



The effects of sevelamer carbonate on blood glucose and inflammatory factors in patients with diabetic kidney disease; a controlled clinical trial

Shadi Botshekan¹, Leila Mahmoodnia^{1*}, Ali Momeni¹, Tina Jafari², Ali Hasanpour Dehkordi^{3*}, Mohammadsaleh Ghafari Goosheh⁴

¹Department of Internal Medicine, Faculty of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran

²Nutrition and Dietetics subspecialty, Faculty of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran

³Associate Professor, Social Determinants of Health Research Center, School of Allied Medical Sciences, Shahrekord University of Medical Sciences, Shahrekord, Iran

⁴Department of Parasitology and Mycology, Faculty of Medicine, Shahrekord University of Medical Sciences, Shahrekord, Iran

ARTICLE INFO

Article Type:

Original

Article History:

Received: 11 May 2020

Accepted: 30 June 2020

Published online: 1 August 2020

Keywords:

Hemoglobin A1c
Inflammatory factors
Diabetic nephropathy
Sevelamer carbonate diabetic
Kidney disease
Chronic kidney disease
End-stage renal disease

ABSTRACT

Introduction: Diabetic nephropathy (diabetic kidney disease) is a complication of diabetes that begins and progresses with several factors, including hyperglycemia, inflammation and oxidative stress.

Objective: This study demonstrates the effect of sevelamer carbonate administration on hemoglobin A1c levels, blood sugar and inflammatory factors in diabetic nephropathy patients.

Patients and Methods: In this clinical trial, 48 diabetic patients under treatment of at least one drug who have proteinuria (urinary protein to creatinine ratio greater than 0.5) ≥ 2 times during the past 18 months, received sevelamer carbonate or placebo for two months. Patients' blood samples were taken before and after the intervention. Data were analyzed by SPSS software.

Results: According to the results, fasting blood sugar (FBS), hemoglobin A1c (HbA1c), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) showed no significant difference between the study groups before and after the intervention ($P > 0.05$). The mean ICAM-1 (intercellular adhesion molecule-1) and VCAM-1 (vascular cell adhesion molecule-1) showed no significant difference between the study groups before the intervention ($P > 0.05$). However we found a meaningful difference after the intervention, which was significantly lower in the intervention group ($P < 0.05$).

Conclusion: Sevelamer carbonate administration in patients with diabetic nephropathy has a significant effect on decreasing ICAM-1 and VCAM-1 levels.

Trial registration: The trial protocol was approved in the Iranian Registry of Clinical Trial (identifier: IRCT20191111045401N1; <https://en.irct.ir/trial/43662>, ethical code; IR.SKUMS.REC.1397.181).

Implication for health policy/practice/research/medical education:

Various risk factors such as elevated blood sugar, oxidative stress, elevated concentration of advanced glycosylation end-products and inflammation are involved in diabetic nephropathy. Sevelamer carbonate is a phosphate binding drug that has been proven to have anti-inflammatory and hypoglycemic effects. In our clinical trial, treatment of diabetic nephropathy patients with sevelamer carbonate led to a significant decrease of ICAM-1 (intercellular adhesion molecule-1) and VCAM-1 (vascular cell adhesion molecule-1) adhesion molecules which suggests the role of sevelamer carbonate in the recovery of endothelial dysfunction.

Please cite this paper as: Botshekan S, Mahmoodnia L, Momeni A, Hasanpour Dehkordi A, Ghafari Goosheh M. The effects of sevelamer carbonate on blood glucose and inflammatory factors in patients with diabetic kidney disease; a controlled clinical trial. J Nephroarmacol. 2021;10(2):e10. DOI: 10.34172/npj.2021.10.

Introduction

Diabetic nephropathy (diabetic kidney disease) is one of the serious complications of diabetes which occurs in 30-40% of diabetic patients. It is the most prevalent cause of chronic kidney disease (CKD), end-stage renal

disease (1) and kidney transplantation (2). In addition to causing CKD, diabetic nephropathy increases the rate of death caused by cerebrovascular and peripheral arterial diseases (3). The occurrence and progression of diabetic nephropathy involves multi-factorial risk factors

including hyperglycemia, inflammation and oxidative stress. Advanced glycation end products (AGEs) play a major role in these risk factors; since they cause both inflammation and oxidative stress (4). AGEs bind to its specific receptor named (*RAGE*). *RAGE*-AGEs complex leads to production of several pro-inflammatory cytokines, tumor necrosis factor- α (TNF- α), interleukin (IL)-6, and pro-fibrotic cytokines such as beta-transforming growth factor. AGEs activate NF- κ B transcription factor which leads to expression and release of inflammatory molecules and reactive oxygen species (5). Although hyperglycemia forms AGEs, clinical studies suggest that AGE content of the diet, plays a major role in this area too (6). The obtained data suggests that reduction of AGEs content of diet can be a useful solution for decreasing the complications of diabetes. The finding has been approved by studies in which, using foods containing high levels of AGE has caused insulin resistance, increased inflammation and decreased antioxidant immune system (6,7).

In diabetic kidney disease, there are both inflammatory vascular lesions and glomerulosclerosis, which is manifested by exudative glomerular changes, mesangial sclerosis and hyalinizing alterations in blood vessels. These morphologic lesions gradually decrease glomerular filtration rate during several years (8). Inflammatory cytokines stimulate endothelial cells, then the stimulated endothelium secretes ICAM-1 (intercellular adhesion molecule1) and VCAM-1 (vascular cell adhesion molecules1) (9).

Hyperglycemia increases production of AGE and oxidative stress which causes more adhesion molecules binding to the surface of activated endothelial cells (10). Adhesion molecules that facilitate leukocyte-endothelial adhesion and leukocyte infiltration in the diabetic kidneys. Induction of these pathways leads to vascular endothelium dysfunction and increased capillary permeability (8), leading to major damage to small vessels of the glomeruli. It has been revealed that exposure of endothelial cells to uremic milieu leads to expression of monocyte-1 absorbent protein, IL-8, membrane cofactor protein-1 (MCP-1) and VCAM-1. This finding suggests the relationship between vascular damage, systemic inflammation and uremic toxicity (11).

The fundamental treatment for diabetic nephropathy is inhibition of renin-angiotensin-aldosterone system (RAAS) by angiotensin converting enzyme (ACE) inhibitors or angiotensin II receptor inhibitors. Studies suggest that despite improvement of diabetic nephropathy with these drugs, diabetic nephropathy stills occurs and progresses in these patients. Therefore, other mechanisms may be involved in this area (12).

Sevelamer carbonate is a phosphate binder used for controlling serum phosphorus level and preventing hyperphosphatemia in CKD patients undergoing dialysis (13). Clinical studies have suggested that sevelamer

carbonate may decrease the serum level of low-molecular weight uremic toxins such as AGEs (14). Sevelamer carbonate has decreased systemic inflammatory response in rat models and hemodialysis patients (15). Furthermore, it can decrease the expression of ICAM-1 and VCAM-1 (16,17). By decreasing hemoglobin A1c (HbA1c), AGEs, inflammation and low-density lipoprotein (LDL-C) risks, sevelamer carbonate can decrease the progression of diabetic nephropathy, albuminuria and deaths related to cardiovascular disease (18,19).

Objectives

Regarding the blood sugar decreasing effect of sevelamer carbonate and on micro-inflammation, this study aimed to investigate the effect of sevelamer carbonate on HbA1c, blood sugar and inflammatory factors in patients with diabetic nephropathy (diabetic kidney disease).

Patients and Methods

Study design

In the present controlled clinical trial, 48 patients from Shahrekord nephrology clinic with diabetic mellitus with existing proteinuria (with the urinary protein-creatinine ratio of more than 0.5) under treatment by at least a drug were included in the study. The inclusion criteria included being affected by diabetic nephropathy, the age of above 18 and informed consent for participation in the study. The exclusion criteria included pregnancy, detected liver disease, active peptic ulcer, using carbamazepine and drug intolerance. After sampling, the patients' information including age, height, weight and body mass index (BMI) were recorded in the questionnaires. The patients were randomly assigned to control and intervention groups based on the random number table. The intervention group received sevelamer carbonate (1600 mg, three times per day, used during fasting) for two months and the control group received placebo tablets. Blood sampling was conducted before and after the intervention, since the levels of blood sugar, HbA1c, and inflammatory factors (VCAM-1, ICAM-1, CRP, and ESR) were tested by the ELIZA method in our hospital laboratory (10). The use of aluminum-containing drugs was stopped two months before the study.

Ethical issues

The research conducted in accordance with the tenets of the Declaration of Helsinki. The Ethics Committee of Shahrekord University of Medical Sciences approved this study (IR.SKUMS.REC.1397.181). Accordingly, written informed consent was taken from all participants before any intervention. The study was extracted from internal medicine residential thesis of Shadi Botshekan at this university. The trial protocol was approved in the Iranian Registry of Clinical Trials (identifier: IRCT20191111045401N1; <https://en.irct.ir/trial/43662>).

Statistical analysis

Data were analyzed using SPSS version 22 software. To describe the data, frequency indices and percentage were used for qualitative variables and mean \pm standard deviation was used for quantitative variables. The normal distribution of variables was evaluated by Kolmogorov–Smirnov test. To test the differences between the two studied groups, the independent t test (for quantitative normal variables), Kruskal-Wallis H and Mann-Whitney U tests (for quantitative abnormal variables) were used. In all tests, the significance level was considered at $P < 0.05$.

Results

In the present study, 48 patients with diabetic nephropathy were studied in the intervention and control groups (Figure 1). The patients' average ages in the control and intervention groups were respectively 67.04 ± 7.75 years and 70.79 ± 9.25 years ($P > 0.05$). The mean BMI in the intervention group (29.33 ± 2.32 kg/m²) was significantly lower than the mean BMI of the control group (30.87 ± 2.36 kg/m²) ($P < 0.05$). Therefore BMI was considered as a confounding variable in both groups. However, the analysis did not indicate any difference between the results of the two groups.

The control group included 14 women and 10 men and the intervention group included 11 women and 13 men. There was no significant difference between the two groups in terms of gender ($P > 0.05$). According to Table

1, the patients' mean HbA1c, FBS and ESR in two groups were not significantly different before the intervention ($P > 0.05$); however, the results were significantly different after the intervention while the intervention group reported lower means than the control group ($P > 0.05$). According to Tables 2 and 3, before the intervention, two subjects of the control group and three subjects of the intervention group reported positive CRP (≥ 1 mg/L); whereas after the intervention, two subjects of each group reported positive CRP.

Discussion

In the present study, 48 patients with diabetic nephropathy were treated in the intervention (sevelamer carbonate) and control (placebo) groups for 8 weeks. We found no significant difference between HbA1c and FBS in the two groups before and after the intervention. Yubero-Serrano et al in a clinical trial on diabetic patients (with HbA1c of above 6.5%) with CKD (stages 1-4) reported that receiving 1600 mg sevelamer carbonate for 8 weeks leads to a significant decrease of AGEs without any significant change in HbA1c or albumin-creatinine ratio. Likewise, the significant decreases of HbA1c and albumin-creatinine ratio were respectively reported in women and people below 65 years who had diabetic kidney disease through the study of Yubero-Serrano et al (17). Vlassara et al reported that prescribing sevelamer carbonate for diabetic patients with CKD leads to a significant decrease of serum AGE

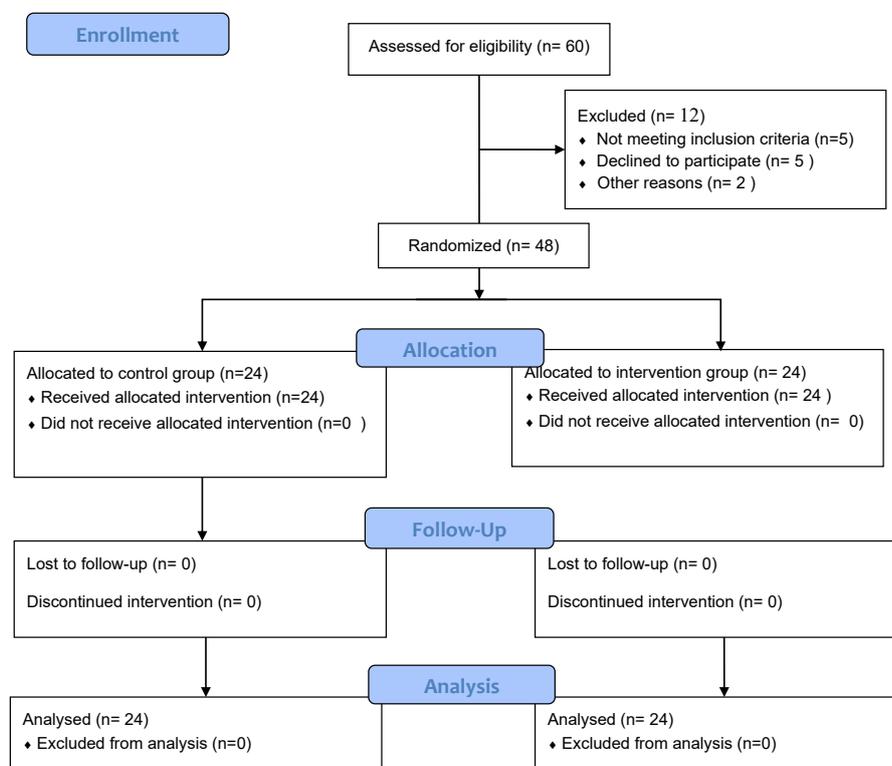


Figure 1. Consort flowchart of the study.

Table 1. Comparison of HbA1c, FBS, and inflammatory factors in the studied groups before and after the intervention

Variable	Level	Control Mean ± SD	Intervention Mean ± SD	P value
FBS (mg/dL)	Before the intervention	166.41±46.27	170.08±35.29	0.75
	After the intervention	167.33±39.63	151.75±31.57	0.139
HbA1c %	Before the intervention	8.50±1.64	8.27±1.15	0.579
	After the intervention	8.60±1.88	7.81±1.28	0.098
ESR (mm/h)	Before the intervention	19.62±13.81	20.00±12.02	0.921
	After the intervention	17.87±10.31	15.41±10.31	0.413
ICAM-1 (ng/L)	Before the intervention	396.12±176.91	360.26±193.93	0.507
	After the intervention	393.92±166.95	287.15±204.44	0.054*
VCAM-1 (ng/L)	Before the intervention	21.75±25.09	21.09±26.39	0.063
	After the intervention	20.52±17.19	17.93±27.29	0.011*

Table 2. Comparison of CRP distribution in the studied groups before the intervention

Group	CRP(mg/L)									
	2	3	4	5	6	7	8	10	12	Total
Control	5	7	3	3	4	1	1	0	0	24
	20.8	29.2	12.5	12.5	16.7	4.2	4.2	0	0	100
Intervention	3	10	3	4	1	1	0	1	1	24
	12.5	41.7	12.5	16.7	4.2	4.2	0	4.2	4.2	100

Table 3. Comparison of CRP distribution in the studied groups after the intervention

Group	CRP(mg/L)								Total
	0	2	3	4	5	6	7		
Control	12	1	2	1	1	5	2	24	
	50	4.2	8.3	4.2	4.2	20.8	8.3	100	
Intervention	13	1	3	0	2	3	2	24	
	54.2	4.2	12.5	0	8.3	12.5	8.3	100	

and HbA1c (10). Recent findings showed that sevelamer carbonate can improve glucose metabolism by decreasing AGEs. Additionally, recent studies have reported that decreased AGEs are accompanied by increased insulin sensitivity and improved glucose metabolism (7).

In the present study, no significant difference between mean ESR and positive CRP cases in the two groups before and after the intervention was seen. Before the intervention, two subjects of the control group and three subjects of the intervention group reported positive CRP (≥ 6 mg/L); whereas after the intervention, two subjects of each group reported positive CRP. Yamada et al reported that prescription of sevelamer carbonate for hemodialysis patients leads to a significant decrease of high sensitive CRP (hs-CRP) serum levels after 12 and 24 weeks (20). Previously Stinghen et al reported that administration of sevelamer carbonate for hemodialysis patients for one month leads to a significant decrease of hs-CRP compared to the control group (21). Vlassara et al reported that administration of sevelamer carbonate for patients with diabetic nephropathy for two months leads to a significant decrease of inflammatory markers like

TNF- α (10). Accordingly, Chennasamudram et al found that prescription of sevelamer carbonate for patients undergoing peritoneal dialysis for eight weeks led to a significant decrease of CRP levels (22). Shantouf et al performed a study to investigate the effects of sevelamer carbonate and calcium binder on inflammatory markers and lipids in hemodialysis patients. They found that sevelamer carbonate is a reliable treatment for hemodialysis patients with a high risk of cardiovascular diseases, while it significantly decreases LDL-c and inflammatory markers such as CRP (18). In our study, the low effect of sevelamer carbonate on CRP and ESR can be due to the few number of positive CRP cases and the shorter period of intervention compared to the above mentioned studies. In general, CRP is not a reliable inflammation factor and it is affected by various conditions. Furthermore, no certain normal range has been reported for that, however, CRP serum level of above 6 mg/L is an indicator of inflammation (23). In order to confirm the anti-inflammatory effects of sevelamer carbonate in patients with nephropathy, it is suggested to use other inflammation markers such as TNF- α too.

In this study, no significant difference between the means of ICAM-1 and VCAM-1 in two groups before the intervention was detected. However a significant difference was reported after the intervention while the intervention group had a significantly lower acute phase reactant result. Several studies have investigated the effect of sevelamer carbonate on endothelial function. Gregorio et al found that exposure of endothelial cells to AGEs increases the expression of RAGE and inflammatory biomarkers and activates endothelial factors, PAI-plasminogen activator inhibitor-1, MCP-1, IL-8, IL-6, serum amyloid A and monocyte chemotactic factor, while treatment by sevelamer carbonate recovers the mentioned factors to the normal levels. In fact the results suggested that sevelamer carbonate decreases the expression of RAGE and the markers of endothelial dysfunction caused by AGEs in uremic environment (5). Animal studies have indicated that sevelamer carbonate can decrease the expression of adhesion molecules including ICAM-1 and VCAM-1 as the vascular damage markers and cell and serum AGE levels.

Sevelamer carbonate also can strengthen antioxidant defense and decrease circulating peroxidation levels (16,24). A study investigating CKD patients showed that eight weeks of sevelamer carbonate treatment can improve endothelial function by significantly increasing flow mediated dilation (from 6.1% to 7.1%) and decreasing fibroblast growth factor-23 (25). In the present study, treatment of patients with diabetic nephropathy with sevelamer carbonate led to a significant decrease of ICAM-1 and VCAM-1 adhesion molecules which suggests the role of sevelamer carbonate in recovery of endothelial dysfunction.

Conclusion

According to the results, treatment of diabetic nephropathy patients with sevelamer carbonate led to a significant decrease of ICAM-1 and VCAM-1 adhesion molecules which suggests the role of sevelamer carbonate in the recovery of endothelial dysfunction. Sevelamer carbonate decreased ESR as an inflammation marker, FBS and HbA1c as glucose metabolism markers. However, the difference with the control group was not significant. Therefore, sevelamer carbonate can be used as an effective drug for recovery of endothelial dysfunction and prevention of nephropathy progression. However, further studies should be performed to investigate its other effects, acceptance and the probable side effects.

Limitations of the study

Possibility of complications for patients who were identified and controlled with repeated follow-up

Authors' contribution

SB, LM, TJ, MGG and AH were the principal investigators

of the study and they were included in preparing the concept and designing of the study. SB, LM and AM were involved in performing study tests and data acquiring. LM and SB revised the manuscript. All authors participated in preparing the final draft of the manuscript.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

Funding/Support

The study was extracted from the internal medicine residential thesis of Shadi Botshekan at Shahrekord University of Medical Sciences, which supported by the university.

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