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MEDICAL SCIENCES / DAHİLİ TIP BİLİMLERİ

Sevelamer Improves Vascular Stiffness and Decreases Serum Uric Acid Levels in Patients Ongoing Hemodialysis

Hemodiyaliz Hastalarında Sevelamer Vasküler Sertliği Düzeltmekte ve Serum Ürik Asit Düzeyini Azaltmaktadır

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Abstract

Objectives: Sevelamer can act as a prebiotic with its pleiotropic effects. The aim of this study was to evaluate the effects of sevelamer on serum uric acid, HbA1c and lipid profile levels and the progression of arterial stiffness.

Materials and Methods: A total of 151 patients undergoing maintenance hemodialysis and using the same phosphorus binders under three years follow-up were enrolled. Patients were divided into two groups according to usage of phosphate binders (PB) as sevelamer based PB (group 1) and calcium based PB (group 2). Biochemical parameters were assessed in three year follow-up period. Arterial stiffness determined at the initial and at the end of the 3rd year by aortic pulse wave velocity (PWv).

Results: Mean uric acid levels had significantly decreased in group 1 where remained stable in group 2 in three years follow-up period. 22.4% of patients in group 1 showed a reduction more than 2 mg/dL in mean uric acid levels. HbA1c levels were lower in diabetic group 1 than group 2. PWv values were similar in both groups at the inital of the study. However; PWv values of group 1 were lower than group 2 at the 3rd year of the study

Conclusion: Sevelamer improves the cardiovascular risk by pleiotropic effects through lowing uric acid, low density lipoprotein-cholesterol and HbA1c concentrations and avoiding the excess calcium intake. Sevelamer improves the cardiovascular risk profile and prevents the progression of arterial stiffness when compared to calcium based PB in hemodialysis patients.

Keywords: Sevelamer, hemodialysis, uric acid, vascular stiffness

Öz

Amaç: Sevelamer, pleotropik etkisi ile prebiyotik olarak etki gösterebilir. Bu çalışmanın amacı sevelamerin ürik asit, HbA1c, lipid profili ve arteryel sertlik progresyonu üzerine etkisinin gösterilmesidir.

Gereç ve Yöntem: Hemodiyalize giren ve aynı fosfor bağlayıcıyı (FB) 3 yıl kullanan 151 hasta çalışmaya dahil edildi. Hastalar kullandıkları FB'ye göre sevelamer bazlı FB (grup 1) ve kalsiyum bazlı FB (grup 2) olarak 2 gruba ayrıldı. Üç yıllık takipte biyokimyasal parametreler kayıt edildi. Arteryel sertlik başlangıçta ve 3. yılın sonunda aortik nabız dalga hızı (PWv) ölçümü ile belirlendi.

Bulgular: Üç yıllık takipte ortalama ürik asid düzeyleri grup 1'de azalmışken grup 2'de stabil kaldı. Grup 1'deki hastaların %22,4'ünde ortalama ürik asid düzeylerinde 2 mg/dL'den fazla azalma saptandı. Diyabetik hastalarda HbA1c düzeyleri grup 1'de grup 2'ye göre daha düşüktü. PWv düzeyleri çalışmanın başında her 2 grup için de benzerdi. Ancak 3. yılın sonunda PWv düzeyleri grup 1'de grup 2'ye göre daha düşük saptandı.

Sonuç: Sevelamer pleiotropik etki ile ürik asit düzeyini, düşük yoğunluklu lipoprotein-kolesterolü, HbA1c düzeyini azaltarak, fazla kalsiyum alımını engelleyerek kardiyovasküler riski azaltmaktadır. Hemodiyalize giren hastalarda sevelamer, kalsiyum bazlı fosfor bağlayıcılara göre arteryel sertlik progresyonunu da azaltarak kardiyovasküler risk profilini düzeltir.

Anahtar Kelimeler: Sevelamer, hemodiyaliz, ürik asit, vasküler sertlik

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Introduction

Hyperphosphatemia is one of the most important factor for cardiovascular morbidity and mortality in maintenance hemodialysis (MHD) patients (1). When concerning about phosphate binders (PB) sevelamer is a non-absorbable calcium and aluminium free-PB (2). In addition to improving phosphate levels, sevelamer has pleiotropic effects as binding bile acids, lipids, advanced glycation endproducts and uric acid (3). Although it is well known that elevated serum uric acid associates with an increased risk of cardiovascular events and mortality in the general population (4), its clinical impact and the pathogenic role in MHD patients is not clear.

Arterial stiffening that is accelerated by hypertension, metabolic syndrome, diabetes, atherosclerosis and renal disease, and has a strong correlation with cardiovascular events and all-cause mortality (5). Previous studies reported that management of hyperphosphatemia with sevelamer hydrocloride might improve aortic calcifications and cardiovascular morbidity in MHD patients over 1 year period in addition to its anti-inflammatory properties and urate lowering effects (6). Treat to Goal (TTG) trial reported sevelamer was more efficient in slowing the progression of calcification (7).

The aim of this study was to evaluate the effect sevelamer hydrochloride and calcium acetate based PB on markers of inflammation, bone and mineral metabolism, as well as serum uric acid levels and the progression of arterial stiffness in the three year follow up period of MHD patients.

Materials and Methods

Study Population

We performed an observational study among 600 MHD patients in 3 years period. One hundred and fifty one patients who were ongoing MHD three times a week and used only one type of PB were selected from a group of 600 MHD patients according to following exclusion criteria 1) Demanding combination or switching of PB in the past three years 2) Kt/V <1.4, 3) chronic inflammatory disease of unknown etiology (defined as mean C-reactive protein (CRP) >10 mg/L), 4) having malignancy or chronic liver disease, 5) heart failure and/or ischemic heart disease, 6) diagnosed or had a surgery for peripheral vascular disease, 7) pregnancy or breast feeding, 8) history of parathyroidectomy, 9) uncontrolled hypertension defined as mean predialysis systolic blood pressure >160 or diastolic blood pressure >100 mmHg, 10) previous major gastrointestinal tract surgery, 11) use of anti-arrhythmic drugs 12) active alcohol abuse.

The study was approved by Başkent University Institutional Review Board and Ethics Committee (approval no.: KA12/83, date: 27.08.2013). Informed written consent was obtained from each subject before enrolling into the study.

Patients were divided into two groups according to usage of PB as sevelamer based PB (group 1; n=99) and calcium based PB (group 2; n=52). Twenty-four patients in group 1 and 26 patients in group 2 had type 2 diabetes mellitus (DM). Flow chart of patients was given in Figure 1.

Biochemical Assays

All patients' demographical, clinical and biochemical parameters were analyzed. Venous blood samples were drawn after an overnight fast. All blood samples were collected pre dialysis. The Kt/V (single pool) was calculated using urea kinetic modeling equations as described elsewhere (8). Albumin-corrected calcium was calculated by adding 0.8 mg/dL for each g/dL serum albumin below 4.0 g/dL. Lipid was measured every 6 months, parathyroid hormone (iPTH; by chemiluminescence immunoassay, Cobast®, Roche Diagnostics GmbH), alkaline phosphatase and glycosylated hemoglobin (HbA1C; by high-

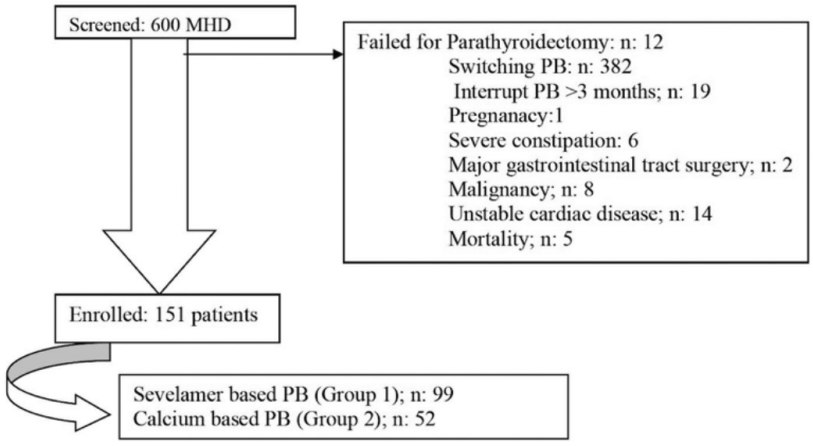

Figure 1: Patient flow chart

MHD: Maintenance hemodialysis, PB: Phosphate binders

performance liquid chromatography) levels were measured every 3 months and serum fasting plasma glucose (FPG), uric acid, CRP, calcium, phosphorus, albumin levels, and complete blood count were measured in monthly periods.

Medications and Other Measurements

Vitamin D receptor activators dose adjustments were performed according to Ca, P and iPTH levels. The dose of calcitriol were increased if the decline in PTH was less than 30% of previous value. The doses of paricalcitol and calcitriol were increased if the decline in PTH level was <30% the baseline value, if the Ca level was <10.5 mg/dL. The doses of the drugs were reduced if the PTH level was <300 pg/mL or if the serum Ca level was >10.5 mg/dL at any time. According to our country's health assurance, sevelamer based PB were added in case of hyperphosphatemia, either Ca x P product was >55 even if Kt/V >1.4 or Ca x P product >70 in any Kt/V value. PB was interrupted for one month if serum P was <3.5 mg/dL and was restrated if serum P was >5.5 mg/dL.

We also calculated and recorded the estimated alimentary calcium intake from dietary records and the cumulative doses of calcitriol or paricalsitol and elementary calcium of calcium based PB at the end of the study.

Pulse Wave Velocity Analysis

Pulse wave velocity analysis (PWv) were assessed at the initial and once for each year (first, second and third year of treatment. Aortic PWv was measured by carotid and femoral artery pressure waves. The path length was calculated as 80% of the direct distance measured between the carotid and femoral measurement sites, as recommended by the Reference Values for Arterial Stiffness' Collaboration group. PWv was calculated as the path length divided by transit time (m/s) (9).

Table 1: Demographic characteristics of patients

Patient characteristics	Group 1 (n=98)	Group 2 (n=52)
% of total (n=151)	66%	34%
Age (years) (mean ± SD)	52.8±14.8	53.4±13.8
Gender (male)	48	29
CKD etiology		
Diabetes mellitus (%)	16.0	17.2
Hypertension (%)	23.9	21.3
PCKD (%)	1.9	0.6
Unknown etiology (%)	15.9	10
Others (%)	7.0	2.8
Mean arterial blood pressure (mmHg)	138±16	134±21
Comorbidity score	5.4±2.5	5.1±2.6
Duration of dialysis (years) (mean ± SD)	9.7±5.1	9.0±5.1
Mean annual elementary calcium load in phosphate binders (kg/year)	0	0.21±0.06
Mean annual calcitriol intake (mcg/year)	88.4±3.0	213±12.3
Mean annual paricalcitol intake (mcg/year)	202±19.4	78.4±13.0

BMI: Body mass index, CKD: Chronic kidney disease, PCKD: Polycystic kidney disease, SD: Standard deviation

Statistical Analysis

Statistical Package for Social Sciences (version 14.0; SPSS) was used. Kolmogorov-Smirnov test is used for distribution analysis of data. Values displaying normal distribution were expressed as mean (standard deviation). Variables were compared using Mann-Whitney U and Kruskal-Wallis tests according to distribution normality. P<0.05 was considered statistically significant.

Results

Demographic characteristics of patients were summarized in Table 1. The mean serum calcium, phosphorus, PTH, CRP and urea reduction rate levels were similar in both groups. the mean dose of calcium based PB was 1400±80 mg/day and The mean dose of sevelamer was 1200±50 mg/day. The mean annual elemental calcium load was 0.21±0.06 kg/year. The mean annual calcitriol and paricalsitol dosages were 88.4±3.0 mcg/year and 202±19.4 mcg/year in group 1; 213±12.3 mcg/year and 78.4±13.0 mcg/year in group 2, respectively.

Serum low density lipoprotein-cholesterol (LDL-C) levels (149.2±10.4 mg/dL vs 124.6±15.3 mg/dL) decreased significantly in group 1 (p<0.005), while remained stable (150.6±8.4 mg/dL vs 148.4±10.5 mg/dL) in group 2. PWv values were similar (group 1: 6.2±1.6 m/sec, group 2: 6.4±1.8 m/sec) in both groups at the initiation of the study. However PWv values of group 1 patients (4.7±1.0 m/sec) was significantly lower compared to group 2 (7.4±2.5 m/sec) at the 3rd year of the study (p<0.005). There was no statistical significance in means of gender related difference in the arterial stiffness in both groups. When compared to initial values; mean uric acid levels significantly decreased in group 1 (8.6±0.2 mg/dL vs. 5.4±0.4 mg/dL) while remained stable in group 2 (8.5±0.6 mg/dL vs. 8.2±0.5 mg/dL) in three years follow up period. 22.4% of patients in group 1 and 3.8% of patients in group 2 had a reduction more than 2 mg/dL in mean uric acid levels. In correlation analysis of overall study population, sevelamer decreased serum uric acid values in hyperuricemic patients (serum urate >6 mg/dL), on the contrary, it did not affect serum uric acid values in normouricemic patients (serum urate ≤6 mg/dL) (p<0.05).

In subgroup analysis of patients with DM, FPG and HbA1c levels significantly decreased in group 1 (FPG: 105.1±29.9 mg/dL vs. 92.2±25.9 mg/dL; HbA1c: 7.4±0.6% vs 6.4±0.2%) when compared to group 2 (FPG: 104.6±24.8 mg/dL vs 103.8±35.8 mg/dl; HbA1c: 7.6±0.5% vs 7.5±0.4%).

The comparison of initial and follow-up values are summarized in Table 2. Distrubution of baseline serum uric

acid, HbA1c and PWv values are given in Figure 2. In linear regression analysis; age (p<0.01), duration of dialysis (p=0.03), LDL-C (p<0.005) and HbA1c (p<0.005) were detected as the predictors of PWv; moreover duration of dialysis (p=0.002), PWv (p=0.001) and age (p=0.045) were the predictors of serum uric acid levels. The correlation analysis showed a significant correlation between mean serum uric acid levels and PWv values at the 3rd year of the study (Figure 3).

At the beginning of the study, when patients were divided into two groups according to mean uric acid levels with a cut-off value of 6.0 mg/dL; 64 MHD patients had higher uric acid levels at the 3rd year of the study. Although change in PWv in the three year follow-up period was not significant between two groups, 3rd year PWv value was significantly higher in this population (p=0.031).

Discussion

Cardiovascular disease (CVD) is the leading cause of mortality among MHD patients (10,11). Vascular calcification, in particular medial calcification, is more common in this population. It has been suggested that repeated episodes of hypercalcemia may lead to increase microcrystal formation and increase the risk

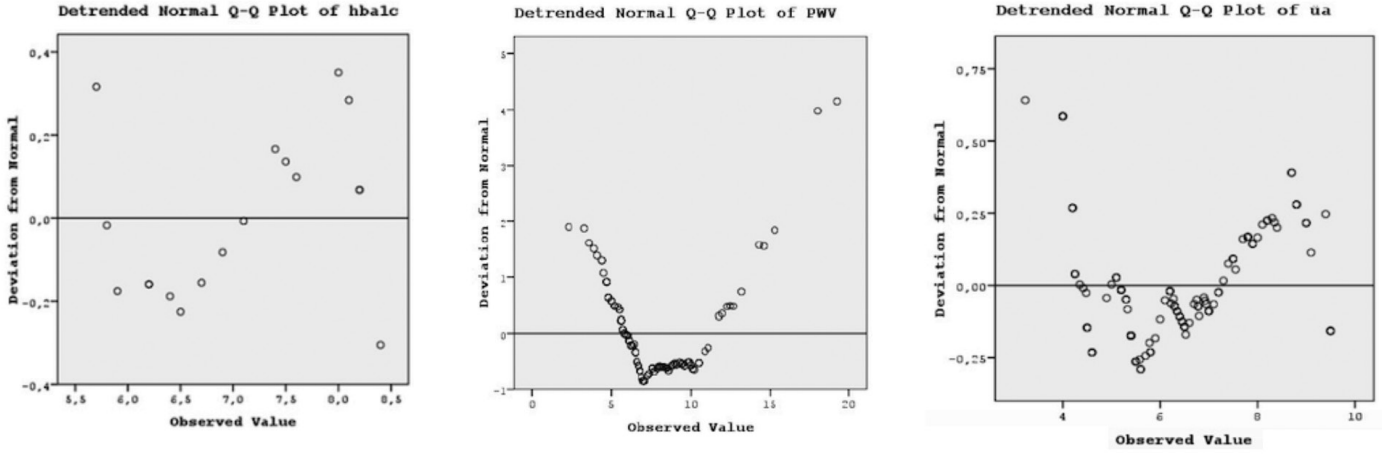

Figure 2: Distribution of baseline mean serum HbA1c, uric acid and PWv values

PWv: Pulse wave velocity

Table 2: Clinical and laboratory parameters of study groups

	Pre-treatment of sevelamer	After treatment of sevelamer group 1 (n=98)	Pre-treatment of calcium based PB	After treatment of calcium based PB: group 2 (n=52)	p value
Type 2 diabetes mellitus (n)	24	24	26	26	
Fasting plasma glucose (mg/dL)	105.1±29.9	92.2 ± 25.9	104.6±24.8	103.8 ± 35.8	0.005
Calcium (mg/dL)	8.8±0.4	8.4±0.6	8.7±0.6	8.9±0.5	0.420
Phosphorus (mg/dL)	7.2±0.5	5.2±1.3	7.5±2.4	5.8±1.6	0.312
PTH (pg/dL)	456.2±245.4	485±266	465.4±275	417±284	0.524
CRP (mg/L)	8.4±5.6	9.9±8.7	12.6±5.8	13.3±6.7	0.410
Albumin (g/dL)	3.7±0.4	3.8±0.2	3.7±0.6	3.8±0.1	0.544
Uric acid (mg/dL)	8.6±0.2	5.4±0.4	8.5±0.6	7.8±0.5	0.001
Percentage of decreasing of uric acid level >2 mg/dL (%)		22.4%		3.8%	0.001
Total cholesterol (mg/dL)	185±12.4	180.6±14.4	192±11.6	178.5±10.6	0.310
HDL-cholesterol (mg/dL)	56.5±11.2	54.8±12.5	52.5±10.5	48.6±16.2	0.246
LDL-cholesterol (mg/dL)	149.2±10.4	124.6±15.3	150.6±8.4	148.4±10.5	<0.005
Triglyceride (mg/dL)	185.5±7.5	186.1±10.2	190.5±9.5	198.5±8.4	0.748
URR (%)	72	72	68	71	0.512
HbA1c (%)	7.4±0.6	6.4±0.2	7.6±0.5	7.5±0.4	0.005
PWv (cm/sn)	6.2±1.6	4.7±1.0	6.4±1.8	7.4± 2.5	0.001

PTH: Parathyroid hormone, CRP: C-reactive protein, URR: Urea reduction rate, PWv: Pulse wave velocity, PB: Phosphate binders, LDL: Low density lipoprotein, HDL: High density lipoprotein

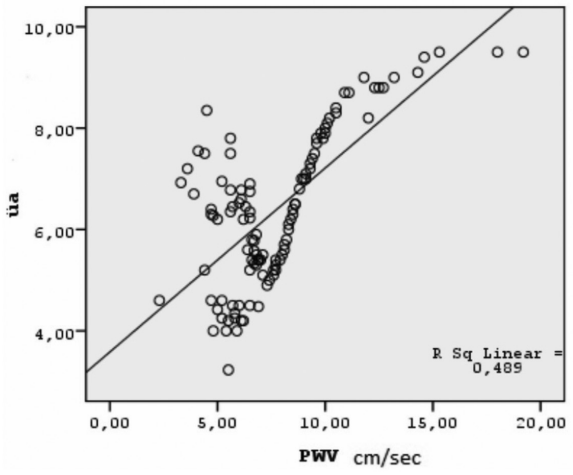

Figure 3: Correlation between PWv and serum uric acid levels

PWv: Pulse wave velocity

of vascular calcification (12). Calcium load in MHD patients is frequently due to the calcium based PB in addition to dietary intake of calcium and dialysate calcium value. TTG trial was an important prospective study in 200 MHD patients that showed sevelamer was more effective to improve progression of coronary and aortic calcification than calcium based PB (7). Conflicting with TTG trial and present study, CARE-2 study did not demonstrate a significant superiority of sevelamer versus calcium-based binders in reducing the progression of vascular calcification (13). However, this trial cannot be compared with the TTG study because CARE-2 patients had higher pre-existing cardiovascular risks. The dialysis clinical dutcomes revisited study evaluated whether sevelamer administration was associated with a survival benefit in MHD patients and showed that sevelamer compared with calcium-based binders administration reduced all-cause hospitalizations without changing mortality rates (14). Although there is evidence that hyperphosphatemia promotes arterial stiffening through structural vascular alterations such as medial calcification, in our study population serum phosphate levels and dialysis adequency were similar in the initial and end of the study both in two groups (15). Besides, in present study, patients with sevelamer based PB group had significantly lower PWv levels at the third year of the study that supports TTG trial. We can disclose this result with lower cumulative calcium load because all patients were given the same standard dietary advice and dieticians working to achieve the same standards in addition to same dialysate calcium content. However as a limitation of our study, we didn't analyse the hospitalization rates and mortality of patients.

In addition to calcium load related vascular calsifications, elevated serum uric acid have been shown to be associated with impaired endothelium-mediated relaxation, vascular stiffness and a restrictive left ventricular filling pattern (16). In the literature, few studies investigate the effect of uric acid on arterial stiffness in patients with chronic renal failure. Although they suggests an independent association between uric acid and stiffness in this population, there is insufficient evidence to determine whether lowering uric acid concentrations would be useful for preventiontion of vascular calsification (17,18). In our study, patients treated with sevelamer had lower serum uric acid levels and higher percentage of change in serum uric acid levels more than 2 mg/dL. While it has been suggested that uric acid may simply be a consequence of the increased uric acid absorption secondary to hyperinsulinemia, there is growing data that uric acid may predict the development of metabolic syndrome (19,20).

As discussed above, sevelamer has also anti-inflammatory pleiotropic effects by binding endotoxins and sequester bile acid-LPS complexes in the intestinal tract (21). Stinghen et al. (22) demonstrated that sevelamer leads to a decrease in high-sensitivity CRP, which was accompanied by a paralel decrease in endotoxemia. However we couldn't find a significant difference between two groups in terms of CRP. This result was not unexpected because we excluded the patients with severe inflammation or serious co-morbid diseases that elevates CRP.

Type 2 DM is associated with several comorbidities including nephropathy and especially CVD. HbA1c is commonly used as a marker of long term glycemic status. Elevated HbA1c has also been regarded as an independent risk factor for CVD in subjects with or without diabetes (23). In present study, FPG and HbA1c levels were significantly decreased in diabetic patients by sevelamer based PB, suggesting that glucose metabolism was improved by sevelamer hydrocloride as similar to a recent study (24). In addition, when compared to calcium based PB, sevelamer treatment significantly reduced mean LDL-C levels in present study as similar to previous studies in the literatüre (25,26) Thus, sevelamer hydrochloride can be used as a new agent to ameliorate LDL-C and glucose metabolism to prevent cardiovascular morbidity and mortality in diabetic MHD patients. When we add together all results, sevelamer decreases FPG, uric acid and calcification-induced vascular remodeling as well as ameliorates lipid profile. Thus we thought that sevelamer decreases cardiovascular morbidity by improving metabolic syndrome.

Study Limitations

The study has also several limitations. First of all, this was an observational study without randomization of the participants. Second, the small number of overall and diabetic population. Thus a prospective study with a large number of patients is further warranted to clearly suggest the pleiotropic effects of sevelamer. Third, it cannot be assumed that the prescription characteristics of a particular medication for a given patient remains unchanged over the course of follow-up of these

patients. Finally, we didn't evaluated the patients' compliance with the dietary recommendations.

Conclusion

In conclusion we suggest that sevelamer, an oral calcium free phosphate adsorbent decreases serum uric acid, HbA1c and LDL-C levels, besides, sevelamer prevents the progression of arterial stiffness and improves the cardiovascular risk of MHD when compared to calcium based PB.

Ethics

Ethics Committee Approval: The study was approved by Başkent University Institutional Review Board and Ethics Committee (approval no.: KA12/83, date: 27.08.2013).

Informed Consent: Informed written consent was obtained from each subject before enrolling into the study.

Authorship Contributions

Surgical and Medical Practices: E.T., S.S., Concept: Z.B., Design: M.E., S.S., Data Collection and/or Processing: B.G.D., Analysis and/or Interpretation: E.T., M.E., Literature Search: B.G.D., Writing: B.G.D.

Conflict of Interest: According to the authors, there are no conflicts of interest related to this study.

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