in BP and eGFR and changes in ACR. We found a significant correlation between ACR and the markers of glucose control including insulin, HbA1C, FBS, and HOMA-IR. Our data suggested that reducing albuminuria by sitagliptin was due to the changes in blood glucose hemostasis and TG. Mori *et al*.,[25] in their study, also concluded that the beneficial effect of sitagliptin in reducing albuminuria was attributed to its glycemic control. Although in Mori's study, no significant correlation was found between percentage changes in ACR and markers of diabetic control, FBS, HbA1C, and ACR decreased significantly after 6 months of sitagliptin therapy without any considerable change in eGFR level.

Other studies reported that sitagliptin improves albuminuria and increases GFR and sodium diuresis. Kawasaki *et al*.'s study[26] showed that the strongest predictive factors for ACR were SBP and eGFR. In contrast, changes in ACR were not correlated with changes in HbA1C in this study.

The role of DPP-4I in reducing albuminuria through different mechanisms is indisputable. However, in order to find these mechanisms, further randomized controlled trials are required to assess the effects of DPP-4I on the inhibition of inflammatory factors of glomeruli, sodium excretion, and the reduction of the cardiovascular risk factors.

Our study showed statistically significant changes in markers of glycemic control, BP, and uric acid inflammatory markers in those patients who received sitagliptin for 3 months. Sitagliptin can reduce ACR through glycemic and BP control and also decrease uric acid inflammatory markers. Uric acid is a substance that binds to nucleotide-binding oligomerization domain-like receptors (NLRs) in response to renal cellular damage, and can activate the immune system, which leads to a rise in inflammatory markers in kidney.[30] DPP-4Is attenuate renal injury via reducing oxidative stress in kidney. Regression logistic results, however, revealed only a significant correlation between ACR reduction and glycemic control markers. We reasoned that sitagliptin can affect urine albumin excretion through lowering inflammatory factors like uric acid. In addition, the beneficial effects of uric acid in lowering the BP or the positive effects of blood glucose control on lipid metabolism and reducing the risk of cardiovascular diseases may indirectly affect the urinary protein excretion.

CONCLUSION

The present study provided evidence that sitagliptin had a renoprotective effect on Iranian type 2 diabetics. Reduction in albuminuria without decreasing eGFR is probably mediated by anti-hyperglycemic and anti-inflammatory action of sitagliptin.

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Conflicts of interest

There are no conflicts of interest.

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