Research Article

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Total cholesterol/HDL cholesterol ratio and monocyte/HDL cholesterol ratio are related with subclinical hypothyroidism in polycystic ovary syndrome

Total kolesterol/HDL kolesterol oranı ve monosit/HDL kolesterol oranı polikistik over sendromunda subklinik hipotiroidi ile ilişkilidir

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Abstract

Objectives: There is an association between serum thyrotropin (TSH) and lipid profile. However, there is a little information regarding the relation between subclinical hypothyroidism (SCH), atherogenic indices and inflammation in polycystic ovary syndrome (PCOS). Herein, we aimed to evaluate the impact of SCH on lipids and inflammatory markers in newly diagnosed PCOS patients.

Methods: Two groups were performed for total 99 PCOS patients: SCH (TSH>2.5 mIU/L) and euthyroid groups (TSH<2.5 mIU/L). Complete blood count, lipids, atherogenic indices were evaluated, inflammatory markers as platelet/lymphocyte ratio (PLR), neutrophil/lymphocyte ratio (NLR), monocyte/high density lipoprotein ratio (MHR) and mean platelet volume/platelet ratio (MPR) were calculated.

Results: SCH group had higher WBC, PLT, PCT, PLR, MPR and non-high density lipoprotein cholesterol levels. Differences between MHR, total cholesterol/HDL cholesterol (TC/HDL), triglycerides/HDL cholesterol (TG/HDL) and low density lipoprotein/HDL cholesterol (LDL/HDL) levels

were significantly higher ($p=0.001$; 0.01 ; 0.01 ; 0.02 , respectively), TC/HDL cholesterol levels were positively correlated with TSH ($p=0.028$, $r=0.402$) in SCH group. TC/HDL levels were also correlated with WBC, PLT, PDW, PCT, MPR and MHR ($p=0.003$; 0.011 ; 0.031 ; 0.037 ; 0.006 ; 0.002 ; $r=0.515$; 0.442 ; -0.382 ; 0.370 ; -0.471 ; 0.523 , respectively).

Conclusions: TC/HDL and MHR may serve as beneficial markers for evaluating the inflammatory state of PCOS with SCH. Screening thyroid hormones and curing SCH in PCOS may lower lipids, decelerate developing hypothyroidism and cardiovascular morbidities.

Keywords: atherogenic markers; inflammation; monocyte to HDL ratio; polycystic ovary syndrome; subclinical hypothyroidism.

Öz

Amaç: Serum tirotropin (TSH) ve lipid profili arasında bir ilişki mevcuttur. Ancak, polikistik over sendromunda (PCOS) subklinik hipotiroidizm (SCH), aterojenik indeksler ve enflamasyon ile ilgili az sayıda bilgi bulunmaktadır. Burada, yeni tanı almış PCOS hastalarında lipidler ve enflamasyon belirteçleri üzerine SCH'nın etkisini değerlendirmeyi amaçladık.

Gereç ve Yöntem: Toplam 99 PCOS hastası için iki grup oluşturuldu: SCH (TSH>2.5 mIU/L) ve ötiroid grup (TSH<2.5 mIU/L). Tam kan sayımı, lipidler, aterojenik indeksler ve enflamasyon belirteçleri değerlendirildi.

Bulgular: SCH grubunda WBC, PLT, PCT, platelet/lenfosit oranı (PLR), monosit/platelet oranı (MPR) ve yüksek

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dansiteli lipoprotein kolesterol harici lipidlerin düzeyleri daha yüksekti.

Monosit/HDL kolesterol oranı (MHR), total kolesterol/HDL kolesterol oranı (TC/HDL), trigliserid/HDL kolesterol (TG/HDL) ve düşük dansiteli lipoprotein/HDL kolesterol (LDL/HDL) düzeyleri SCH grubunda belirgin olarak daha yüksekti ($p=0.001$; 0.01 ; 0.01 ; 0.02 ; sırasıyla). SCH grubunda, TC/HDL kolesterol düzeyleri TSH düzeyleri ile pozitif olarak korele idi ($p=0.028$, $r=0.402$). TC/HDL düzeyleri ayrıca WBC, PLT, PDW, PCT, MPR ve MHR düzeyleri ile de korele idi ($p=0.003$; 0.011 ; 0.031 ; 0.037 ; 0.006 ; 0.002 ; $r=0.515$; 0.442 ; -0.382 ; 0.370 ; -0.471 ; 0.523 ; sırasıyla). ROC eğrisi analizine göre MHR, SCH görülen PCOS ile en fazla ilişkili enflamasyon belirticidi (AUC:0.672; $r=0.007$)

Sonuç: TC/HDL ve MHR, SCH görülen PCOS için enflamatuvar durumun değerlendirilmesinde yararlı belirteçler olarak kullanılabilir. Tiroid hormonlarının araştırılması ve PCOS'de SCH'nin tedavi edilmesi lipidlerin düzeyini düşürebilir, gelişmekte olan hipotiroidizmi ve kardiyovasküler morbiditeleri geciktirebilir.

Anahtar kelimeler: aterojenik belirteçler; enflamasyon; monosit/ HDL oranı; polikistik over sendromu; subklinik hipotiroidizm.

Introduction

Polycystic ovary syndrome (PCOS) is a high frequent endocrinopathy affecting reproductive age women [1]. Its etiology is multifactorial and pathogenesis has completely unexplained. There are susceptible genes involving pathways of androgenesis and steroidogenesis. These genes are thought to be contributors to PCOS pathophysiology [2, 3]. As 'Androgen Excess and PCOS Society' defined, the diagnosis of the disease is based on (1) the presence of ovarian dysfunction signs as anovulatory oligomenorrhea causing menstrual disorders, (2) biochemical or clinical hyperandrogenism and (3) ultrasound proved polycystic ovaries [4]. Subclinical hypothyroidism (SCH) is defined as serum free thyroxine (fT4) levels are in reference interval, and thyrotropin (TSH) levels are above the reference range [5]. According to the study of Bedaiwy et al., we defined SCH as thyroid-stimulating hormone >2.5 mIU/L, and serum fT4 levels are in reference interval without symptoms of overt hypothyroidism [6].

SCH prevalence is higher in females, and 5–10% of PCOS patients have SCH [7, 8]. SCH is an important clinical condition with the potential to develop into overt hypothyroidism [7]. In addition, especially in hypercholesterolemic

postmenopausal women, SCH is a risk factor for myocardial infarction [9]. Emerging reports have shown the relation between thyroid functions and dyslipidemia in patients with PCOS [10–12]. Recent studies have also shown that low-grade systemic chronic inflammation is related to PCOS pathogenesis [13]. To date, several inflammatory markers as interleukins (IL1a, IL1b, IL6, IL18 etc.), tumor necrosis factor- α (TNF- α) or high sensitive C-reactive protein (CRP) have been investigated in patients with PCOS. Emerging studies also have assessed novel inflammatory markers in PCOS patients [13–15]. Another recent study was reported by Rudnicka et al. They compared PCOS patients with non-hyperandrogenic, normal-ovulating, age- and BMI-matched women peers and suggested in their study that low-grade chronic inflammation occurred in PCOS patients, and more specifically, those patients had statistically significantly higher WBC and CRP concentrations [16].

In our study, we aimed to evaluate SCH in our PCOS group. Also, we wanted to investigate the impact of SCH on lipid profile and inflammatory marker levels of PCOS patients.

Materials and methods

Our study included a total of 99 patients who were presented with complaints of clinical symptoms of PCOS at the endocrinology outpatient clinic between January 2017 and January 2018. The participants were newly diagnosed PCOS patients according to the Rotterdam criteria [17]. Their biochemical tests were evaluated. Patients group was divided into two subgroups according to TSH levels. 33 patients were formed SCH group having $TSH > 2.5$ mIU/L and 63 patients were formed euthyroid group having $TSH < 2.5$ mIU/L. Patients' complete blood count parameters, including white blood cell (WBC), platelet (PLT) indices parameters as PLT, mean platelet volume (MPV), plateletcrit (PCT) and platelet distribution width (PDW), assessed using flow cytometry and fluorescent technologies by an automatized hematology analyzer Sysmex XN-1000 (Sysmex Corporation, Kobe, Japan) and other inflammatory markers as platelet to lymphocyte ratio (PLR), neutrophil to lymphocyte ratio (NLR), monocyte to high-density lipoprotein ratio (MHR) and mean platelet volume to platelet ratio (MPR) was calculated.

We recorded patients lipid parameters evaluated by colorimetric enzymatic assays [assessed by Olympus AU2700 autoanalyzer (Beckman Coulter, Tokyo, Japan) and calculated atherogenic indices as total cholesterol to high-density lipoprotein (TC/HDL) cholesterol ratio, triglycerides to HDL (TG/HDL) cholesterol ratio, low-density lipoprotein to HDL (LDL/HDL) cholesterol ratio and non-HDL cholesterol (TC–HDL cholesterol).

History of surgical operation of thyroid, hormonal replacement therapy, isotretinoin treatment, acute or chronic liver/renal disease and pregnancy were the exclusion criteria for patients.

Our study was performed in accordance with the Helsinki Declaration and Erciyes University Medical Faculty Ethical Committee approved the study protocol (2019/841).

Table 1: Comparison of baseline characteristics and laboratory findings between two PCOS groups.

	Group 1 (subclinical Hypothyroidism)	Group 2 (Euthyroidism)	p-Value
Number of patients	33	63	–
Age, years	24.39 ± 6.28	23.92 ± 5.86	0.720
WBC ($4.5\text{--}10 \times 10^3/\text{mm}^3$)	7.81 ± 1.60	7.68 ± 1.74	0.710
PLT ($150\text{--}450 \times 10^3/\text{mm}^3$)	331.12 ± 81.84	315.11 ± 68.49	0.310
MPV (9–12 fL)	10.39 ± 1.19	10.50 ± 0.85	0.590
PCT (0.17–0.40 %)	0.34 ± 0.06	0.33 ± 0.06	0.430
PDW (10–16 fL)	12.50 ± 2.38	12.65 ± 2.03	0.740
PLR	142.72 ± 50.94	134.20 ± 35.75	0.340
MHR	0.014(0.010–0.017)	0.010(0.009–0.013)	0.007
MPR	0.035 ± 0.010	0.034 ± 0.013	0.680
NLR	1.74(1.30–2.47)	1.63(1.33–2.23)	0.032
TSH (0.55–4.78 mIU/L)	2.78(2.51–3.44)	1.66(1.17–2.37)	<0.001
ft4 (0.54–1.24 ng/dL)	0.82 ± 0.13	0.89 ± 0.17	0.083
Total cholesterol/HDL cholesterol	3.48(2.97–4.59)	2.40(2.88–3.04)	0.010
Triglycerides/HDL cholesterol	2.34(1.75–4.10)	1.87(1.26–2.77)	0.010
LDL cholesterol/HDL cholesterol	2.24 ± 0.68	1.92 ± 0.56	0.020
Non HDL cholesterol	120.0 ± 31.90	116.48 ± 28.07	0.589

WBC, White blood cell; PLT, platelet; MPV, mean platelet volume; PCT, plateletcrit; PDW, platelet distribution width; PLR, platelet to lymphocyte ratio; MHR, monocyte to high density lipoprotein ratio; MPR, monocyte to platelet ratio; NLR, neutrophil to lymphocyte ratio; TSH, thyrotropin; ft4, free thyroxine. Student's *t*-test was used for group comparison; data were summarized as mean ± SD. Mann-Whitney *U* test was used; data were summarized as median and interquartile range (25–75%). $p < 0.05$, statistically significant.

Statistical analysis

We used SPSS software version 23.0 for Windows (SPSS Inc., USA) for statistical analyses. We performed the Kolmogorov-Smirnov test to assess the distribution of biochemical, hematological and hormonal parameters. We used Student's *t*-test to compare variables with normal distribution. We compared non-normally distributed variables with the Mann-Whitney *U* test. We presented normally distributed, continuous variables by mean ± standard deviation (SD), and non-normally distributed, continuous variables by the median and interquartile range (25–75%). Spearman's correlation coefficients were used to assess the association between parameters. The *p* values of <0.05 were accepted as statistically significant, and *p* values lower than 0.001 were shown as $p < 0.001$.

Results

Baseline characteristics and biochemical test results of two groups were shown in Table 1. The mean ages of SCH group and the euthyroid group were 24.39 ± 6.28 and 23.92 ± 5.86 years, respectively ($p = 0.721$). SCH group had numerically higher WBC, PLT, PCT, PLR, MPR and non-HDL levels than the euthyroid group but the differences were not statistically significant ($p > 0.05$). SCH group had lower MPV and PDW levels ($p > 0.05$). The mean levels of MHR, NLR, TC/HDL cholesterol, TG/HDL cholesterol and LDL cholesterol/HDL cholesterol were statistically significantly higher in SCH group ($p < 0.05$) (Table 1).

Only MHR was significantly related with SCH in PCOS patients among the inflammatory markers group. Then, Spearman's correlation analysis was performed to evaluate the correlations between TSH levels and other biochemical parameters of SCH group. As a result, only TC/HDL cholesterol levels were statistically significantly and positively correlated with TSH levels of SCH group, among other atherogenic indices. TC/HDL cholesterol levels of SCH group were also statistically significantly correlated

Table 2: Spearman's correlations between TC/HDL-c and inflammatory markers in PCOS patients with SCH group.

TC/HDL-c	PCOS patients with SCH	
	r value	p-Value
WBC	0.515	0.003
PLT	0.442	0.011
PCT	0.370	0.037
PDW	−0.382	0.031
MHR	0.523	0.002
MPR	−0.471	0.006
NLR	0.490	0.641
TSH	0.402	0.028

WBC, White blood cell; PLT, platelet; PCT, plateletcrit; PDW, platelet distribution width; MHR, monocyte to high density lipoprotein ratio; MPR, monocyte to platelet ratio; NLR, neutrophil to lymphocyte ratio; TSH, thyrotropin. *r*: Correlation coefficient, $p < 0.05$: Statistically significant.

with inflammatory markers as WBC, PLT, PDW, PCT, MPR and MHR (Table 2).

Discussion

PCOS is a common endocrinopathy effecting reproductive age women [1]. Prevalence of dyslipidemia and SCH are the risk factors of metabolic and cardiac diseases are also higher in these patients. Therefore, we planned our study focusing on SCH in PCOS patients, its relations with atherogenic indices and also inflammatory markers, and its impact on these parameters.

Emerging studies had reported the SCH prevalence of PCOS patients and they also reported that PCOS might aggravate the SCH development [18]. In the study of Tagliaferri et al. it was indicated that obesity and insulin resistance, which are the parts of the pathogenesis of the disease, mediated this SCH development in PCOS patients [19]. Researchers also mentioned that serum TC and TG levels were higher in PCOS with SCH and PCOS is more likely to exhibit hyperlipidemia [20, 21]. They also concluded that compared to healthy populations, PCOS is related with high incidence of SCH [21]. Comply with the literature, in our study; we found lipid profile parameters and atherogenic indices were higher in SCH group of PCOS patients, too. TC/HDL cholesterol levels were statistically significantly and positively correlated with SCH group of PCOS patients. HDL cholesterol has anti-inflammatory, antioxidant, and antithrombotic effects [22], but monocyte has inflammatory and atherogenic effects [23]; so, MHR that combined the predictive efficacy of these two markers, monocyte and HDL, reflects the inflammatory situation.

Researchers discussed inflammation and immune system in PCOS, and they showed that low progesterone (low anti-inflammatory effect) and overstimulated estrogen levels (high immune-stimulatory effect) may cause autoimmunity and low-grade chronic inflammation [20]. Concordantly, in our study, we found higher inflammatory markers in SCH group, too. WBC, PLT, PCT, PLR and MPR levels were numerical, NLR and MHR levels were also statistically significantly higher in SCH group. To the best of our knowledge, this is the first study indicating mean MPR in PCOS patients in the literature.

In the long term, SCH might cause an increase in the risk of developing various cardiovascular comorbidities [21]. Therefore, greater awareness is needed for PCOS women with SCH.

Our study had some limitations. First, our sample size was relatively small. Second, it was a retrospective study so we couldn't get patients serum samples and we couldn't

study other inflammatory markers or antibodies to diagnose autoimmune thyroiditis. So, further prospective studies with a larger sample size are needed to support our findings.

In summary, we deduced that serum TSH levels should be measured in PCOS patients with dyslipidemia. Screening thyroid hormones and maybe treating SCH in PCOS patients may lower their lipid levels and may also decelerate developing overt hypothyroidism.

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Informed consent: Informed consent was not obtained from participants because of the retrospective design of the study.

Ethical approval: Approval was obtained prior to the study from Erciyes University Clinical Research Ethics Committee (2019/841).

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