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THERAPEUTIC EFFICACY OF PITAVASTATIN ON METABOLIC PARAMETERS IN DIABETIC AND NON-DIABETIC PATIENTS: SINGLE CENTER, RETROSPECTIVE, CLINICAL STUDY IN TÜRKİYE

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ABSTRACT

Objective: *We aimed to investigate the lipid-lowering efficacy of pitavastatin treatment in nondiabetic patients and patients with type 2 diabetes as well as the possible differences in diabetes regulation and treatment efficacy.*

Material and Method: *A total of 53 patients using only 2 mg of pitavastatin were included in our retrospective study. For examination the patients were divided into 4 groups. Those without a diagnosis of diabetes were the first group, those with a diabetes diagnosis and HbA1c values between 6% and 7.5% at both visits were the second group, those with HbA1c values above 7.5% at both visits were the third group, and those with HbA1c values were above 7.5% at the first visit. and below 7.5% at the second visit were determined as the fourth group. The lipid values, alanine transaminase (SGPT), aspartate transaminase (SGOT), and creatine phosphokinase (CPK) values of the patients in the groups were compared before and after treatment.*

Results: *The differences between the first and second visits (with percentages in parentheses) of the mean lipid values of the patients in the first, second, third and fourth groups were – 98.6 mg/dL (33.2%) (p<0.01), – 50.7 mg/dL (19.5%), – 52.2 mg/dL (21.7%), and – 58.2 mg/dL (23.3%) for total cholesterol; – 90 mg/dL (42.6%) (p<0.01), – 57.5 mg/dL (31.9%), – 55.4 mg/dL (34.8%), and – 64.9 mg/dL (37.9%) for low-density lipoprotein (LDL) cholesterol. There was no significant change in SGPT, SGOT, or CPK levels in all of the groups. No adverse effects were noted that would terminate the pitavastatin-related treatment.*

Conclusion: *Moderate doses of pitavastatin provided effective and safe lipid control in nondiabetic patients and diabetic patients receiving antidiabetic therapy.*

Keywords: *Pitavastatin, diabetes mellitus, hyperlipidemia.*

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PİTAVASTATİNİN DİYABETİK VE NON DİYABETİK HASTALARDA METABOLİK PARAMETRELERE TERAPÖTİK ETKİNLİĞİ: TÜRKİYE'DEN, TEK MERKEZLİ RETROSPEKTİF KLİNİK ÇALIŞMA

ÖZET

Amaç: Diyabetik olmayan hastalarda ve tip 2 diyabetli hastalarda pitavastatin tedavisinin lipid düşürücü etkinliğinin yanı sıra diyabetin düzenlenmesi ve tedavi etkinliğindeki olası farklılıklarını araştırmayı amaçladık.

Materyal ve Metot: Retrospektif çalışmamıza sadece 2 mg pitavastatin kullanan toplam 53 hasta dahil edildi. Hastalar muayene için 4 gruba ayrıldı. Diyabet tanısı olmayanlar birinci grup, diyabet tanısı olup HbA1c değeri her iki vizitte de %6 ile %7,5 arasında olanlar ikinci grup, HbA1c değeri her iki vizitte de %7,5'in üzerinde olanlar üçüncü grup ve HbA1c değeri ilk ziyarette %7,5'in üzerinde olup ikinci ziyarette %7,5'in altında olanlar ise dördüncü grup olarak belirlendi. Gruplardaki hastaların tedavi öncesi ve sonrası lipit değerleri, alanin transaminaz (SGPT), aspartate transaminaz (SGOT) ve kreatin fosfokinaz (CPK) değerleri karşılaştırıldı.

Bulgular: Birinci, ikinci, üçüncü ve dördüncü gruptaki hastaların ortalama lipid değerlerinin birinci ve ikinci vizit (yüzdeler parantez içinde) arasındaki farklar total kolesterol için -98,6 mg/dL (%33,2) (p<0,01), -50,7 mg/dL (%19,5), -52,2 mg/dL (%21,7) ve -58,2 mg/dL iken. (%23,3); Düşük yoğunluklu lipoprotein (LDL) kolesterol için –90 mg/dL (%42,6) (p<0.01), –57,5 mg/dL (%31,9), –55,4 mg/dL (%34,8) ve –64,9 mg/dL (%37,9) şeklinde idi. Tüm gruplarda SGPT, SGOT veya CPK seviyelerinde anlamlı bir değişiklik olmadı. Pitavastatine bağlı tedaviyi sonlandıracak bir yan etki not edilmedi.

Sonuç: Diyabetik olmayan hastalarda ve antidiyabetik tedavi alan diyabetik hastalarda orta doz pitavastatin etkili ve güvenli lipid kontrolü sağlamıştır.

Anahtar kelimeler: Pitavastatin, diabetes mellitus, hiperlipidemi.

INTRODUCTION

Lipid-lowering therapies for cardiovascular protection have been investigated for a long time. Statins, also known as HMG CoA reductase inhibitors, are a group of lipid-lowering therapies that have proven themselves in terms of primary and secondary cardiovascular protection.[1-3] Pitavastatin, a new member of the statins group, is an agent that has attracted clinicians' attention with its low side effect profile and positive metabolic effects, as compared to other statins.[4-6] Diabetes is a major risk factor in the development of cardiovascular events, and lipid-lowering treatments for cardiovascular protection are strongly recommended in patients diagnosed with diabetes.[7] The fact that the pitavastatin molecule is a drug that was discovered later than other statins and that it has been used recently in Türkiye made us think that there is a need to increase clinical experience with this drug in our country. So, we aimed to investigate the lipid-lowering efficacy and safety profile in terms of side effects of moderate-dose pitavastatin treatment in nondiabetic patients and patients with type 2 diabetes. While planning the study, we thought that this drug could be used more in the diabetic patient population since statins were used due to increased cardiovascular risk in diabetic patients with lower cholesterol values, and we aimed to include not only nondiabetic patients but also diabetic patients in the study to reach more patients and investigate the efficacy of the drug in diabetics.

MATERIAL AND METHOD

A total of 53 patients who were followed up between January 2018 and January 2020 in the internal diseases outpatient clinic of Fatih Sultan Mehmet Training and Research Hospital were included in our retrospective cross-sectional study. The inclusion criteria were being over 18 years of age, using only 2 mg of pitavastatin continuously to treat hyperlipidemia for at least 6 weeks, and having complete information such as physical examination findings and biochemical parameters in the patient" electronic files for follow-ups just before and after the start of the statin. Patients under 18 years of age, pregnant patients, patients with chronic renal failure, patients who received non-pitavastatin statin treatment or who did not use pitavastatin regularly, and patients whose physical examination and biochemical parameters were missing from the hospital's electronic records were excluded from the study.

The patient files were scanned for physical examination findings, body mass indexes, systolic and diastolic blood pressures, smoking status, waist/hip circumference ratio, periods between pitavastatin initiation and after control, levels of lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, total cholesterol, triglycerides, creatine phosphokinase (CPK), aspartate transaminase (SGOT), alanine transaminase (SGPT), and HbA1c before and after pitavastatin use. A Tosoh

G8 Model High-Performance Liquid Chromatography Analyzer (Tosoh Bioscience, Tokyo, Japan) was used to measure HbA1c, and an ARCHITECT c16200i photometric device (Abbott Diagnostics, Lake Forest IL, USA) was used to measure the other biochemical parameters. The patients were divided into 4 groups for examination: those who were not diagnosed with diabetes and those with a diabetes diagnosis and an HbA1c value between 6 and 7.5 at both visits, an HbA1c value above 7.5 at both visits, and an HbA1c value above 7.5 at the first visit and below 7.5 at the second visit.

The data obtained from the patients were analyzed with Stata version 14. Shapiro Wilks test was used as homogeneity test. Fisher Freeman Halton Exact test was used to evaluate the possible difference between groups in terms of categorical variables. The parameters' means and standard deviations were calculated. The differences of groups among non-categorical parameters were analyzed using paired t-tests. A value of $p< 0.05$ was considered significant. Our study was conducted by the Principles of the Declaration of Helsinki. We were informed by Ethical Committee Decision FSM EAH-KAEK 2020/129, dated September 10, 2020, that there was no ethical harm in conducting our study.

RESULTS

A total of 53 patients (25 men and 28 women) were included in the study. There were 10 patients in the first and third groups, 17 patients in the second group, and 16 patients in the fourth group. The mean ages of the patients by the group in years were 54.5 (10.1), 57.3 (8.9), 66 (12.1), and 56.4 (7.4), respectively. The mean age of the third group was significantly higher than that of the other groups (p=0.002). The rates of patients diagnosed with known hypertension in the groups were 40% in the first group, 29% in the second group, 70% in the third group, and 43% in the fourth group.

There was no statistically significant difference between the groups in terms of the frequency of diagnosis of hypertension. (p:0.245) The mean systolic blood pressure in groups 1 through 4 in mm Hg was 119.5 (17), 122.4 (16.1), 138.8 (15.3), and 125.4 (19.2), respectively, and their waist/hip ratios were 0.90 (0.05), 0.94 (0.07), 0.94 (0.06), and 0.95 (0.06), respectively.

The systolic blood pressure of the patients in the third group was significantly higher (p=0.006), while the waist/hip ratio of the patients in the first group was significantly lower (p=0.03). There was no significant difference between the groups in terms of diastolic blood pressure, smoking status, and duration of pitavastatin use until the second visit. The patient baseline characteristics of the patients are shown in Table 1.

Table 1. Baseline Characteristics of 4 Groups.

	Group 1	Group 2	Group 3	Group 4	*p*
Male/female, n **Total, n**	2/8 10	6/11 17	5/5 10	12/4 16	
Age, mean (SD)	54.5 (10.1)	57.3 (8.9)	66 (12.1)*	56.4 (7.4)	0 .002*
BMI, mean (SD)	30.7 (5.2)	30.1 (4.3)	31.5 (4.7)	32.7 (6.8)	>0.05
Hypertension %, (n)	40 (4)	29 (5)	70 (7)	43 (7)	>0.05
SBP, mm Hg, mean (SD)	119.5 (17)	122.4 (16.1)	138.8 (15.3) **	125.4 (19.2)	0.006**
DBP, mm Hg, mean (SD)	74.5 (12.1)	75.8 (10.5)	80 (8.6)	80.8 (5.1)	>0.05
Smoking status %	10	17	20	12	>0.05
Waist-to-hip ratio, mean (SD)	0.90 (0.05) α	0.94 (0.07)	0.94 (0.06)	0.95 (0.06)	0.03 α
Duration of pitavastatin (weeks)	9.8	11.4	10.5	11.3	>0.05

SBP: Systolic blood pressure, **DBP:** diastolic blood pressure, **SD:** standard deviation, **BMI:** body mass index
*** :** Mean age of group 3 is significantly higher than other groups
****:** The mean systolic blood pressure in group 3 was found to be significantly higher than the other groups.
α: In group 1, the mean waist-hip ratio was found to be significantly lower than the other groups.

The mean total cholesterol levels of the patients in the first, second, third, and fourth groups before and after pitavastatin were 296.7/198.1, 259.7/209, 240.3/188.1, and 249.5/191.3 mg/dL; their LDL cholesterol levels were 211.1/121.1, 180.1/122.6, 159.1/103.7, and 171.5/106.6 mg/dL; their triglyceride levels were 201.7/142.6, 164.1/140.3, 177.5/205.2, and 191.3/147.8 mg/dL; and their HDL cholesterol levels were 44.7/48, 49.1/48.2, 44.3/45.8, and 42.8/44.6 mg/dL, respectively. The differences between the first and second visits (with percentages in parentheses) of the mean lipid values of the patients in the first, second, third and fourth groups were –98.6 mg/dL (33.2%), –50.7 mg/dL (19.5%), –52.2 mg/dL (21.7%), and –58.2 mg/dL (23.3%) for total cholesterol; –90 mg/dL (42.6%), –57.5 mg/dL (31.9%), –55.4 mg/dL (34.8%), and –64.9 mg/dL (37.9%) for LDL cholesterol; –59.1 mg/dL (29.4%), –23.8 mg/dL (14.5%), +27.7 mg/dL (15.6%), and –43.5 mg/dL (22.7%) for triglycerides; and +3.3 mg/dL (7.3%), –0.9 mg/dL (1.8%), +1.5 mg/dL (3.3%), and +1.8 mg/dL (4.2%) for HDL cholesterol, respectively. In terms of lipid profile, after pitavastatin treatment, significantly higher differences were found among the first group in total cholesterol, LDL cholesterol, and triglycerides. Triglyceride levels, which decreased at similar rates in the first, second, and fourth groups, were significantly increased at the second visit in the third group, contrary to the other groups. The mean HbA1c percentage before/after

Table 2. Biochemical parameters before and after pitavastatin treatment

	Group 1		Group 2		Group 3		Group 4	
	Pre.	Post.	Pre.	Post.	Pre.	Post.	Pre.	Post.
Total cholesterol, mg/dL, mean(SD)	296.7 (36.2)	198.1 (25.1)	259.7 (36.7)	209.0 (29.5)	240.3 (27.8)	188.1 (37.3)	249.5 (28.4)	191.3 (38.5)
difference (%)	98.6 (33.2)*		50.7 (19.5)		52.2 (21.7)		58.2 (23.3)	
LDL cholesterol, mg/dL, mean(SD)	211.1 (33.2)	121.1 (22.1)	180.1 (32.9)	122.6 (27.4)	159.1 (22.5)	103.7 (24.9)	171.5 (32.1)	106.6 (26.1)
difference (%)	90 (42.6)**		57.5 (31.9)		55.4 (34.8)		64.9 (37.9)	
Triglycerides, mg/dL, mean(SD)	201.7 (76.1)	142.6 (49.4)	164.1 (82.9)	140.3 (77.7)	177.5 (71.5)	205.2 (113.8)	191.3 (50.8)	147.8 (54.3)
difference (%)	59.1 (29.4)***		23.8 (14.5)		+27.7 (15.6)****		43.5 (22.7)	
HDL cholesterol, mg/dL, mean(SD)	44.7 (12.6)	48 (13.6)	49.1 (11.4)	48.2 (13.8)	44.3 (9.6)	45.8 (10.2)	42.8 (9.1)	44.6 (10.3)
difference (%)	+3.3 (7.3)		0.9 (1.8)		+1.5 (3.3)		+1.8 (4.2)	
HbA1c, %	5.6	5.8	6.6	6.8	8.4	8.1	9.3	6.4
CPK, mg/dL, mean(SD)	131.2 (91.7)	126.6 (88.8)	66.8 (37.3)	80.5 (41.2)	102.3 (52.1)	91.6 (39.2)	85.8 (49.4)	100.4 (83.8)
SGPT, mg/dL, mean(SD)	23.8 (17.6)	18.4 (5.4)	25.4 (7.9)	23.5 (4.1)	22.1 (10.5)	20.6 (8.5)	24.1 (16.2)	17.6 (6.9)
SGOT, mg/dL, mean(SD)	19.6 (5.8)	17.5 (4.4)	21.7 (7.5)	21.8 (6.8)	21.4 (11.3)	19.8 (7.8)	16.7 (4.3)	16.6 (3.2)

Pre.: before pitavastatin treatment, **Post.:** after pitavastatin treatment, **HbA1c:** glike hemoglobin, **SD:** standard deviation
CPK: creatine phosphokinase; **SGPT:** alanine transaminase; **SGOT:** aspartate transaminase, **LDL:** lipoprotein, **HDL:** high-density lipoprotein
* Difference of Total Cholesterol in group 1, $p = .0011$, ** Difference of LDL cholesterol in group 1, $p = .003$
*** Difference of Triglyceride in group 1, $p = .031$, **** Difference of Triglyceride in group 3, $p = .0016$

Pitavastatin was 5.6%/5.8%, 6.6%/6.8%, 8.4%/8.1%, and 9.3%/6.4%; the mean CPK levels were 131.2/121.6 mg/dL, 66.8/80.5 mg/dL, 102.3/91.6 mg/dL, and 85.8/100.4 mg/dL; the mean SGPT levels were 23.8/18.4 mg/dL, 25.4/23.5 mg/dL, 22.1/20.6 mg/dL, and 24.1/17.6 mg/dL; and the mean SGOT levels were 19.6/17.5 mg/dL, 21.7/21.8 mg/dL, 21.4/19.8 mg/dL, and 16.7/16.6 mg/dL in the first to fourth groups, respectively. As expected, HbA1c was significantly lower in the fourth group at the second visit. There was no significant change in SGPT, SGOT, or CPK levels in all of the groups. Table 2 shows the lipid levels and changes of the patient groups at both visits.

DISCUSSION

Our study has provided additional information to the literature in terms of being a study investigating the efficacy and safety profile of pitavastatin, which has recently been used in our country. According to our study, pitavastatin treatment was an effective and safe treatment in both diabetics which with and without controlled diabetes and non-diabetic patients.

Blood lipid level disorders, especially high LDL cholesterol, have an important place in the development of atherosclerotic cardiovascular diseases, which can be prevented with LDL-cholesterol-lowering treatments.[8] Pitavastatin is a new-generation synthetic HMG-CoA reductase inhibitor and a type of statin, which is the focus of LDL-lowering therapies, that experts recommend due to its positive effects.[9] Unlike other statins, Pitavastatin is minimally metabolized in the liver by Cytochrome p450 2C9 and 2C8 enzymes due to the cyclopropyl group it contains.[10] Fewer drug interactions with this molecule have been detected than for rosuvastatin and atorvastatin, which are statins with high potency.[11] New-onset diabetes and glucoregulation disorder, which has become an important issue with statins in recent years, have not been detected significantly in patients taking Pitavastatin.[12]

We investigated the lipid changes in these groups and their effects on biochemical parameters such as CPK, SGOT, and SGPT. As can be seen in Table 1, factors such as the time when the group members had their second visit were close to each other in all groups. The lack of significant difference in the groups in terms of body mass index and cigarette exposure is important, in terms of the statistically healthy results of the parameters we compared. However, we took the considered HbA1c levels grouping process but did not distinguish by the drugs used by patients with diabetes. Therefore, patients may be receiving insulin or oral antidiabetic medication in the diabetic groups.

In our study, pitavastatin treatment improved lipid parameters in nondiabetic and diabetic patients at risk of cardiovascular disease. Regarding another goal of our study, the LDL-cholesterol-lowering response of pitavastatin differed at different diabetes levels and with diabetes regulation. Significantly higher benefits were observed in patients without a diabetes diagnosis as compared to the other groups, and the group with diabetes regulation had the next highest benefit. The patients who were diabetic but did not have significant regulation benefited the least. This shows the importance of diabetes regulation in controlling LDL cholesterol. In a pitavastatin dose-determination study conducted in Japan, a 42% LDL cholesterol reduction was found with 2 mg pitavastatin.[13] In another study conducted on diabetics, a 37.6% decrease in LDL cholesterol was found with 2 mg pitavastatin.[14] The LDL-lowering response of pitavastatin found in our study was close to the responses of other studies conducted with a 2 mg dose, in both nondiabetics and diabetic patients.

In our study, pitavastatin had positive effects on triglyceride and HDL levels, which are superior to those reported for other statins, except for HDL in group 2 and triglycerides in group 3.[15,16] The increase in triglycerides in group 3 was not statistically significant (p=0.17). However, although not significant, the increase in triglyceride levels for group 3 may be related to the significantly higher average age of this group and the fact that this group had the worst diabetes control. Simultaneously, the rate of patients diagnosed with essential hypertension was high in this group, and their mean systolic blood pressure was higher than that of other groups. Similar to what we found in our study, the positive effect of pitavastatin on HDL cholesterol levels is now a point emphasized by experts who are interested in the subject.[17]

The changes in CPK, SGOT, and SGPT changes (except group 4 for SGPT) were not statistically significantly different between the groups. There was a statistically significant decrease in SGPT levels in group 4 (p=0.049). This situation may be caused by both the positive metabolic effect of Pitavastatin and diabetes regulation. No serious side effects were observed in any of the patients, muscle complaints were not experienced, and drugs were not discontinued due to impaired drug tolerance. However, considering that the average follow-up period was 9.8-11.4 weeks among the patients in our study, it should be kept in mind that drug side effects may increase with drug exposure.

A review of the online medical literature written in English showed that our study is the first to investigate the effects of pitavastatin on diabetic patients in Türkiye which has a retrospective clinical setting. This is one of the strengths of our study. However, it should be noted that there are some cell studies in which positive pleiotropic effects and inflammation-reducing effects of pitavastatin, especially on endothelium, were determined recently in our country.[18,19] Another strength of our study is that it investigates the effects of pitavastatin treatment in patients with regulated diabetes.

The weaknesses of our study are that it is retrospective, the sample size is small, and the patients who received diabetes treatment were not separated in terms of insulin versus oral antidiabetic use, so the effects of different diabetic drug groups cannot be tested.

CONCLUSION

In our study, which is one of the rare studies on pitavastatin in our country, a moderate dose of pitavastatin provided effective and safe lipid control in non-diabetic and diabetic patients receiving antidiabetic treatment, similar to the studies in the literature.

*The authors declare that there are no conflicts of interest.

REFERENCES

1. Okazaki S, Yokoyama T, Miyauchi K, et al. Early statin treatment in patients with acute coronary syndrome: demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: the ESTAthe BLISH study. Circulation 2004; 110: 1061-1068.
2. Sever PS, Dahlöf B, Poulter NR, et al. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial—Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003; 361: 1149-1158.
3. Horwich TB, MacLellan WR, Fonarow GC. Statin therapy is associated with improved survival in ischemic and non-ischemic heart failure. J Am Coll Cardiol 2004; 43: 642-648.
4. Liu PY, Lin LY, Lin HJ, et al. Pitavastatin and Atorvastatin double-blind randomized comparative study among high-risk patients, including those with Type 2 diabetes mellitus, in Taiwan (PAPAGO-T Study) [published correction appears in PLoS One 2014; 9: e114175]. PLoS One 2013; 8: e76298. Published 2013 Oct 1. doi:10.1371/journal.pone.0076298
5. Gumprecht J, Gosho M, Budinski D, Hounslow N. Comparative long-term efficacy and tolerability of pitavastatin 4 mg and atorvastatin 20-40 mg in patients with type 2 diabetes mellitus and combined (mixed) dyslipidaemia. Diabetes Obes Metabol 2011: 13: 1047-1055.
6. Choi JY, Choi CU, Hwang SY, et al. Effect of pitavastatin compared with atorvastatin and rosuvastatin on new-onset diabetes mellitus in patients with acute myocardial infarction. Am J Cardiol 2018; 122: 922-928.
7. Authors/Task Force Members; ESC Committee for Practice Guidelines (CPG); ESC National Cardiac Societies. 2019 ESC/EAS guidelines for the management of dyslipidaemias: Lipid modification to reduce cardiovascular risk. Atherosclerosis 2019; 290: 140-205. doi: 10.1016/j.atherosclerosis.2019.08.014. Epub 2019 Aug 31. Erratum in: Atherosclerosis 2020; 292: 160-162. Erratum in: Atherosclerosis 2020; 294: 80-82. PMID: 31591002.
8. Borén J, Chapman MJ, Krauss RM, et al. Low-density lipoproteins cause atherosclerotic cardiovascular disease: pathophysiological, genetic, and therapeutic insights: a consensus statement from the European Atherosclerosis Society Consensus Panel. Eur Heart J 2020; 41: 2313-2330. doi:10.1093/eurheartj/ehz962

9. Chan P, Shao L, Tomlinson B, Zhang Y, Liu ZM. An evaluation of pitavastatin for the treatment of hypercholesterolemia. Expert Opin Pharmacother 2019; 20: 103-113. doi:10.1080/14656566.2018.1544243

10. Catapano AL. Pitavastatin - pharmacological profile from early phase studies. Atheroscler Suppl 2010; 11: 3-7. doi:10.1016/S1567-5688(10)71063-1

11. Corsini A, Ceska R. Drug-drug interactions with statins: will pitavastatin overcome the statins' Achilles' heel? Curr Med Res Opin 2011; 27: 1551-1562. doi:10.1185/03007995.2011.589433

12. Vallejo-Vaz AJ, Kondapally Seshasai SR, Kurogi K, et al. Effect of pitavastatin on glucose, HbA1c and incident diabetes: A meta-analysis of randomized controlled clinical trials in individuals without diabetes. Atherosclerosis 2015; 241: 409-418. doi:10.1016/j.atherosclerosis.2015.06.001

13. Saito Y, Yamada N, Teramoto T, et al. Clinical efficacy of pitavastatin, a new 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, in patients with hyperlipidemia. Dose-finding study using the double-blind, three-group parallel comparison. Arzneimittelforschung 2002; 52: 251-255. doi:10.1055/s-0031-1299888

14. Sone H, Takahashi A, Shimano H, et al. HMG-CoA reductase inhibitor decreases small dense low-density lipoprotein and remnant-like particle cholesterol in patients with type-2 diabetes. Life Sci 2002; 71: 2403-2412. doi:10.1016/s0024-3205(02)02038-6

15. Yokote K, Bujo H, Hanaoka H, et al. Multicenter collaborative randomized parallel group comparative study of pitavastatin and atorvastatin in Japanese hypercholesterolemic patients: collaborative study on hypercholesterolemia drug intervention and their benefits for atherosclerosis prevention (CHIBA study). Atherosclerosis 2008; 201: 345-352. doi:10.1016/j.atherosclerosis.2008.02.008

16. Kurihara Y, Douzono T, Kawakita K, and Nagasaka Y. A large-scale, Long-term, Prospective Post-marketing Surveillance of Pitavastatin (LIVALO Tablet). Jpn Pharmacol Ther 2008; 36: 709-731.

17. Tokgözoğlu L. HDL-kolesterol üzerine pitavastatinin etkisi [Efficacy of pitavastatin on HDL-cholesterol]. Turk Kardiyol Dern Ars 2017; 45(Suppl 3): 5-7. Turkish. doi: 10.5543/tkda.2017.24524. PMID: 28952471.

18. Demir B, Onal B, Ozyazgan S, et al. The effects of pitavastatin on nuclear factor-kappa B and ICAM-1 in human saphenous vein graft endothelial culture. Cardiovasc Ther 2019; 2: 2549432. doi: 10.1155/2019/2549432. PMID: 31772607; PMCID: PMC6739759.

19. Onal B, Alaylioglu M, Yenmis G, et al. Pleiotropic effects of pitavastatin: a pilot study using the saphenous vein endothelial cell model of endothelial injury and prevention of atherosclerosis. Eur Rev Med Pharmacol Sci 2022; 26: 5210-5217. doi: 10.26355/eurrev_202207_29310. PMID: 35916819.