MONOCYTE TO HDL-CHOLESTEROL RATIO IN MALE WITH HYPOGONADOTROPIC HYPOGONADISM

ERKEK İDİOPATİK HİPOGONADOTROPİK HİPOGONADİZMLİ HASTALARDA MONOSİT/ HDL ORANI

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ABSTRACT

INTRODUCTION: Previous studies have shown that idiopathic hypogonadotropic hypogonadism (IHH) patients with low testosterone levels lead to an impaired glucose metabolism and an increased cardiovascular risk. Monocyte to high-density lipoprotein cholesterol (HDL-C) ratio (MHR) also has been shown to be an indicator of inflammation and cardiovascular risk. The purpose of the present study is to investigate MHR in the male with IHH.

MATERIAL AND METHODS: This study includes 31 men with IHH without previous treatment for the disease and 44 healthy men. The blood samples, anthropometric measures, and physical examination were undertaken by all the participants.

RESULTS: Mean ages of the IHH patients and the healthy controls were 22.5±7.2 years vs. 22.9±6.4 years. There was no statistically significant difference between the patients and controls in terms of the mean HDL-C, mean monocyte count, and mean MHR. The MHR also was not correlated with the other hematological parameters, inflammatory parameters, and the total testosterone level.

CONCLUSION: MHR has been shown to be an indicator of cardiovascular risk in previous studies but we could not detect an increased MHR value in patients with IHH in this study.

Keywords: *Monocyte, HDL-cholesterol, inflammation, Idiopathic hypogonadotropic hypogonadism*

ÖZET

AMAÇ: Önceki çalışmalar, düşük testosteron düzeylerine sahip idiopatik hipogonadotropik hipogonadizm (İHH) hastalarında bozulmuş glukoz metabolizmasına ve artmış kardiyovasküler riske yatkınlık olduğunu göstermiştir. Monosit/yüksek yoğunluklu lipoprotein kolesterol (HDL-C) oranı (MHR) de inflamasyon ve kardiyovasküler risk göstergesi olarak gösterilmiştir. Bu çalışmanın amacı, İHH tanılı erkek hastalarda MHR'yi araştırmaktır.

GEREÇ VE YÖNTEMLER: Bu çalışmaya daha önce tedavi almamış İHH tanısı olan 31 erkek hasta ve sağlıklı 44 erkek dahil edildi. Tüm katılımcıların kan örneklemesi, antropometrik ölçümleri ve fizik muayeneleri yapıldı.

BULGULAR: İHH hastalarının yaş ortalaması 22,5±7,2 yıl ve sağlıklı kontrollerin yaş ortalaması ise 22,9±6,4 yıl idi. Hastalar ve kontroller arasında ortalama HDL-kolesterol, ortalama monosit sayısı ve ortalama MHR açısından istatistiksel olarak anlamlı bir fark yoktu. MHR ayrıca diğer hematolojik parametreler, enflamatuar parametreler ve toplam testosteron seviyesi ile korele değildi.

SONUÇLAR: Önceki çalışmalarda MHR'nin kardiyovasküler riskin bir göstergesi olduğu gösterilmiştir, ancak bu çalışmada İHH hastalarında artmış bir MHR değeri tespit edemedik.

Anahtar kelimeler: *Monosit, HDL-kolesterol, inflamasyon, idiopatik hipogonadotropik hipogonadizm*

INTRODUCTION

Male hypogonadism is a clinical condition that occurs as a result of testosterone (hormonogenesis) and sperm production (spermatogenesis) failure or a combination of both. This condition can be a consequence of hypothalamic or pituitary dysfunction (hypogonadotropic) or primary testicular failure (hypergonadotropic) (1).

Idiopathic hypogonadotropic hypogonadism (IHH) is a rare disease and predominantly affects male patients (2). IHH may result from either inadequate or non-pulsatile hypothalamic gonadotropin-releasing hormone (GnRH) secretion or insufficiency of pituitary gonadotropin secretion. IHH is characterized by delayed/absent puberty and infertility and various other clinical anomalies (2,3). The plasma testosterone level is

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lower in patients with IHH. Latest studies have shown that there is an opposite relationship between the plasma testosterone levels and inflammatory markers (4). Systemic inflammation also acts as a significant role in the development and progression of atherosclerosis and cardiovascular diseases (CVD) (5,6) which are the most common mortality reason in the world (7). The studies have shown that the testosterone replacement therapy prevents the atherosclerosis (8) and improved some components of the metabolic syndrome and a number of inflammatory markers in hypogonadal patients (9).

Monocytes and monocyte-derived macrophages are essential cells group of the innate and acquired immunity and primarily functioning in immune defense, tissue remodeling, and inflammation. Monocytes and macrophages play essential roles in the initiation and resolution of inflammation and as well as the release of proinflammatory and prooxidant cytokines at the site of the inflammation (10,11). These cells have a key role in atherosclerosis development (12). Macrophages derived from monocytes in the atherosclerotic plaque play an active role in the formation of foam cells containing oxidized LDL (13). High-density lipoprotein (HDL) molecule has beneficial effects against cardiovascular disease such as exhibiting antioxidative, anti-inflammatory endothelial/vasodilatory, antithrombotic, and cytoprotective functions (13,14). HDL inhibits the oxidation of LDL via the paraoxonase enzyme, thus HDL also prevents from atherosclerosis by reversing the stimulatory effect of oxidized LDL on monocyte infiltration (15). Therefore, the ratio of the monocyte to the HDL cholesterol level (MHR) was defined as an easy-to-calculate cardiovascular prognostic marker indicating the degree of inflammation and oxidative stress in the latest studies (16). As a new indicator of the degree of inflammation, oxidative stress, and CVD marker, this ratio can combine the prognostic and predictive effectiveness of two widely used and accessible laboratory parameters (17,18).

To the best of our knowledge MHR has not been evaluated in IHH. The purpose of the present study is to investigate whether there is an association between hypogonadotropic hypogonadism and monocyte-to-HDL cholesterol ratio (MHR) which is a new marker associated with inflammation.

MATERIAL AND METHODS

Thirty-one isolated and untreated IHH male patients were recruited in Erzurum Regional Training and Research Hospital Outpatient Clinic of Endocrinology, and 44 healthy control individuals were recruited into the study at the same hospital Outpatient Clinic of Internal Medicine. None of the patients previously received any medical treatment for IHH. IHH is diagnosed if the morning serum testosterone level is less than 299 ng/dL and free testosterone of less than 5.1 pg/ml. Whoever had a chronic illness, panhypopituitarism, hypo-/hyperthyroidism, nephrotic syndrome, or used steroids or any drugs causing hypogonadism were excluded from the study. Also, none of the study subjects ever smoked or drank alcohol. All procedures were followed in accordance with ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All participants gave their written informed consent to participate in the study, and the study was approved by the local ethics institute of Health Sciences University Training and Research Hospital, Erzurum, Turkey (2018/05-28).

Total testosterone and free testosterone levels were analyzed using Abbott Architect i2000 SR (Abbott Türkiye, Istanbul, Turkey) device by the Chemiluminescent Microparticle Immunoassay (CMIA) method. Ten cubic centiliter venous blood specimens were drawn for hormonal analysis from all patients and healthy volunteers from the antecubital vein between 08:00 and 10:00 in the morning after 12-hour fasting. Testosterone measurements were evaluated at least twice for the diagnosis of IHH. Free testosterone was measured in required cases. Again, hypophyseal or hypothalamic masses were excluded by the hypophyseal MRI. The MHR was defined as the absolute monocyte count divided by the HDL-C value.

Statistical Analysis

After testing the normality and homogeneity of variants, the Independent-Samples t-Test and the Mann-Whitney U Test were used. The results were expressed as mean ± standard deviation (SD). The p-value <0.05 was accepted as statistically significant. All statistical analyses in this study were performed using SPSS for Windows, version 17.0.

RESULTS

There were 31 men with IHH and 44 healthy men in the study. The patient and control groups were selected from similar ages and similar BMI in our study. Our IHH patient and the control group BMIs and ages, respectively, were 21.6±4.9 kg/m2 vs. 19.5±3.2 kg/ m2 (mean±SD, p=0.24) and 22.5±7.2 year vs. 22.9±6.4 years (p=0.65). There was no statistically significant difference between the baseline characteristics of the groups such as age, height, weight, and BMI. **(Table 1)**

Table 1 The sociodemographic characteristics of the patients with Idiopathic Hypogonadotropic Hypogonadism (IHH) group and the control group.

Characteristics	IHH Patient Group (n=31)	Control Group (n=44)	P
Age (years)	22.5±7.2	22.9±6.4	0.65
Height (cm)	167±10	168±8.0	0.76
Weight (kg)	61.3±17.2	58.6±11.3	0.75
BMI (kg/m2)	21.6±4.9	19.5±3.2	0.24

BMI: body mass index

The liver function tests, thyroid function tests, cholesterol levels, fasting blood glucose, and the hemogram components such as the white blood cell,

monocyte, neutrophil, and lymphocytes didn't show any statistically significant difference between the groups. The hemoglobin level and the mean creatinine level of the patient group were lower than the healthy controls' (p<0.001). As expected, the level of the total testosterone, free testosterone, LH, and FSH were lower in the patients than in the healthy controls (all the related p values <0.001). **(Table 2)**

In terms of the inflammatory markers; CRP levels were higher in the patient group than the healthy controls (p=0.01). The uric acid level was also higher in the control group, but it was not statistically significant (p=0.10). The MHR was similar in both groups (p=0.57). (Table 2) The MHR also was not correlated with the other hematological parameters, inflammatory parameters, and the total testosterone level.

Table 2 The clinical and biochemical features of Idiopathic Hypogonadotropic Hypogonadism (IHH) group and the control group.

Characteristics	IHH Patient (n=31)	The Controls (n=44)	P
Hemoglobin (gr/dl)	14.2±1.6	15.7±0.9	<0.001
White blood cell (x10.e3/uL)	7.59±3.18	7.44±1.74	0.64
Monocyte (x10.e3/uL)	0.58±0.38	0.60±0.20	0.20
Neutrophil (x10.e3/uL)	4.38±2.72	3.95±1.12	0.89
Lymphocytes (x10.e3/uL)	2.55±0.82	2.62±0.78	0.69
Monocyte-to-HDL cholesterol ratio	0.015±0.014	0.081±0.4	0.57
C-reactive protein (mg/dl)	1.2±1.2	0.2±0.2	0.01
Uric acid (mg/dl)	4.1±0.9	4.8±1.5	0.10
Creatinine (mg/dl)	0.6±0.1	0.8±0.1	<0.001
Fasting blood glucose (mg/dl)	91±6.1	87.3±7.8	0.054
Alanine amino transferase (U/L)	19.9±10.1	18.5±8.4	0.41
Aspartate amino transferase (U/L)	24.1±6.9	22.3±7.0	0.38
Total cholesterol (mg/dl)	157±27	152±20	0.58
LDL-cholesterol (mg/dl)	89.4±25.3	95.4±20.0	0.71
HDL-cholesterol (mg/dl)	49.3±16.6	46.7±8.3	0.72
Triglycerides (mg/dl)	107.8±104.0	95.3±44.0	0.58
Total thyroid stimulating hormone (mIU/L)	2.2±1.8	1.8±0.8	0.62
Free triiodothyronine (pg/ml)	3.6±0.7	3.7±0.5	0.61
Free thyroxine (ng/dl)	1.2±0.6	1.2±0.2	0.11
Total testosterone (ng/dl)	43.9±43.9	524.6±275.1	<0.001
Free testosterone (ng/dl)	8.9±13.7	19.7±10.5	<0.001
Luteinizing hormone (mIU/ml)	1.4±3.7	3.3±1.0	<0.001
Follicle-stimulating hormone (mIU/ml)	1.7±2.3	3.8±2.0	<0.001
Estradiol (pg/ ml)	30.7±15.2	45.4±32.7	0.49
Estrogen (pg/ ml)	30.6±11.5	46.7±32.1	0.43
Progesteron (ng/ml)	0.3±0.2	0.4±0.1	0.06
Dehydroepiandrosterone (µg/dl)	175.3±127.6	218.4±82.5	0.15
Adrenocorticotropic hormone (pg/ml)	26.0±17.2	21.3±10.9	0.42
Cortisol (µg/dl)	14.0±5.8	15.3±4.4	0.25
Prolactin (ng/dl)	9.0±17.0	8.2±4.9	0.14
Growth hormone (ng/ ml)	1.6±2.6	1.0±1.6	0.10
Insulin-like growth factor (ng/ ml)	265.4±124.2	316.4±92.1	0.15

DISCUSSION

Men with idiopathic hypogonadotropic hypogonadism (IHH) have lower plasma testosterone levels. IHH patients with low serum testosterone levels have an increased serum inflammatory markers levels, and these situations play an important role in the development and progression of impaired glucose metabolism, atherosclerotic plaque, and cardiovascular diseases (CVD) (19-20). Therefore low serum testosterone levels increase the incidence of cardiovascular events and chronic systemic inflammation (21).

Since it was known that chronic systemic inflammation increases insulin resistance and CV events, preventive medicine has gained more importance (22). Therefore, detection and awareness of chronic systemic inflammation have become more important for early interventions and preventions in patients at risk. Besides the erythrocyte sedimentation rate, C-reactive protein (CRP), and uric acid, several systemic inflammatory markers such as neutrophil-lymphocyte ratio (NLR), mean platelet volume (MPV), platelet-to-lymphocyte ratio (PLR), and monocyte-to-HDL cholesterol ratio (MHR) have been identified as new inflammatory markers in the last decades.

In the literature, the ratio of the monocyte-to-HDL cholesterol (MHR) was defined as an easy-to-calculate cardiovascular prognostic marker indicating the extent of the inflammation and oxidative stress in recent studies (16). This MHR can be used with the other prognostic and predictive accessible laboratory parameters to show chronic systemic inflammation. Although there are many publications about MHR in the literature, there is no study evaluating MHR in patients with IHH.

In a study conducted by Yilmaz et al. it is reported that smoking increases the MHR and this increase is an indicator of a systemic inflammatory process (17). Also, it was shown that increased MHR indicates an increased cardiovascular risk in patients with chronic renal failure in pre-dialysis period (18), an effective prediction of the presence and progression of subclinical carotid atherosclerosis in type 2 diabetic patient (23), and the association with increased mortality and morbidity during the first 3 months in patients with acute intracranial hemorrhage (24).

In our study, the MHR values as a new inflammatory marker were not significantly different between the patients and the controls while the CRP levels were significantly higher in the patients than in the healthy controls. The levels of CRP were higher in our patients than the healthy controls, whereas there was no significant difference for LDL, TG, fasting blood glucose, and uric acid levels between these two groups.

In conclusion, in our study, the MHR values were not significantly different between the patients and the controls. This result can indicate that the sensitivity of MHR is low. Therefore, more randomized controlled trials related to MHR is needed in larger IHH patient groups.

Declaration of conflict of interest

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