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MONOCYTE TO HDL-CHOLESTEROL RATİO İN MALE WİTH HYPOGONADOTROPHİC HYPOGONADİSM

Medical Science

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ABSTRACT

OBJECTİVES: The purpose of the present study is to investigate monocyte to high-density lipoprotein cholesterol (HDL-C) ratio (MHR) in the male with idiopathic hypogonadotropic hypogonadism (IHH).

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

RESULTS: 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 and the total testosterone.

CONCLUSİON: Previous studies have shown that IHH patients with low testosterone levels lead to an impaired glucose metabolism, and an increased cardiovascular risk. MHR also has been shown to be an indicator of cardiovascular risk in previous studies. In this study, we could not find an increased MHR value in patients with IHH.

KEYWORDS

Monocyte/HDL cholesterol ratio, Idiopathic hypogonadotrophic hypogonadism

INTRODUCTION

Testicular disfunction, i.e. hypogonadism, can result from a primary testicular disorder (hypergonadotropic) or occur secondary to hypothalamic-pituitary dysfunction (hypogonadotropic). Gonadotropin deficiency may be congenital or acquired and may arise from hypothalamic or pituitary disorders. (1) Idiopatic Hypogonadotropic hypogonadism (IHH) is classified as a secondary hipogonadism, and it is a rare disease characterized by delayed/absent puberty and infertility due to an inadequate secretion or action of gonadotrophin-releasing hormone (GnRH), with an otherwise structurally and functionally normal hypothalamic-pituitary-gonadal (HPG) axis. IHH also can be called congenital or isolated Hypogonadotropic hypogonadism. (2,3) The plasma testosterone level is lower in patients with IHH. Recent studies have shown that there is an inverse relationship between the plasma testosterone levels and inflammatory markers. (4) Also, sistemic inlammation plays an important role in the development and progression of atherosclerosis and cardiovascular diseases (CVD) which are the most common mortality reason in the world. (5) The studies have shown that the testosterone replacement therapy prevents the atherosclerosis and the CVD in HH patients. (6)

There are several systemic inflammatory markers such as sedimentation, C-reactive protein (CRP), and uric acid. In the last decades, the new inflammatory markers such as the neutrophil-lymphocyte ratio (NLR), and mean platelet volume (MPV) have been identified. (7) The Monocyte-to-HDL cholesterol ratio (MHR) is one of these new inflammatory markers, too. Monocytes and macrophages are the most abundant cells that secrete proinflammatory and prooxidant cytokines as part of all inflammatory reactions which play a central role in the pathogenesis of atherosclerosis. (8) During the development of the atherosclerotic lesions, blood monocytes are recruited into the intima and subintimal layers of the vessel wall, where these cells can take up oxidized low-density lipoprotein (ox-LDL) and other lipids through their scavenger receptors. Recruited monocytes facing fatty deposits undergo the activation and accumulation as foam cells. (8,9) On the other hand, high-density lipoprotein (HDL) molecule exhibits anti-inflammatory and antioxidant properties via several pathways, including inhibiting transmigration of monocytes in response to oxidized low-density lipoprotein (LDL), expression of endothelial adhesion proteins, and promoting reverse transport of oxidized molecules. (5) Therefore, the ratio of the monocyte count to the HDL cholesterol level (MHR) was defined as an easy-calculate cardiovascular prognostic marker indicating the extent of inflammation and oxidative stress in recent studies. (7) As a new indicating the extent of inflammation, oxidative stress, and CVD marker, this ratio can combine the prognostic and predictive effectiveness of two widely used and accessible laboratory parameters. (8,10-12)

The purpose of the present study is to investigate whether there is an association between hypogonadotrophic hypogonadism and monocyte-to-HDL cholesterol ratio (MHR) which is a new marker associated with inflammation.

MATERIALS 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. All patients didn't previously receive any medical treatment for IHH. The disease was identified as total testosterone of less than 229 ng/dl and free testosterone of less than 5.1 pg/ml. The cases were not given any medicine affecting platelet function at least for 2 weeks (e.g. acetyl salicylate, antiepileptics, heparin and so on) before the initiation of the study. Whoever had a chronic illness, panhypopituitarism, hypo and hyperthyroidsm, nephrotic syndrome, steroid use or use of any drug causing hypogonadism were excluded for the study. Also, none of the study subjects smokes and drinks alcohol. All procedures were in accordance with the 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).

After an overnight fasting of 12-hour, venous blood was collected from

the antecubital vein. The NLR was defined as the absolute neutrophil count divided by the absolute lymphocyte count.

Statistical Analysis

After testing the normality and homogeneity of variants, the Independent-Sample 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. Mean age of the IHH patients was 22.5±7.2 years while the mean age of the healty control group was 22.9±6.4 years. There were no statistically significant difference between the baseline characteristics such as age, height, weight, and BMI of the groups. (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 hemogram components such as the white blood cell, monocyte, neutrophil, and lymphocytes didn't show any statistically significant difference beetween the groups while the control group mean hemoglobin level was lower than the study group (p<0.001), and the IHH patient creatinine level was 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) When we looked at the inflammatory markers, CRP levels were lower in the patient group (p=0.01), but the UA level and the MHR were similar in both groups. (Table 2)

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

Characteristics	IHH Patients (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

Male with idiopatic hypogonadotropic hypogonadism (IHH) have lower plasma testosterone levels. IHH patients with low testosterone levels lead to an increase serum inflammatory markers levels, and this increased inflammatory markers levels play an important role in the development and progression of impaired glucose metabolism, atherosclerotic plaque, and cardiovascular diseases (CVD). (13-17) Besides the sedimentation, 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 decates. (18) In this study, however, we could not show an increased MHR value in patients with IHH.

Serum inflammatory marker levels can be increased with obesity and increasing age. Also, obesity can lead to a decrease in serum testosterone levels. It is also thought that low serum testosterone levels increase the incidence of cardiovascular events and chronic systemic inflammation. (13-15) To rule out this confusion, the patient and control groups were selected similar ages and similar BMI in our study. Our IHH patient and the control group BMIs were 21.6±4.9 vs. 19.5±3.2 (mean±SD, p=0.24). Although the mean BMI values of the patient group was slighty higher than the controls', against long odds, the monocyte-to-HDL cholesterol ratio was not a significant difference between the groups.

Although the underlying mechanism is not fully understood, testosterone replacement therapy (TRT) provides glycemic control and reduces the serum inflammatory markers in several studies. (16,17) This replacement therapy improves also the endothelial function by reducing the inflammation in the endothelium. (19-25) On the contrary, some studies detected that the incidence of CV events in the testosterone arm was almost twice as high as than the placebo arm. (26) Long-term TRT results contradict each other, so more comprehensive studies have been ongoing. (27-29) To rule out these treatment effects, isolated and untreated IHH male patients were recruited in our study.

Since it was known that the chronic systemic inflammation increases the insulin resistance and the CV events, preventive medicine has gained more importance. (30-32) Therefore, detection and awareness of chronic systemic inflammation have become more important for early intervention and prevention in patients at risk. In recent studies, it was shown that MHR is an easy-calculate marker to indicate the extent and effects of systemic inflammation. (16,22) This MHR can be used with the other prognostic and predictive accessible laboratory parameters to show the chronic systemic inflammation. (23-25) This inflammatory marker was found to be higher in smokers, in patients with marked atherosclerotic plaques, and in pre-dialysis patients. 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 our study, the MHR values were not significant different between the patients and the controls while the CRP levels were significantly higher in the patients than in 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.

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