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Effect of pitavastatin on erythrocyte membrane fatty acid content in patients with chronic kidney disease: two-arm parallel randomized controlled trial

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Background: Statins reduce the risk of cardiovascular events in patients with chronic kidney disease (CKD). Although diabetes mellitus (DM) is a reported side effect of statin treatment, some studies have indicated that pitavastatin does not cause DM. The present study investigated the effect of pitavastatin on the fatty acid (FA) content of erythrocyte membranes, which affects the occurrence of DM and cardiovascular diseases. In addition, changes in adiponectin and glycated hemoglobin (HbA1c) levels were evaluated after pitavastatin treatment.

Methods: A total of 45 patients were enrolled, 28 of whom completed the study. Over 24 weeks, 16 patients received 2 mg pitavastatin and 12 patients received 10 mg atorvastatin. Dosages were adjusted after 12 weeks if additional lipid control was required. There were 10 and nine patients with DM in the pitavastatin and atorvastatin groups, respectively. Erythrocyte membrane FAs and adiponectin levels were measured using gas chromatography and enzyme-linked immunosorbent assay, respectively.

Results: In both groups, saturated FAs, palmitic acid, trans-oleic acid, total cholesterol, and low-density lipoprotein cholesterol levels were significantly lower than those at baseline. The arachidonic acid (AA) content in the erythrocyte membrane increased significantly in the pitavastatin group, but adiponectin levels were unaffected. HbA1c levels decreased in patients treated with pitavastatin. No adverse effects were associated with statin treatment.

Conclusion: Pitavastatin treatment in patients with CKD may improve glucose metabolism by altering erythrocyte membrane AA levels. In addition, pitavastatin did not adversely affect glucose control in patients with CKD and DM.

Keywords: Chronic kidney disease; Diabetes mellitus; Fatty acid; Pitavastatin

Introduction

Patients with chronic kidney disease (CKD) have a higher mortality rate than the general population, and the mortality rate is even higher in patients with diabetes mellitus (DM) [1,2]. This is because patients with CKD have traditional risk factors for cardiovascular complications, such as DM, hypertension, and dyslipidemia, as well as nontraditional risk factors such as microalbuminuria and decreased hemoglobin levels [3]. The use of statins before dialysis in patients with CKD reduces the incidence of cardiovascular disease. Therefore, it is crucial to measure and treat lipid levels at the time of CKD diagnosis [4,5].

A critical side effect of statins is the development of new-onset DM. Reports suggest that atorvastatin and simvastatin can increase

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the incidence of type 2 DM [6]. However, pitavastatin has not been reported to contribute to the development of type 2 DM [7]. Because the mechanisms underlying statin-induced DM remain unclear, each statin characteristic related to glucose metabolism should be evaluated.

Erythrocyte membrane fatty acids (FAs) are associated with changes in blood glucose levels and risk of developing type 2 DM [8]. Pitavastatin has been reported to modulate the FA content in erythrocyte membranes [9,10]. Further studies are required to investigate the effects of pitavastatin on erythrocyte membrane FAs and its potential role in the development of DM.

This study primarily aimed to examine the changes in erythrocyte membrane FA content in patients with CKD after pitavastatin therapy. We also assessed the effect of pitavastatin on elevating adiponectin and glycated hemoglobin (HbA1c) levels, which are reported effects of other statins.

Methods

Ethical statements: This study was approved by the Institutional Review Board (IRB) of Dong-A University Hospital (IRB No: DAUHIRB-15-153), and written informed consent was obtained from all participants.

1. Study design and patients

We conducted a two-arm parallel randomized controlled trial. Random allocation was performed at the beginning of the study. After entering the assigned codes into the Research Randomizer, participant numbers were automatically generated and randomly allocated to the treatment and control groups. During random allocation, considerations were given to the institution and sex. A predetermined random allocation table was used, and an additional random allocation was conducted based on an estimated glomerular filtration rate (eGFR) threshold of 60 mL/min/1.73 m^2. This study was registered at ClinicalTrials.gov (https://clinicaltrials.gov/ct2/show/NCT02863185).

1) Inclusion criteria

Forty-five patients were enrolled in this randomized controlled study, of whom 28 successfully completed the study. Patients aged 20 to 80 years with CKD stages 1 to 5 who were not receiving dialysis were enrolled in this study. The inclusion criteria were as follows: (1) not currently taking statins and (2) having coronary artery disease or equivalent risk factors with low-density lipoprotein (LDL) cholesterol levels ≥ 100 mg/dL, having two or more cardiovascular risk factors with LDL cholesterol levels ≥ 130 mg/dL, or having LDL cholesterol levels > 160 mg/dL.

2) Exclusion criteria

The exclusion criteria were a history of taking statins or omega-3 FAs; taking sevelamer hydrochloride within 3 months; a history of statin-associated side effects; hospitalization due to cardiovascular disease, infection, or acute kidney injury within 3 months; pregnant or about to become pregnant; examination using a contrast agent within 2 weeks; dyslipidemia due to nephrotic syndrome; a history of liver cirrhosis or malignancy; and an albumin level < 3.0 g/dL.

3) Withdrawal criteria

The withdrawal criteria were intake of other lipid-lowering drugs (e.g., other statin drugs, omega-3 FAs, or sevelamer hydrochloride) during the study period, withdrawal of consent, hospitalization for more than 1 month during the research period, severe muscle pain or dark brown urine after taking the drug, aspartate transaminase (AST) or alanine transaminase (ALT) level increased more than three times the upper limit, decreased renal function by > 30%, discontinuation of the study drug for more than 2 months.

After excluding patients who withdrew or dropped out, 28 of the 45 patients successfully completed this study. Specifically, six patients declined to provide final samples, three patients discontinued their participation, the blood samples of four patients were lost, and four patients were excluded from the analysis due to acute kidney injury, which was determined to be unrelated to statin treatment (Fig. 1). Of the remaining 28 patients, 16 received 2 mg pitavastatin and 12 received 10 mg atorvastatin for 24 weeks. In cases where LDL cholesterol levels were not well controlled at the 12-week mark of the study, the doses were increased to 4 mg for pitavastatin and 20 mg for atorvastatin. Ten patients in the pitavastatin group and nine in the atorvastatin group had DM.

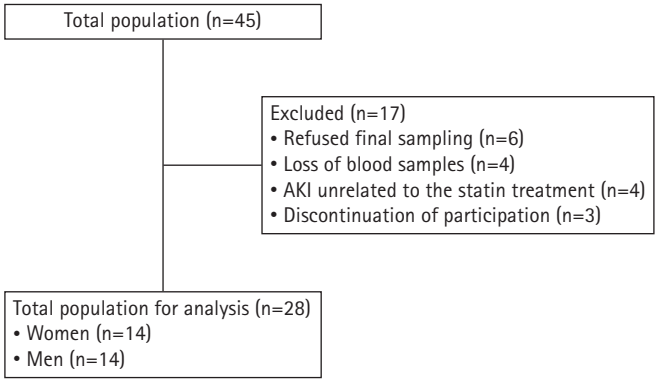

Fig. 1. Consort diagram of the study population. AKI, acute kidney injury.

2. Clinical outcomes

1) Biochemical and hematologic evaluation

eGFR was calculated using dietary modifications of the renal disease formula using age- and sex-adjusted serum creatinine (sCr) as follows: eGFR (mL/min/1.73 m^2) = 175 × sCr−1.154 × age−0.203 × 0.742 (in women) × 1.21. Cystatin C-based eGFR was calculated for women with serum cystatin C levels ≤ 0.8 mg/dL as follows: eGFR = 133 × (serum cystatin C/0.8)−0.499 × (0.996) × age × 0.932. For women with serum cystatin C levels > 0.8 mg/L, eGFR was calculated as follows: eGFR = 133 × (serum cystatin C/0.8)−1.328 × (0.996) × age × 0.932. For men with serum cystatin C levels ≤ 0.8 mg/dL, eGFR was calculated as follows: eGFR = 133 × (serum cystatin C/0.8)−0.499 × (0.996) × age. For men with serum cystatin C levels > 0.8 mg/L, eGFR was calculated as follows: eGFR = 133 × (serum cystatin C/0.8)−1.328 × (0.996) × age.

2) Laboratory measurements

We analyzed the serum levels of total cholesterol, triglycerides, LDL cholesterol, high-density lipoprotein (HDL) cholesterol, and HbA1c. Proteinuria was measured using the random spot urine test, and adiponectin levels were measured using an enzyme-linked immunosorbent assay (BioVendor Laboratory Medicine, Modřice, Czech Republic).

3) Gas chromatography

The erythrocyte membrane FA content was measured at baseline and after 24 weeks by gas chromatography (Shimadzu 2010AF, Shimadzu Scientific Instrument, Kyoto, Japan). The isolated erythrocytes underwent methylation by adding boron trifluoride methanol-benzene for 10 minutes at 100°C. FAs were identified by comparison with known standards (GLC-727; Nu-Chek Prep, Elysian, MN, USA). FA methyl esters were analyzed by gas chromatography using a 100 m SP-2560 capillary column (Supelco, Bellefonte, PA, USA). The omega-3 index is a measure of eicosapentaenoic acid and docosahexaenoic acid (DHA) content in erythrocyte membranes, and the erythrocyte membrane FA content is expressed as a percentage of the total FA weight.

3. Statistical outcomes

In previous studies, the average change in oleic acid levels among erythrocyte membrane FAs after omega-3 FA administration in patients with CKD undergoing dialysis was 2.5 weight %. The standard deviation was 2.0 weight %, and we estimated that the value with pitavastatin was less than that with omega-3 FAs. To detect an effective mean difference in erythrocyte membrane oleic acid content of 1.5 ± 2.0 weight % at a two-sided significance level of 0.05, a sample size of 18 patients per group was required to achieve a minimum power of 80% and an expected dropout rate of 20%. The participants were divided into two equal groups based on an eGFR threshold of 60 mL/min/1.73 m^2 and were subsequently analyzed. Data are expressed as mean ± standard deviation. The differences between the two groups were analyzed using the Mann-Whitney U test. The Wilcoxon rank sum test was used for initial data and changes after 24 weeks, and the chi-square test was used for qualitative variables. All analyses were performed using SPSS ver. 18.0 for Windows (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $p < 0.05$.

Results

1. Baseline characteristics and changes in biochemical laboratory data

The pitavastatin and atorvastatin treatment groups underwent blood biochemical analyses and examination of erythrocyte membrane FA content before starting treatment, and there were no significant differences between the two groups.

Regardless of the type of statin used, both groups showed a significant decrease in total cholesterol ($p < 0.001$) and LDL cholesterol ($p < 0.001$) compared to baseline; however, there were no significant changes in the levels of adiponectin. Patients with DM showed a significant decrease in HbA1c levels from 7.6% ± 1.5% to 7.3% ± 1.3% ($p = 0.038$) (Table 1). In patients with and without DM, there was a significant decrease in total cholesterol and LDL cholesterol levels after statin treatment. Regardless of baseline eGFR, there was a significant decrease in total cholesterol and HDL cholesterol levels in both patient groups receiving statin treatment. There were no significant changes in HbA1c or adiponectin levels according to baseline eGFR.

2. Changes in erythrocyte membrane fatty acid content

Table 2 shows the changes in the composition of erythrocyte membrane FAs after statin treatment, irrespective of the type of statin. There was a significant decrease in the content of saturated FAs, palmitic acid, and trans-oleic acid ($p = 0.016$, $p < 0.001$, and $p = 0.015$, respectively), while arachidonic acid (AA) content showed a significant increase compared with its baseline level ($p = 0.006$).

3. Changes in biochemical parameters and erythrocyte membrane fatty acid content according to the type of statin

There was a significant decrease in the levels of total cholesterol, LDL cholesterol, and ALT ($p < 0.001$, $p < 0.001$, and $p = 0.031$, re-

Table 1. Baseline clinical and biochemical characteristics of the subjects

Characteristic	Baseline (n=28)	24 weeks (n=28)	*p*-value
Age (yr)	63.0±9.0		
Male sex	14 (50.0)		
Diabetes mellitus	19 (67.9)		
Systolic BP (mmHg)	131.1±17.1	132.8±14.1	0.543
Diastolic BP (mmHg)	72.9±11.7	72.8±8.7	0.974
Calcium (mg/dL)	9.2±0.6	9.2±0.5	0.774
Phosphorus (mg/dL)	3.7±0.5	3.6±0.6	0.789
Glucose (mg/dL)	149.2±83.8	127.9±39.5	0.228
BUN (mg/dL)	21.1±8.0	22.1±10.4	0.391
Creatinine (mg/dL)	1.3±0.6	1.4±0.7	0.210
eGFR (mL/min/1.73 m^2)	61.8±27.2	62.8±28.1	0.504
CKD-EPI (mL/min/1.73 m^2)	60.1±25.5	60.9±26.7	0.551
Uric acid (mg/dL)	6.3±1.8	5.8±1.5	0.012[a]
Total cholesterol (mg/dL)	222.7±43.4	157.9±25.7	<0.001[a]
Albumin (g/dL)	4.2±0.5	4.2±0.4	0.301
AST (U/L)	20.8±7.7	23.9±8.1	0.008[a]
ALT (U/L)	17.4±9.5	20.4±7.1	0.030[a]
Triglyceride (mg/dL)	224.2±128.2	189.0±135.2	0.156
HDL (mg/dL)	47.3±8.9	47.3±8.9	0.906
LDL (mg/dL)	154.8±24.5	96.7±19.0	<0.001[a]
Cystatin C (mg/L)	1.4±0.6	1.5±0.7	0.079
Cystatin C GFR (mL/min/1.73 m^2)	58.3±25.8	57.3±25.6	0.339
CRP (mg/dL)	0.2±0.1	0.2±0.2	0.658
UPCR (g/g)	1.0±1.7	1.3±2.3	0.083
HbA1c (%)	7.6±1.5	7.3±1.3	0.038[a]
Adiponectin (μg/mL)	10.4±5.3	10.0±5.2	0.192

Values are presented as mean±standard deviation or number (%).
BP, blood pressure; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein; UPCR, urine protein-creatinine ratio; HbA1c, glycated hemoglobin.
[a] $p<0.05$, mean values are significantly different from the baseline data.

Table 2. Change in erythrocyte membrane fatty acid content after statin treatment

Variable	Baseline (n=28)	24 weeks (n=28)	*p*-value
Saturated	41.3±2.2	40.3±1.9	0.016[a]
Myristic	0.3±0.1	0.3±0.1	0.458
Palmitic	23.4±1.4	22.3±1.2	<0.001[a]
Stearic	16.4±0.9	16.8±1.0	0.827
Lignoceric	0.5±0.2	0.4±0.1	0.787
Monounsaturated	17.1±1.1	17.1±1.2	0.370
Palmitoleic	0.5±0.2	0.2±0.2	0.501
Trans-oleic	0.20±0.1	0.17±0.0	0.015[a]
Oleic	14.9±1.3	15.1±1.6	0.282
Polyunsaturated	42.1±3.3	42.9±3.3	0.178
Omega-6	28.6±2.7	29.2±2.7	0.067
Linoleic	10.7±1.2	10.4±1.8	0.244
AA	13.6±1.8	14.3±1.5	0.006[a]
Omega-3	13.5±2.3	13.7±2.8	0.697
Alpha-linolenic	0.2±0.1	0.3±0.1	0.287
EPA	1.8±0.8	1.7±0.8	0.714
DHA	8.9±1.6	9.1±1.6	0.577
Omega-3 index	10.7±2.1	10.9±2.2	0.745
AA/EPA	9.1±4.3	10.4±5.2	0.053
AA/DHA	1.56±0.3	1.62±0.3	0.255
Omega-6/omega-3	2.2±0.5	2.3±0.6	0.544
Total trans-fatty acid	0.5±0.1	0.4±0.1	0.227

Values are presented as mean±standard deviation.
AA, arachidonic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.
[a] $p<0.05$, mean values are significantly different from the baseline data.

spectively) in the patients treated with pitavastatin (Table 3). Patients with DM treated with pitavastatin for 24 weeks showed a significant decrease in HbA1c levels ($p=0.045$) (Fig. 2). Patients treated with atorvastatin had significantly lower total cholesterol, LDL cholesterol, and uric acid levels ($p=0.005$, $p=0.002$, and $p=0.045$, respectively). Patients treated with pitavastatin showed a significant increase in AA content ($p=0.020$), whereas those treated with atorvastatin showed a significant decrease in palmitic acid content ($p=0.005$) (Table 4). Fig. 3 shows that AA content significantly increased only in patients treated with pitavastatin. No significant changes were observed in the AA/DHA ratio or total trans-FA levels in either patient group. In patients with eGFR ≥60 mL/min/1.73 m^2, there was a significant decrease in the levels of saturated FAs, palmitic acid, lignoceric acid, trans-oleic acid, and total trans-FAs after statin treatment ($p=0.023$, $p=0.033$, $p=0.046$, $p=0.023$, and $p=0.039$, respectively). Only palmitic acid was significantly decreased in patients with eGFR <60 mL/min/1.73 m^2 (Supplementary Table 1). Neither group showed significant changes in AA content or the AA/DHA ratio compared to the baseline.

4. Adverse effects and dropout

Pitavastatin did not cause any significant adverse effects. During the analysis, four patients withdrew due to acute kidney injury, which was determined to be unrelated to statin use. In patients treated with pitavastatin or atorvastatin, there was a significant increase in AST ($p=0.008$) and ALT levels ($p=0.030$) after 24 weeks (Table 1), which could have been a side effect of statin treatment; however, there were no serious adverse effects that required treatment discontinuation.

Discussion

This study found that statin treatment modified the FA composition of erythrocyte membranes in patients with CKD. The levels of saturated FAs, palmitic acid, and trans-oleic acid in the erythro-

Table 3. Clinical blood biochemical analyses according to pitavastatin or atorvastatin treatment

Variable	Pitavastatin (n = 16)			Atorvastatin (n = 12)		
	Baseline	24 weeks	*p*-value	Baseline	24 weeks	*p*-value
Age (yr)	60.4 ± 9.1			66.4 ± 8.0		
Male sex	8 (50.0)			6 (50.0)		
Diabetes mellitus	10 (62.5)			9 (75.0)		
Systolic BP (mmHg)	129.6 ± 19.6	132.8 ± 15.6	0.518	133.2 ± 13.6	132.8 ± 12.5	0.937
Diastolic BP (mmHg)	71.7 ± 12.1	72.5 ± 8.7	0.717	74.5 ± 11.4	73.3 ± 9.2	0.906
Calcium (mg/dL)	9.3 ± 0.5	9.2 ± 0.5	0.448	9.1 ± 0.7	9.1 ± 0.5	0.721
Phosphorus (mg/dL)	3.7 ± 0.5	3.7 ± 0.6	0.900	3.6 ± 0.5	3.6 ± 0.7	0.906
Glucose (mg/dL)	151.9 ± 106.5	118.2 ± 36.1	0.570	145.5 ± 41.8	140.8 ± 41.6	0.480
BUN (mg/dL)	20.1 ± 8.4	22.6 ± 10.1	0.163	22.4 ± 7.7	21.5 ± 11.4	0.637
Creatinine (mg/dL)	1.2 ± 0.6	1.3 ± 0.7	0.162	1.4 ± 0.6	1.5 ± 0.8	0.657
eGFR (mL/min/1.73 m^2)	68.5 ± 30.7	68.4 ± 31.3	0.796	52.9 ± 19.3	55.3 ± 22.2	0.272
CKD-EPI (mL/min/1.73 m^2)	66.5 ± 28.2	66.2 ± 29.3	0.623	51.5 ± 19.2	53.8 ± 22.1	0.346
Uric acid (mg/dL)	6.0 ± 2.0	5.6 ± 1.5	0.468	6.7 ± 1.4	6.1 ± 1.5	0.045[a]
Total cholesterol (mg/dL)	232.4 ± 37.0	164.3 ± 22.5	< 0.001[a]	209.8 ± 49.4	149.3 ± 28.0	0.005[a]
Albumin (g/dL)	4.2 ± 0.4	4.3 ± 0.4	0.243	4.0 ± 0.5	4.1 ± 0.4	0.878
AST (U/L)	20.4 ± 5.4	23.2 ± 5.4	0.069	21.2 ± 10.3	24.8 ± 11.0	0.090
ALT (U/L)	17.2 ± 6.0	20.0 ± 6.1	0.031[a]	17.8 ± 13.2	20.8 ± 8.4	0.068
Triglyceride (mg/dL)	210.6 ± 113.7	188.0 ± 153.2	0.423	242.3 ± 148.6	190.4 ± 113.2	0.099
HDL (mg/dL)	49.1 ± 11.0	48.4 ± 9.2	0.776	45.3 ± 7.4	45.8 ± 8.5	0.789
LDL (mg/dL)	159.9 ± 24.8	98.9 ± 16.8	< 0.001[a]	147.9 ± 23.4	93.8 ± 22.1	0.002[a]
Cystatin C (mg/L)	1.3 ± 0.6	1.4 ± 0.7	0.222	1.5 ± 0.5	1.6 ± 0.7	0.480
Cystatin C GFR (mL/min/1.73 m^2)	65.1 ± 30.2	63.3 ± 29.5	0.233	49.9 ± 16.4	49.8 ± 18.4	0.724
CRP (mg/dL)	0.1 ± 0.1	0.2 ± 0.2	0.268	0.2 ± 0.1	0.1 ± 0.1	0.789
UPCR (g/g)	1.1 ± 2.0	1.5 ± 2.7	0.349	0.7 ± 1.1	0.9 ± 1.5	0.146
HbA1c (%)	7.6 ± 1.4	7.1 ± 1.2	0.045[a]	7.7 ± 1.6	7.4 ± 1.4	0.237
Adiponectin (μg/mL)	9.3 ± 4.9	8.9 ± 4.2	0.410	11.9 ± 5.7	11.4 ± 6.1	0.638

Values are presented as means ± standard deviation or number (%).

BP, blood pressure; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; AST, aspartate aminotransferase; ALT, alanine aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CRP, C-reactive protein; UPCR, urine protein-creatinine ratio; HbA1c, glycated hemoglobin.

[a] $p < 0.05$, mean values are significantly different from the baseline data.

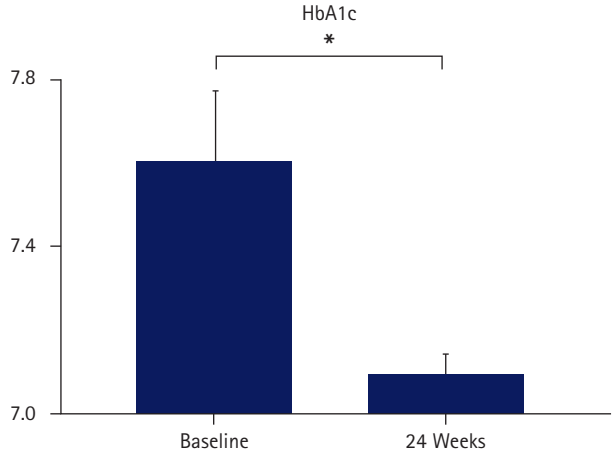

Fig. 2. Changes in HbA1c before and after the administration of pitavastatin to patients with hyperlipidemia and diabetes mellitus. HbA1c, glycated hemoglobin. *$p < 0.05$, mean values are significantly different from the baseline data.

cyte membrane decreased, similar to the decrease in total cholesterol and LDL cholesterol levels. It is widely acknowledged that saturated FAs raise levels of LDL cholesterol, and the consumption of trans-FAs is associated with an increased risk of cardiovascular disease [11-14]. Based on these observations, pitavastatin and atorvastatin may reduce the risk of cardiovascular disease by reducing LDL cholesterol and saturated FA levels.

There are several hypotheses for statin-induced new-onset DM, including reduced 3-hydroxy-3-methylglutaryl coenzyme A reductase activity, decreased adiponectin levels, increased insulin resistance, and impaired pancreatic beta cell function [15]. However, unlike other statins, pitavastatin has been reported to have no effect on serum glucose levels [16]. Pitavastatin was found to increase AA levels and decrease DHA/AA ratios [9]. Previous studies have demonstrated that AA and DHA prevent DM by regulating insulin secretion [17]. In our study, patients who received pitavastatin showed a significant increase in AA levels and a decrease in HbA1c

Table 4. Change in erythrocyte membrane fatty acid content after pitavastatin or atorvastatin treatment

Variable	Pitavastatin (n=16)			Atorvastatin (n=12)		
	Baseline	24 weeks	*p*-value	Baseline	24 weeks	*p*-value
Saturated	41.2±2.3	40.4±2.2	0.088	41.3±2.0	40.3±1.9	0.084
Myristic	0.3±0.1	0.3±0.1	0.959	0.4±0.1	0.3±0.1	0.308
Palmitic	23.3±1.3	22.6±1.3	0.088	23.4±1.6	22.0±1.0	0.005[a]
Stearic	17.1±1.2	16.9±1.3	0.918	17.0±1.0	17.3±0.9	0.209
Lignoceric	0.5±0.1	0.5±0.1	0.642	0.5±0.2	0.5±0.2	>0.999
Monounsaturated	16.0±1.4	16.2±1.8	>0.999	15.9±1.6	16.2±1.9	0.433
Palmitoleic	0.4±0.1	0.5±0.2	0.605	0.6±0.2	0.5±0.2	0.209
Trans-oleic	0.2±0.1	0.2±0.0	0.056	0.2±0.0	0.2±0.0	0.099
Oleic	15.0±1.3	15.2±1.6	0.717	14.7±1.4	15.1±1.7	0.347
Polyunsaturated	42.0±3.4	42.8±3.5	0.278	42.2±3.3	43.0±3.2	0.347
Omega-6	28.1±2.8	29.1±2.7	0.070	29.3±2.6	29.4±2.9	0.480
Linoleic	10.8±1.4	10.5±2.0	0.215	10.6±0.9	10.3±1.5	0.209
AA	13.3±1.7	14.3±1.4	0.020[a]	13.9±1.9	14.4±1.6	0.209
Omega-3	13.9±2.7	13.7±2.8	0.877	12.9±1.5	13.6±2.8	0.583
Alpha-linolenic	0.2±0.1	0.3±0.2	0.918	0.2±0.1	0.2±0.1	0.308
EPA	1.9±0.9	1.9±0.8	0.918	1.7±0.7	1.5±0.9	0.754
DHA	9.3±1.7	9.0±1.7	0.438	8.4±1.2	9.2±1.5	0.117
Omega-3 index	11.2±2.4	10.9±2.3	0.756	10.1±1.3	10.7±2.2	0.433
AA/EPA	8.4±3.7	9.3±5.0	0.255	9.9±4.9	11.9±5.2	0.209
AA/DHA	1.5±0.4	1.6±0.3	0.063	1.7±0.3	1.6±0.3	0.530
Omega-6/omega-3	2.1±0.6	2.2±0.7	0.642	2.3±0.3	2.3±0.5	0.814
Total trans-fatty acid	0.5±0.1	0.4±0.1	0.148	0.5±0.1	0.5±0.1	0.875

Values are presented as means±standard deviation.
AA, arachidonic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid.
[a] $p<0.05$, mean values are significantly different from the baseline data.

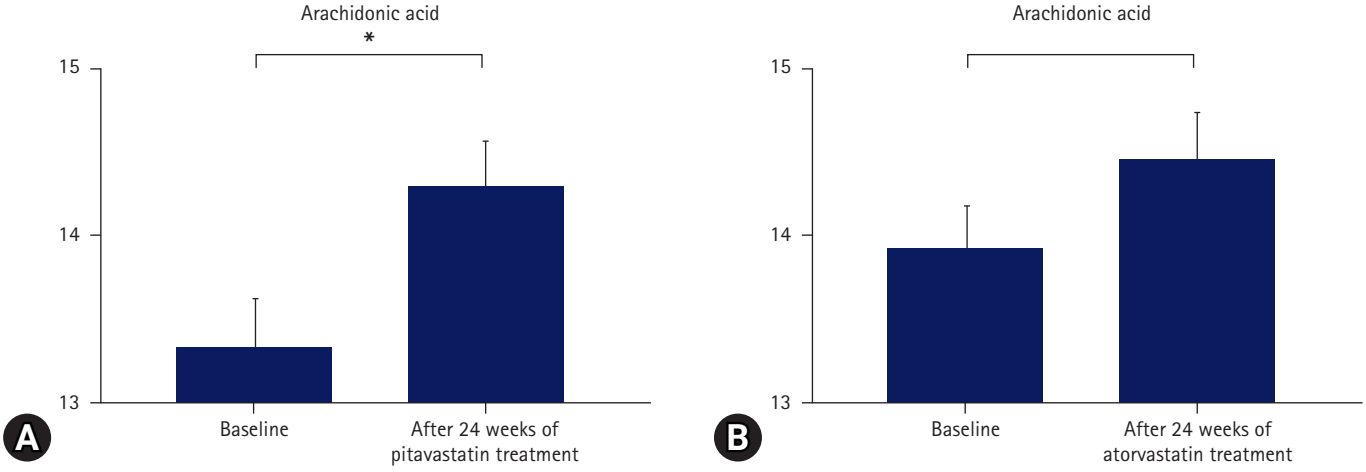

Fig. 3. Changes in arachidonic acid in erythrocyte membrane fatty acids after receiving (A) 24 weeks of pitavastatin and (B) 24 weeks of atorvastatin. *$p<0.05$, mean values are significantly different from the baseline data.

levels. Although there were no significant changes in the AA/DHA ratio, our findings indicate that pitavastatin treatment may reduce HbA1c levels by increasing AA levels. In a meta-analysis of 13 prospective randomized controlled trials involving 91,140 patients without DM treated with statins, a mean follow-up period of 4 years was conducted to observe the occurrence of DM [18]. Since there was a significant decrease in HbA1c levels among the 10 patients with DM treated with pravastatin and no significant change in HbA1c levels among the nine patients treated with atorvastatin, pitavastatin may not be harmful to glucose control.

Decreased adiponectin levels are closely associated with worsening insulin resistance, which is associated with the onset of DM

[19]. A previous study reported that after 6 months of pitavastatin treatment in 117 patients with hyperlipidemia, there was a significant decrease in total cholesterol and LDL cholesterol and an increase in adiponectin levels [20]. Our study showed no significant changes in adiponectin levels in patients treated with pitavastatin; however, the reason for this is unclear. Due to the limited number of enrolled patients in our study, we suspect that there may not have been sufficient observations to adequately assess changes in adiponectin levels.

Studies have suggested that atorvastatin significantly reduces serum uric acid levels compared to other statins [21,22]. In our study, we also observed a significant reduction in serum uric acid levels after 24 weeks of atorvastatin treatment; however, such changes were not observed with pitavastatin treatment. It is unclear why there is a difference between atorvastatin and pitavastatin in terms of the changes in uric acid levels. A possible cause may be decreased uric acid production due to atorvastatin. Decreasing uric acid levels with atorvastatin treatment may be beneficial for preserving renal function in patients with CKD.

Adverse effects can occur in patients treated with statins; myopathy is the most commonly observed side effect, but hepatotoxicity can also occur [23,24]. In our study, there was a significant increase in ALT and AST levels after statin use. No cases of myopathy were observed in this study. Although the increase in liver enzyme levels was not severe enough to discontinue treatment, careful monitoring is necessary to avoid possible side effects.

This study had several limitations. First, our study included an inadequate sample size. We planned to recruit 72 participants; however, only 45 patients were enrolled and 28 completed the study. Enrollment was stopped due to insufficient recruitment and a prolonged recruitment period. This insufficient enrollment may have affected our results. Second, we did not initially plan to assess insulin resistance. Third, we did not check for glycated albumin, and HbA1c is not reliable in patients with anemia and a lower eGFR.

In conclusion, pitavastatin and atorvastatin treatments controlled cholesterol levels and modified FA content, thereby reducing cardiovascular risk. Although our study did not show significant changes in adiponectin levels, we observed a decrease in HbA1c levels and an increase in AA levels in the pitavastatin group. Based on these findings, we believe that pitavastatin use in patients with CKD may benefit glucose metabolism and alter erythrocyte membrane AA levels, and that pitavastatin does not have detrimental effects on glucose control in patients with CKD and DM.

Supplementary materials

Supplementary Table 1 can be found at https://doi.org/10.12701/jyms.2024.00094.

Article information

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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Author contributions

Conceptualization, Supervision: SEK, WSA; Data curation: SML, WSA; Formal analysis: SEK, SML, WSA; Funding acquisition, Investigation: WSA; Methodology: MK; Writing-original draft: MK, WSA; Writing-review & editing: all authors.

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References

1. Afkarian M, Sachs MC, Kestenbaum B, Hirsch IB, Tuttle KR, Himmelfarb J, et al. Kidney disease and increased mortality risk in type 2 diabetes. J Am Soc Nephrol 2013;24:302–8.
2. Tonelli M, Muntner P, Lloyd A, Manns BJ, Klarenbach S, Pannu N, et al. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. Lancet 2012;380:807–14.
3. Kendrick J, Chonchol MB. Nontraditional risk factors for cardiovascular disease in patients with chronic kidney disease. Nat Clin Pract Nephrol 2008;4:672–81.
4. Baigent C, Landray MJ, Reith C, Emberson J, Wheeler DC, Tomson C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011;377:2181–92.
5. Wanner C, Tonelli M; Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group Members. KDIGO Clinical Practice Guideline for Lipid Management in

CKD: summary of recommendation statements and clinical approach to the patient. Kidney Int 2014;85:1303–9.
6. Cederberg H, Stančáková A, Yaluri N, Modi S, Kuusisto J, Laakso M. Increased risk of diabetes with statin treatment is associated with impaired insulin sensitivity and insulin secretion: a 6 year follow-up study of the METSIM cohort. Diabetologia 2015;58:1109–17.
7. Seo WW, Seo SI, Kim Y, Yoo JJ, Shin WG, Kim J, et al. Impact of pitavastatin on new-onset diabetes mellitus compared to atorvastatin and rosuvastatin: a distributed network analysis of 10 real-world databases. Cardiovasc Diabetol 2022;21:82.
8. Mahendran Y, Ågren J, Uusitupa M, Cederberg H, Vangipurapu J, Stančák ová A, et al. Association of erythrocyte membrane fatty acids with changes in glycemia and risk of type 2 diabetes. Am J Clin Nutr 2014;99:79–85.
9. Nozue T, Yamamoto S, Tohyama S, Fukui K, Umezawa S, Onishi Y, et al. Comparison of effects of serum n-3 to n-6 polyunsaturated fatty acid ratios on coronary atherosclerosis in patients treated with pitavastatin or pravastatin undergoing percutaneous coronary intervention. Am J Cardiol 2013;111:1570–5.
10. Nozue T, Michishita I. Statin treatment alters serum n-3 to n-6 polyunsaturated fatty acids ratio in patients with dyslipidemia. Lipids Health Dis 2015;14:67.
11. Briggs MA, Petersen KS, Kris-Etherton PM. Saturated fatty acids and cardiovascular disease: replacements for saturated fat to reduce cardiovascular risk. Healthcare (Basel) 2017;5:29.
12. Iqbal MP. Trans fatty acids: a risk factor for cardiovascular disease. Pak J Med Sci 2014;30:194–7.
13. Kleber ME, Delgado GE, Dawczynski C, Lorkowski S, März W, von Schacky C. Saturated fatty acids and mortality in patients referred for coronary angiography: the Ludwigshafen Risk and Cardiovascular Health study. J Clin Lipidol 2018;12:455–63.
14. Eckel RH, Jakicic JM, Ard JD, de Jesus JM, Houston Miller N, Hubbard VS, et al. 2013 AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation 2014;129(25 Suppl 2):S76–99.
15. Robinson JG. Statins and diabetes risk: how real is it and what are the mechanisms? Curr Opin Lipidol 2015;26:228–35.
16. Cho Y, Lee H, Park HK, Choe EY, Wang HJ, Kim RH, et al. Differential diabetogenic effect of pitavastatin and rosuvastatin, in vitro and in vivo. J Atheroscler Thromb 2020;27:429–40.
17. Das UN. Syntaxin interacts with arachidonic acid to prevent diabetes mellitus. Lipids Health Dis 2022;21:73.
18. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, de Craen AJ, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomized statin trials. Lancet 2010;375:735–42.
19. Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, Tataranni PA, et al. Adiponectin and development of type 2 diabetes in the Pima Indian population. Lancet 2002;360:57–8.
20. Inami N, Nomura S, Shouzu A, Omoto S, Kimura Y, Takahashi N, et al. Effects of pitavastatin on adiponectin in patients with hyperlipidemia. Pathophysiol Haemost Thromb 2007;36:1–8.
21. Akbari A, Razmi M, Rafiee M, Watts GF, Sahebkar A. The effect of statin therapy on serum uric acid levels: a systematic review and meta-analysis. Curr Med Chem 2024;31:1726-39.
22. Milionis HJ, Kakafika AI, Tsouli SG, Athyros VG, Bairaktari ET, Seferiadis KI, et al. Effects of statin treatment on uric acid homeostasis in patients with primary hyperlipidemia. Am Heart J 2004;148:635–40.
23. Thompson PD, Panza G, Zaleski A, Taylor B. Statin-associated side effects. J Am Coll Cardiol 2016;67:2395–410.
24. Bełto wski J, Wójcicka G, Jamroz-Wiśnie wska A. Adverse effects of statins: mechanisms and consequences. Curr Drug Saf 2009;4:209–28.