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Folate, neopterin and kynurenine pathway in patients with statin therapy

Abstract: Statins, widely used antihyperlipidemic drugs,
also have immunomodulatory properties independent
from their lipid lowering effect. Even with slight modula-
tions in the immune system, pteridine levels can display
changes. The effect of statins on pteridines and related
pathways has been demonstrated in a limited number of
studies. The aim of the study was to evaluate the possible
changes in neopterin and folate levels, and tryptophan
(Trp) degradation in hyperlipidemic patients. Patients
who were admitted to the cardiology clinic were randomly
grouped if they were having statin treatment (n=69) or
not (n=36). Serum Trp and kynurenine (Kyn), erythrocyte
folate, and urinary neopterin levels were measured. It
was found that urinary neopterin levels were significantly
higher in patients on statin treatment (p<0.05) while lev-
els of folate, Trp, Kyn, and Kyn-to-Trp ratios (Kyn/Trp)
presented no significant changes (all, p>0.05). The cor-
relation of the measured parameters was also evaluated
and neopterin, folate and tryptophan degradation were
found to be positively correlated. According to the results,
neopterin levels, folate status and Trp degradation were
altered in patients with statin treatment in comparison
with the patients not receiving statin therapy. In order to

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point out the direct effect of statins on pteridines, further
studies presenting both pre- and post-statin treatment of
these parameters are needed.

Introduction

A number of known cardiovascular disease (CVD) risk
factors such as hyperlipidaemia, hypertension, diabetes
mellitus, and smoking may cause endothelial dysfunc-
tion preceding the formation of atherosclerotic lesions
[1]. Atherosclerosis is a main cause of CVDs and also asso-
ciated with chronic immune activation. This process is
mediated by monocyte-derived macrophages and specific
subtypes of T-lymphocytes, and it triggers the formation of
atherosclerosis [2]. Today, several inflammatory biomark-
ers including homocysteine (Hcy) and neopterin levels
have been recognized as a predictor of outcome in CVDs,
making them useful for reflecting the disease severity [3].
Neopterin is an unconjugated pteridine which is released
from human monocyte-derived macrophages upon stim-
ulation with T helper 1 (Th-1) type cytokine interferon-
gamma (IFN-γ) and its concentration reflects cellular
immune activation [4]. Its elevated levels in the patients
with atherosclerosis have been reported before [5]. IFN-γ
also enhances expression of indoleamine (2,3)-dioxyge-
nase (IDO) in various cells, which degrades tryptophan
(Trp) to form kynurenine (Kyn) derivatives. Kyn-to-Trp
ratio (Kyn/Trp), in parallel with neopterin levels, is an esti-
mation of IDO activity and reflects endogenously formed
IFN-γ [6]. Beside Th-1 activation, increased Hcy levels are
considered as independent risk factor for CVDs and its
most important determinant is folates as conjugated pteri-
dine derivatives [7]. On the other hand, low blood folate
concentration is also considered as a risk for CVDs inde-
pendent from altered Hcy levels [7–9]. A possible folate
deficiency could also be the actual risk factor rather than
hyperhomocysteinemia itself [7].

Statins are widely used lipid lowering drugs in
patients with CVDs. In addition to their lipid lowering

properties, there is clinical evidence that statins exhibit anti-inflammatory action due to the extensive immunomodulatory properties [10]. Furthermore, a statin derivative was found to down-regulate neopterin production and Trp degradation in monocytic cells *in vitro* [11]. Data regarding the effects of statins on both of immunomodulation markers and folate levels in patients with CVDs are limited. The aim of the study was to determine erythrocyte folate levels, which reflects tissue folate stores, in parallel with relevant markers of immune status namely neopterin and Kyn/Trp. In addition, the possible effects of statin therapy as well as gender on measured parameters were also evaluated.

Materials and methods

Patients

The study group consisted of 105 patients from the cardiology clinic. Randomly selected patients were classified into two groups according to having statin therapy or not. Group I was recruited from subjects having one of the most prescribed statin treatment (n=69) while patients in Group II were not having any statin therapy (n=36). Patients' demographics are presented in Table 1. Both groups had similar prevalence of hypertension, diabetes mellitus and smoking habit. The principles of the Ethical Committee of the

Table 1: Characteristics of the study patients.

	Statin (+) (n=69)	Statin (−) (n=36)
Variables		
Gender	30 F, 39 M	24 F, 12 M
Age, years	62±2	59±2
Risk factors		
Hypertension (n=38)	34.8%	38.9%
Female (n=24)	58.3%	41.7%
Male (n=14)	64.3%	35.7%
Diabetes mellitus (n=20)	17.4%	22.2%
Female (n=13)	69.2%	30.8%
Male (n=7)	42.9%	57.1%
Smoking habit (n=14)	14.5%	11.1%
Female (n=3)	100%	0%
Male (n=11)	63.6%	36.4%
Medications		
Atorvastatin	100%	0%
Beta-blocker (n=61)	68.1%	38.9%
ACEI/ARB (n=48)	40.6%	55.5%
Calcium channel blocker (n=5)	1.4%	11.1%

Data are expressed as the mean (±SEM) or frequency counts (percentages). F, female; M, male; n, number of the subjects; ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

Hospital according to the Helsinki Declaration were followed during whole study. The approval was received from the Ethics Committee (# 2008.4.1/b, 10/30/2008).

Sampling

Collection of urinary and blood samples was done early in the morning. After centrifugation of blood specimens at 3500 rpm for 15 min at room temperature, sera were separated in order to measure Kyn and Trp levels. For folate determination, blood was drawn into tubes containing EDTA and erythrocytes were collected after centrifugation at the same condition mentioned above. All samples were stored at −20 °C until analysis and kept from direct light exposure.

Measurements

Neopterin and creatinine levels in urine samples were analysed by high performance liquid chromatography (HPLC; HP Agilent, Vienna, Austria). Briefly, an isocratic reversed phase liquid chromatography without any pre-analytical sample preparation was used. Diluted urine samples were passed through ODS column (250×4.6 mm, 5 μm) with phosphate buffer. Neopterin was detected with a fluorescence detector (excitation 353 nm, emission 438 nm).

Creatinine was detected simultaneously with UV detector at 235 nm. Urinary neopterin levels were expressed as micromole per mole creatinine.

Trp and Kyn levels were also determined by HPLC as described before [6]. Kyn-to-Trp ratio were calculated to estimate the degree of Trp conversion and expressed as micromole per millimole (μmol/mmol).

Erythrocyte folate levels were measured by a modified microbiologic assay as previously described [12].

Cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL), triglyceride, glucose, urea and blood-nitrogen-urea (BUN) levels and alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine kinase (CK) activities were also determined as routine measurements in the Biochemistry Laboratory of University Hospital.

Statistical analysis

The values for each parameter were expressed with standard error of means (SEM). Mann-Whitney U test was performed for comparisons between two independent groups and Spearman rank correlation test was used to investigate the correlations among the parameters. p<0.05 was considered to indicate statistical significance.

Results

Comparison of the biochemical parameters of the study groups were presented in Table 2. AST, BUN and urea levels were significantly different between the patients with/without statin treatment (all, p<0.05). Two study

Table 2: Results of the biochemical parameters in the study patients suffering from CVDs.

Parameters	Total (n=105)		Male (n=51)		Female (n=54)	
	Statin (+) n=69	Statin (−) n=36	Statin (+) n=39	Statin (−) n=12	Statin (+) n=30	Statin (−) n=24
Glucose, mg/dL	158.8±11	134±15.4	148.1±15.8	157.3±38.8	170.3±15.4	120.6±9.6
AST, U/L	64.9±12.2[a]	39 ±9.2	69.8±14.3	38.1±15.4	58.2±21.7	39.3±11.6
ALT, U/L	32.6±4.8	26±4.8	32.4±4.4	20±2.7	32.8±9.8	28.6±6.9
Triglycerides, mg/dL	192.3±16	162.5±11.4	176.4±17.6	158±21.1	212.9±28.7	164.8±13.8
HDL, mg/dL	40.8±1.7	45.5±4.5	39.7±2.5	51±11.6	42.2±1.9	42.7±3.5
Cholesterol, mg/dL	208.5±5.6	197.1±6.4	206.5±8.0	203.9±11.7	210.9±7.5	193.6±7.7
LDL, mg/dL	144.3±4.4	135±5	145.6±6.4	138.3±10.3	142.7±6	133.3±5.5
CK, U/L	397.7±110.8	316.2±93.4	425.9±102.4[b]	455.9±183.2[b]	359.3±225	246.3±106.1
BUN, mg/dL	21±2[a]	31±4	20±2[a]	34±6	23±3	28±5
Urea, mg/dL	45±3[a]	65±8	42±4[a]	72±12	49±6	60±10

Data presented as mean±SEM; [a]p<0.05 vs. patients who have not receiving statin therapy; [b]p<0.05 vs. other gender group.

groups were sub-grouped to investigate whether there was any gender effect on all measured parameters; as it is clinically known that significant differences in several biochemical variables are possible between genders. There was a gender difference in CK activities, and CK activities of male patients with/without statin therapy were significantly higher than female patients with/without statin therapy (both, p<0.05).

In Group I (patients on statin therapy), urinary neopterin levels were 189±13 µmol/mol creatinine (range: 100–526). The neopterin levels of Group II (patients not having statin therapy) were 129±7 µmol/mol creatinine (range: 46–184). The statistical analysis showed that urinary neopterin levels were significantly higher in patients on statin treatment (p<0.05). When the results were compared according to the gender, female patients with/without statin therapy showed a significant increase on neopterin levels compared to the related males as shown in Figure 1A (p<0.05). The difference according to the gender was found to be independent from statin therapy.

Levels of Trp, Kyn and Kyn/Trp were 67.3±2.1 µM, 3.5±0.2 µM and 55.1±3.2 µmol/mmol in Group I and 73.4±3.6 µM, 3.9±0.2 µM and 56.9±4.7 µmol/mmol in Group II, respectively. However, none of these parameters were statistically different between Group I and II, and there was not any statistically difference between males and females (all, p>0.05) (Figure 1B–D).

Erythrocyte folate levels were higher in Group I with 160±15 ng/mL than the Group II with 147±15 ng/mL; however, no significance was observed (p>0.05). On the other hand, erythrocyte folate levels in females with/without statin therapy were significantly higher than male patients with/without statin therapy (both, p<0.05) (Figure 1E).

In order to evaluate the possible effects of other medications used, all patients were grouped according to their cardiovascular drug usage. None of the parameters were found to be changed with the use of beta-blocker, angiotensin converting enzyme/angiotensin receptor blocker (ACEI/ARB) or calcium channel blocker (all, p>0.05).

The results of correlation among the measured variables were presented in Table 3. As shown in the table, neopterin levels were positively correlated with Kyn/Trp in all patients (Rs=0.390; p=0.001). Besides, it was observed that both Kyn/Trp and folate status were negatively correlated with LDL levels (Rs=−0.203; p=0.042, and Rs=−0.200; p=0.043, respectively). The Kyn/Trp were positively correlated with age (Rs=0.228; p=0.023). Neither BUN nor urea levels were correlated with neopterin levels (both, p>0.05; data not shown).

Discussion

Cardiovascular and cerebrovascular diseases are among the leading death factors worldwide, and high cholesterol levels, especially LDL, is a well-established risk factor for these diseases. Beside the improvements in diet and lifestyle, statins are widely used to reduce blood lipid levels. [10, 13, 14]. Studies have shown increased neopterin levels in patients with CVD because of possible activation of macrophages in atherosclerosis [5, 15]. The elevation of neopterin levels might be associated with the severity of CVD, the complexity of atherosclerotic lesions and cardiovascular mortality risk [16–18]. Statins have been shown to inhibit oxidant-induced mitochondrial dysfunction and also have been suggested to inhibit myocardial apoptosis
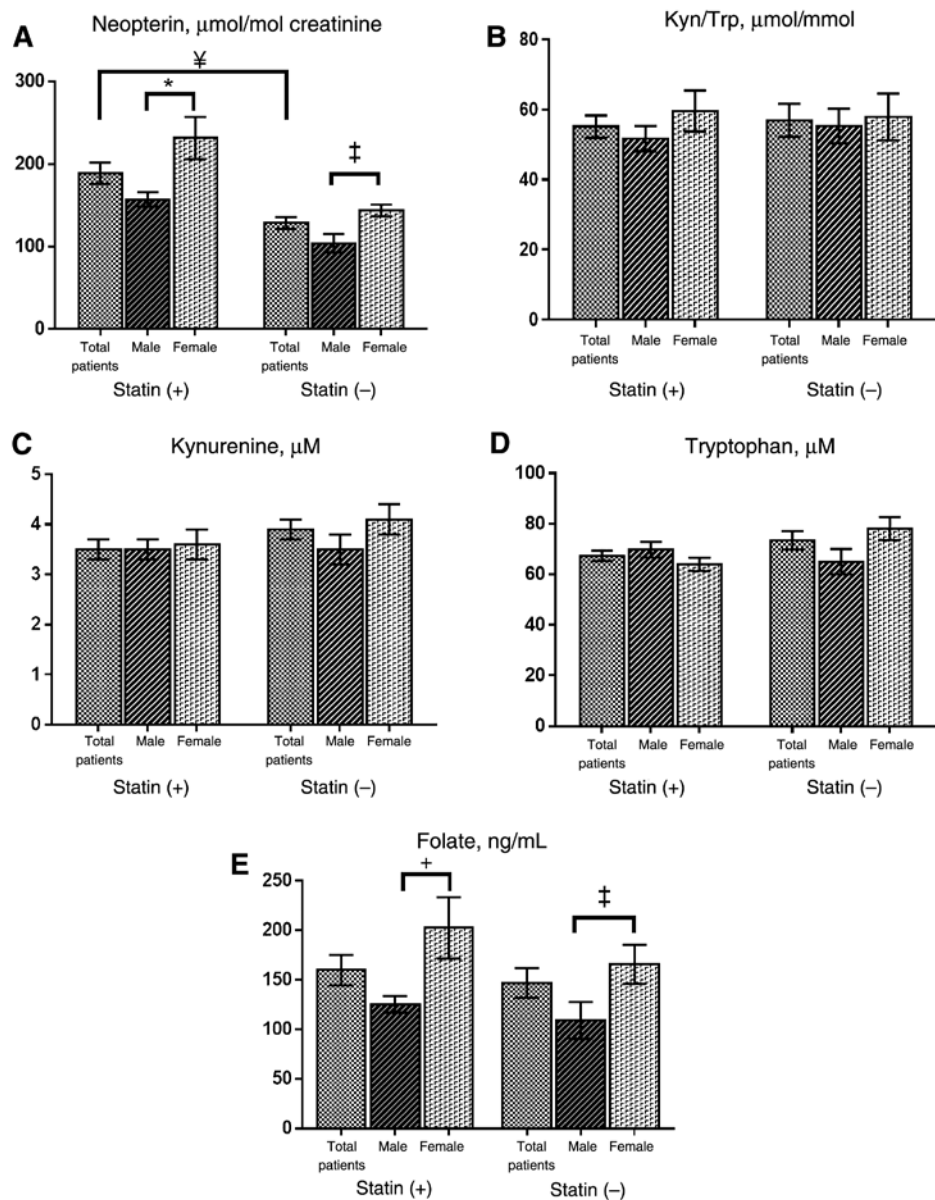
Figure 1: Measured parameters of the hyperlipidemic patients.
Different from ¥patients without statin therapy (p<0.05), *males with statin therapy (p<0.05), and ‡ males without statin therapy (p<0.05).

Table 3: Correlations among the measured parameters in all participants (n=105).

	Folate	Neopterin	Kynurenine/Tryptophan
Folate			
Neopterin	Rs=0.120, p=0.308		
Kynurenine/tryptophan	Rs=0.014, p=0.890	Rs=0.390[b], p=0.001	
Tryptophan	Rs=0.154, p=0.131	Rs=−0.146, p=0.227	Rs=−0.390[b], p=0.000
Kynurenine	Rs=0.031, p=0.763	Rs=0.322[b], p=0.006	Rs=0.710[b], p=0.000
Triglycerides	Rs=0.103, p=0.304	Rs=0.101, p=0.393	Rs=−0.074, p=0.459
HDL	Rs=0.052, p=0.605	Rs=0.159, p=0.177	Rs=−0.027, p=0.789
Cholesterol	Rs=−0.179, p=0.071	Rs=−0.109, p=0.357	Rs=−0.171, p=0.088
LDL	Rs=−0.200[a], p=0.043	Rs=−0.077, p=0.513	Rs=−0.203[a], p=0.042
Age	Rs=0.148, p=0.139	Rs=0.197, p=0.095	Rs=0.228[a], p=0.023

HDL, High density lipoprotein; LDL, low density lipoprotein; Rs, Spearman's correlation coefficients; [a]p<0.05; [b]p<0.01.

[19]. In addition to lowering cholesterol levels, reduction of inflammation and/or oxidative stress associated with atherosclerosis is one of the potential mechanisms contributing to the beneficial effects of lipid lowering treatment with statins. Statins have been shown to reduce neopterin levels both *in vitro* and *in vivo*, confirming their immunomodulatory properties [11, 20–22]. On the other hand, in some cases, statin therapy did not affect inflammatory biomarkers and/or neopterin [23]. These different findings may be explained by an *in vitro* T cell macrophage study indicating dose-dependent effect of statin on neopterin formation and Trp degradation [11]. The study performed by van Haelst et al. [21] showed that short-term effect of the statin caused a decrease of neopterin, while the chronic exposure resulted in a tend to increase. On the other hand, as a limitation of this study, there is no data on neopterin levels before statin therapy, which makes it difficult to comment on the possible relationship between therapy duration and neopterin levels. Even though statin therapy group was composed of patients having both short and long term treatment, we might have found a significant increase in neopterin levels in patients having treatment in comparison with patients without statin therapy. In this respect, these results give a thought if the exposure period of statins might be neglected in cellular immune modulation. Additionally, the increased BUN and urea levels in CVD patients without statin treatment may be pointing out any glomerular damage. Putting it in another way, it is noticed that statin treatment reduced BUN and urea levels. Although it is known that patients with renal disorder have high neopterin levels, no significant correlation between neopterin and BUN/urea levels was found in this study. The reason why is most probably, the evaluation of neopterin levels with creatinine.

Indoleamine 2,3-dioxygenase is also induced by IFN-γ, which is usually high during the cellular immune activation [6]. Simvastatin has been reported to increase IDO expression [24]. On the other hand, in the study performed by Neurauter et al. [11] atorvastatin inhibited Trp degradation in different cell lines. Statins have also been shown to inhibit T cell proliferation and proinflammatory cytokine secretion in a dose dependent manner, simvastatin being the most effective [25]. In this study, statin treatment caused slight and non-significant alterations in Trp degradation. Patients on statin treatment presented low serum Trp levels compared to patients not having statin therapy. The Kyn levels and Kyn/Trp correlate with neopterin levels. According to the results, it can be concluded that statins might be able to modulate T cell response by changing cytokine secretion or cell proliferation.

In this study, the biochemical parameters of lipid levels like triglycerides, LDL and cholesterol are still high and HDL levels are still low in patients on statin treatment compared to the patients without statin therapy. It is also well established that folate metabolism is closely linked to that of Hcy. Numerous studies show that the increased levels of Hcy relating to cardiovascular risk are associated with reduced levels of folate in plasma and erythrocyte [26]. Silberberg et al. [8] found significantly lower plasma folate levels in patients with coronary artery disease, but they did not find any changes in erythrocyte levels. They found plasma folate levels were strongly associated with coronary disease while red cell folate levels were not. As folate is not metabolized by red cells, erythrocyte folate levels are considered to be a better indicator of long-term folate intake and tissue storage [27]. We detected increased folate levels in patients on statin treatment, but it was not statistically significant. In some studies, it was found that statins had no effect on folate status [28, 29]. Lüftjohann et al. [30] reported that administration of simvastatin caused slight increase in plasma concentrations of folate. On the other hand, Dobs et al. [31] suggested that patients comply with a lipid lowering diet even while using an effective lipid lowering medication. This may also affect folate levels of patients on statin therapy. If the patients have adequate diet especially rich in folic acid, folate levels might be elevated in patients on statin treatment. Dalery et al. [32] suggested that Hcy levels could be modulated in part by plasma levels of folate and B vitamins. They reported that there were no significant differences in folate levels between coronary heart disease patients and their controls while females had higher folate levels than males. Similarly, we found that folate levels were higher in females than male patients.

Conclusion

In this study, results showed significant increase in neopterin levels, non-significant alterations in Trp degradation, and non-significant elevation in folate levels with statin therapy. However, it is difficult to link these changes to statin treatment as the main limitation of this study is the lack of statin therapy duration and pre-therapy levels of measured parameters. This makes it impossible to comment if the data reflects the effect of statin therapy or not. Hence, further studies should be performed to clarify these preliminary findings and the effect of statin treatment.

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