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Evaluating Monocyte-to-high-density Lipoprotein Ratio Across Age and Gender in Healthy Individuals

Sağlıklı Bireylerde Monosit Yüksek Yoğunluklu Lipoprotein Oranının Yaş ve Cinsiyete Göre Değerlendirilmesi

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Abstract

Objective: This study aimed to evaluate the monocyte-to-high-density lipoprotein (HDL) ratio (MHR) across age and gender among healthy individuals.

Method: In this single-center retrospective study, we analyzed patients who visited the Kayseri City Hospital Internal Medicine Clinic within a year, were free from chronic diseases, did not take any medications, and had C-reactive protein levels below 5 mg/L and erythrocyte sedimentation rates below 20 mm/h. Patients were categorized into four age groups: 20-39 years (Group 1), 40-59 years (Group 2), 60-79 years (Group 3), and ≥80 years (Group 4). HDL levels, complete blood count values, and demographic characteristics were recorded for all subjects. MHR was calculated by dividing the monocyte count by the HDL level.

Results: No significant differences were observed in HDL level, monocyte count, and MHR across age groups (p=0.46, p=0.26, and p=0.37, respectively). However, a significant difference was found in HDL level (53.52±12.44 vs. 43.25±10.96; p<0.001), monocyte count (0.53±0.16 vs. 0.60±0.18; p<0.001), and MHR (10.59±4.07 vs. 15.03±6.62; p<0.001) between gender groups.

Conclusion: MHR emerged as a biomarker of systemic inflammation, showing no significant variance across age groups among healthy individuals. Nonetheless, gender differences were evident in HDL level, monocyte count, and MHR, possibly attributable to the lower prevalence of cardiovascular diseases in females.

Keywords: HDL cholesterol, inflammation, MHR, monocyte

Öz

Amaç: Bu çalışmanın amacı sağlıklı bireylerde monosit/yüksek yoğunluklu lipoprotein (HDL) oranının (MHO) yaş ve cinsiyet açısından değerlendirilmesidir.

Yöntem: Tek merkezli retrospektif bu çalışmaya Kayseri Şehir Hastanesi İç hastalıkları Kliniği'ne 1 yıl içerisinde başvuran, herhangi bir kronik hastalığı bulunmayan, ilaç kullanımı olmayan ve C-reaktif protein değeri 5 mg/L'nin ve eritrosit sedimantasyon hızı 20 mm/h'nin altında olan 459 hasta dahil edildi. Hastalar 20-39 yaş (Grup 1), 40-59 yaş (Grup 2), 60-79 yaş (Grup 3) ve 80 yaş üzeri (Grup 4) olmak üzere dört gruba ayrıldı. Katılımcıların HDL seviyeleri, tam kan sayımları ve demografik verileri kaydedildi. MHO, monosit sayısının HDL düzeyine bölünmesiyle hesaplandı.

Bulgular: HDL, monosit sayısı ve MHO düzeyi karşılaştırıldığında gruplar arasında anlamlı fark yoktu (sırasıyla, p=0,46, p=0,26, p=0,37). HDL (53,52±12,44 ile 43,25±10,96; p<0,001), monosit sayısı (0,53±0,16 ile 0,60±0,18; p<0,001) ve MHO (10,59±4,07 ile 15,03±6,62; p<0,001) düzeyi bakımından iki cinsiyet grubu arasında istatistiksel olarak 2 grup arasında anlamlı fark tespit edildi.

Sonuç: MHO sistemik enflamasyonun bir biyobelirteci olup sağlıklı bireylerde yaş grupları arasında fark bulunmamıştır. Cinsiyet açısından ise HDL, monosit sayısı ve MHO düzeyleri farklılık göstermektedir. Bu durum kardiyovasküler hastalıkların kadın cinsiyette daha az görülmesi ile açıklanabilir.

Anahtar kelimeler: Enflamasyon, HDL kolesterol, MHO, monosit

Introduction

Many diseases have been associated with aging, primarily attributed to age-related physiological changes. Aging significantly impacts the heart and vascular system, contributing to heightened occurrences of atherosclerosis, hypertension, atrial fibrillation, myocardial infarction, and cerebrovascular events (1). While acute inflammation plays a crucial role in responding to infections and facilitating

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wound healing, it has become evident that chronic inflammation has deleterious effects on various systems, including the immune system. The rise in the population of aging cells and persistent low-grade inflammation with advancing age actively contribute to the development of age-related pathologies (2).

Monocytes/macrophages are the cell types that play a crucial role in releasing pro-inflammatory cytokines and participating in all stages of the inflammatory process (3). Monocytes constitute 3-8% of all leukocytes in peripheral blood and play a significant role in regulating inflammatory processes (4-7). Research has established a connection between monocytes/macrophages and conditions such as coronary artery disease, cerebrovascular events, and post-ischemic stroke injury, as these cells actively participate in the inflammatory processes associated with these health issues (8-10).

In old age, the prominence of low high-density lipoprotein (HDL) cholesterol, rather than low-density lipoprotein (LDL) cholesterol, continues to stand out as a robust risk predictor. HDL may directly impact the aging process. Conversely, aging can also exert influence on HDL concentration and function. The alteration in HDL cholesterol concentration holds significant clinical relevance. It is estimated that a 1% change in HDL cholesterol can modify the risk of myocardial infarction or mortality by 2-3 times in middle-aged individuals (11).

HDL cholesterol is recognized for diminishing the risk of atherosclerotic events through mechanisms such as reversing HDL transport, averting endothelial dysfunction, and exerting anti-apoptotic, anti-oxidant, anti-inflammatory, and anti-thrombotic effects. Furthermore, HDL assumes an anti-atherogenic role by regulating monocyte activation and precursor monocyte cell proliferation, impeding macrophage migration, preventing LDL oxidation, and safeguarding endothelial cells from inflammation and oxidative stress (12).

Recent years have revealed that MHR can serve as a novel marker for inflammation and oxidative stress. A recent review highlighted MHR as a prognostic marker in cardiovascular diseases (13,14). In this context, MHR can function as a readily assessable metric, indicating the presence and prognosis of inflammatory and inflammation-related disorders (15-17). However, there is no conclusive data on whether MHR exhibits significant changes in the healthy population. Our study aimed to assess MHR based on age and gender in a healthy population.

Materials and Methods

Patient Selection

In this retrospective study, we analyzed data from 459 patients without chronic diseases who visited the Internal Medicine Clinic at University of Health Sciences Turkey, Kayseri City Hospital within the past year and had C-reactive protein (CRP) values below 5 mg/dL and erythrocyte sedimentation rate under 20 mm/h. The study adhered to the principles of the Helsinki Declaration and the Patient Rights Act. All eligible patients provided written informed consent, and the study received approval from the Ethics Committee on Clinical Research of Erciyes University (approval #2019/504).

Clinical findings, demographic characteristics, and laboratory data were extracted from the hospital information management system and archives. Biochemical parameters, lipid panel, and peripheral complete blood count were analyzed for all patients. Exclusion criteria encompassed thyroid dysfunction, secondary hypertension, cardiovascular disease, acute and/or chronic infection, autoimmune disease, connective tissue disease, as well as a history of smoking, alcohol consumption, cancer, and the use of medications such as corticosteroids, non-steroidal anti-inflammatory agents, anti-lipid drugs, and immunosuppressive agents.

Patients were categorized into four age groups: 20-39 years (Group 1), 40-59 years (Group 2), 60-79 years (Group 3), and ≥80 years (Group 4). The distribution was as follows: 138 patients in Group 1, 141 patients in Group 2, 128 patients in Group 3, and 52 patients in Group 4. Recorded parameters included total cholesterol, triglyceride, HDL level, complete blood count, erythrocyte sedimentation rates and CRP levels. Non-HDL cholesterol was calculated by subtracting HDL cholesterol from the total cholesterol value. MHR was determined by dividing the monocyte count (μL) by the HDL level (mg/dL).

Statistical Analysis

All statistical analyses were conducted using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA). The normal distribution of data was assessed through the Kolmogorov-Smirnov test. Continuous variables with a normal distribution are expressed as mean ± standard deviation, while categorical variables are presented as percentages and counts. Student's t-test was employed for binary comparisons of normally distributed data, and One-Way ANOVA was used for comparisons involving more than two groups. Kruskal-Wallis and Mann-Whitney U tests were utilized for data with skewed distribution. A p-value <0.05 was considered statistically significant.

Results

Overall, the analysis included data from 459 patients, with 205 women (44.7%) and 254 men (55.3%). Gender distribution did not show a significant difference across the groups. The mean age was 28.77±6.4 years in Group 1, 49.33±5.65 years in Group 2, 69.43±5.91 years in Group 3, and 86.19±4.69 years in Group 4.

In the study population, the mean HDL was 47.83±12.7, while the mean monocyte count was 0.57±0.17, and the mean MHR was 13.04±6.03. The mean MHR varied across the age groups, with values of 12.56±5.66 in Group 1, 13.55±6.24 in Group 2, 13.33±6.45 in Group 3, and 12.23±5.33 in Group 4. Regarding HDL levels, the mean was 48.33±13.36 in Group 1, 46.67±13.03 in Group 2, 48.93±13.04 in Group 3, and 46.98±8.48 in Group 4. Similarly, the mean monocyte count varied across groups, with values of 0.55±0.17 in Group 1, 0.57±0.16 in Group 2, 0.59±0.18 in Group 3, and 0.55±0.18 in Group 4. Table 1 presents the laboratory values in the patient groups. Significant differences were observed

Table 1. Demographic and clinical characteristics of participants

	Group 1 (n=138)	Group 2 (n=141)	Group 3 (n=128)	Group 4 (n=52)	p
Age	28.77±6.4	49.33±5.65	69.43±5.91	86.19±4.69	
Gender (female/male)	70/68	60/81	49/79	26/26	0.171[a]
Cholesterol (mg/dL)	169.29±35.64	194.18±37.68	210.57±42.62	187.07±35.69	**<0.001[b]**
LDL (mg/dL)	93.28±29.81	115.86±31.38	131.39±36.42	113.91±28.76	**<0.001[b]**
Triglyceride (mg/dL)	139.09±117.84	158.91±85.53	161.42±99.9	124.04±56.58	0.098[b]
HDL (mg/dL)	48.33±13.36	46.67±13.03	48.93±13.04	46.98±8.48	0.461[b]
WBC (10^3/μL)	7.55±1.7	7.22±1.84	8.29±±1.1	8.29±1.65	0.711[b]
Neutrophil (10^3/μL)	4.49±1.26	4.16±1.37	4.33±1.62	4.36±1.84	0.483[b]
Lymphocyte (10^3/μL)	2.26±0.68	2.31±0.59	2.1±0.83	1.61±0.61	**<0.001[b]**
Monocyte (10^3/μL)	0.55±0.17	0.57±0.16	0.59±0.18	0.55±0.18	0.261[b]
Hemoglobin (g/dL)	13.78±1.94	13.55±1.93	14.08±1.68	13.54±1.85	0.225[b]
Platelet (10^3/μL)	286.96±65.24	285.31±64.25	252.58±72.27	226.43±71.65	**<0.001[b]**
MPV (fL)	10.06±0.99	10.12±0.93	13.84±0.98	12.3±0.95	0.282[b]
MHR	12.56±5.66	13.55±6.24	13.33±6.45	12.23±5.33	0.379[b]
Non-HDL	119.31±34.41	143.24±35.70	159.69±40.26	139.39±34.57	**<0.001[b]**

[a]: Chi-square, [b]: One-Way ANOVA, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, WBC: White blood cell, MPV: Mean platelet volume, MHR: Monocyte to HDL ratio

Table 2. Significance levels between groups of clinical characteristics

	p-values*					
	Group 1 vs. Group 2	**Group 1 vs. Group 3**	**Group 1 vs. Group 4**	**Group 2 vs. Group 3**	**Group 2 vs. Group 4**	**Group 3 vs. Group 4**
Cholesterol (mg/dL)	**<0.001**	**<0.001**	**0.041**	**0.025**	**0.023**	**0.004**
LDL (mg/dL)	**<0.001**	**<0.001**	**0.002**	**0.008**	**0.002**	**0.015**
Triglyceride (mg/dL)	0.501	0.998	0.216	0.998	0.216	0.157
HDL (mg/dL)	0.693	0.981	0.914	0.464	0.999	0.788
WBC (10^3/μL)	0.988	0.878	0.932	0.744	0.841	0.934
Neutrophil (10^3/μL)	0.400	0.873	0.958	0,864	0.877	0.959
Lymphocyte (10^3/μL)	0.951	0.379	<0.001	0.188	**<0.001**	**<0.001**
Monocyte (10^3/μL)	0.922	0.309	0.990	0.676	0.864	0.379
Hemoglobin (g/dL)	0.823	0.667	0.885	0.236	0.976	0.384
Platelet (10^3/μL)	0,998	**0.002**	**<0.001**	**0.008**	**<0.001**	0.147
MPV (fL)	0.996	0.310	0.841	0.384	0.867	0.946
MHR	0.525	0.729	0.987	0.991	0.534	0.684
Non-HDL	**<0.001**	**<0.001**	**0.010**	**0.016**	**<0.001**	**0.012**

*: Post hoc analysis, Bonferroni correction. LDL: Low-density lipoprotein, HDL: High-density lipoprotein, WBC: White blood cell, MPV: Mean platelet volume, MHR: Monocyte to HDL ratio

in LDL cholesterol, lymphocyte, platelet, and non-HDL values across groups (p<0.001, p<0.001, p<0.001, p<0.001 and p<0.001, respectively) (Table 1, 2).

When stratifying patients by gender, the mean age was 51.24±21.77 years among women and 54.3±19.67 years among men. No significant differences were observed in age distribution between women and men (p=0.171). The mean values for cholesterol, LDL, triglyceride, HDL, white blood cell, neutrophil, lymphocyte, monocyte, platelet, hemoglobin, MPV, MHR, and non-HDL were 195.06±41.49, 115.91±35.46, 139.97±83.22, 53.52±12.44, 8.1±8.79, 4.32±1.42, 2.18±0.7, 0.53±0.16, 13.24±1.67, 280.2±67.1, 12.29±1.38, 10.59±4.07, and 141.5±40.58 in women, respectively. In men, the corresponding values were 180.08±39.51, 106.66±34.07, 160.97±98.93, 43.25±10.96, 7.25±1.87, 4.38±1.57, 2.08±0.76, 0.60±0.18, 14.61±1.84, 251±73.8, 10.02±0.86, 15.03±6.62, and 135.32±37.78. Significant differences were observed in cholesterol, LDL, HDL, monocyte, hemoglobin, platelet, MHR, and non-HDL values across groups. (p=0.001, p=0.02, p=0.059, p<0.001, p<0.001, p<0.001, p<0.001 and p<0.001) (Table 3).

Discussion

In our study, variances were observed among cholesterol, LDL, lymphocyte, thrombocyte, and non-HDL groups. At the same time, when compared between genders, differences were detected in terms of cholesterol, LDL, HDL, monocyte, hemoglobin, platelet, MHR and non-HDL. HDL and non-HDL levels were significantly higher in females compared to males. Additionally, monocyte values were lower in females. There was no significant change in HDL levels with age, but non-HDL levels were observed to vary with age. Likewise, the MHR rate was found to be higher in males, with no observed change with age.

Age-related changes continue to be a focal point of interest in the research field, driven by the desire to extend healthy lifespan. Aging affects various cell types throughout the body, implying that all tissues may harbor aged cells. The impacts of aging have been demonstrated in numerous cell types, including macrophages and T-cells within the immune system (18-20). Structural stromal cells, such as fibroblasts, exhibit a high degree of aging with advancing age. These aged stromal cells lose the ability to undergo cell division and become resistant to apoptosis (21). The prolonged presence of chronic inflammation is a major contributor to the aging process. In our study, we evaluated MHR, employed as an inflammatory marker in research, based on age and gender in healthy individuals.

The study demonstrated that HDL can inhibit tissue factor expression in monocytes by preventing p38 activation and phosphoinositide 3-kinase (22). HDL exerts an anti-inflammatory effect by preventing pro-inflammatory and pro-oxidant effects on monocytes, as well as inhibiting the transport of vascular cholesterol, macrophage migration, and LDL oxidation in the vessel wall (23). It is believed that MHR can also serve as an inflammation marker, attributed to the pro-inflammatory effect of monocytes and the anti-inflammatory and antioxidant effects of HDL cholesterol (24).

Levels of all lipoproteins, including HDL, are significantly lower at birth compared to adolescence, and these levels increase during childhood. HDL concentrations in

Table 3. Comparison of clinical characteristics between genders

	Female (n=205)	Male (n=254)	p*
Cholesterol (mg/dL)	195.06±41.49	180.08±39.51	**0.001**
LDL (mg/dL)	115.91±35.46	106.66±34.07	**0.020**
Triglyceride (mg/dL)	139.97±83.22	160.97±98.93	0.059
HDL (mg/dL)	53.52±12.44	43.25±10.96	**<0.001**
WBC (10^3/μL)	8.1±8.79	7.25±1.87	0.277
Neutrophil (10^3/μL)	4.32±1.42	4.38±1.57	0.741
Lymphocyte (10^3/μL)	2.18±0.7	2.08±0.76	0.200
Monocyte (10^3/μL)	0.53±0.16	0.60±0.18	**<0.001**
Hemoglobin (g/dL)	13.24±1.67	14.61±1.84	**<0.001**
Platelet (10^3/μL)	280.2±67.1	251±73.8	**<0.001**
MPV (fL)	12.29±1.38	10.02±,86	0.191
MHR	10.59±4.07	15.03±6.62	**<0.001**
Non-HDL	141.5±40.58	135.32±37.78	**<0.001**

*: Student's t-test, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, WBC: White blood cell, MPV: Mean platelet volume, MHR: Monocyte to HDL ratio

men decrease during adolescence and early adulthood, remaining lower than in women thereafter (25). Previous studies have demonstrated that HDL cholesterol decreases in both men and women with advancing age during adulthood (26,27). In postmenopausal women, substantial reductions are observed in HDL cholesterol levels due to hormonal alterations. In our study, no significant difference was detected in HDL levels across groups, possibly because all included patients were healthy individuals. However, HDL values were found to be significantly higher in women than men, consistent with the existing literature (27). Consistent with the study by Ridefelt et al. (28), the estimated non-HDL value exhibited significant changes by age and between genders in our study.

Monocytes are influenced by numerous factors associated with atherosclerosis, including immunostimulant substances, growth factors, cytokines, oxidized lipids, platelet-derived activation products, and eicosanoid proteins (29). Circulating monocytes transition into a pro-coagulant phenotype by expressing tissue factor during inflammatory and pro-thrombotic states. Additionally, monocytes induce the secretion of pro-inflammatory cytokines, contributing to the pathogenesis of many inflammatory diseases (30). As individuals age, inflammation processes are heightened in many cell types that play a role in inflammation, such as monocytes and macrophages (31). In our study, we observed alterations in monocyte values with age, although they did not reach statistical significance. Additionally, we found that monocyte values were higher in the male gender.

Circulating levels of IL-6, CRP, TNF-α, IL-1ß, and other inflammatory cytokines are elevated in elderly individuals, thereby increasing the risk of all-cause mortality (32-34). In elderly individuals, lower levels of inflammatory cytokines in peripheral blood are associated with better health outcomes, longer lifespan, and reduced mortality risk (35). Inflammatory cytokines serve as indicators of chronic inflammation and are implicated in various disease processes, including diabetic complications (36). However, routine clinical use can result in high healthcare costs. Simple, readily available markers, such as MHR, are employed as inflammation markers in many studies. In our study, the aim was to investigate the use of MHR as an inflammation marker by stratifying it with age, but no significant difference was detected between age groups. We attribute this result to the inclusion of healthy adults in our study. MHR was found to be significantly higher among men compared to women. In a study conducted by Liu et al. (37), various inflammatory markers were compared based on age and gender. Similar to our study, no differences were found when compared by age, but significant variations were observed between genders. The observed higher prevalence of cardiovascular diseases caused by atherosclerosis in male patients is in line with these findings (38,39).

Study Limitations

The study's limitations include its retrospective, cross-sectional, and single-center design. To obtain more comprehensive results on this issue, a multicenter study involving different ethnicities is recommended. Additionally, a prospective study supported by cardiovascular imaging may offer a more accurate understanding of the link to atherosclerosis.

Conclusion

While the MHR can serve as a guide in atherosclerosis and various inflammatory conditions, it has been observed that its utility in evaluating inflammation status does not vary significantly with age. The gender differences in MHR can be attributed to the lower risk of cardiovascular events in the general population among females.

Ethics

Ethics Committee Approval: The study received approval from the Ethics Committee on Clinical Research of Erciyes University (approval #2019/504).

Informed Consent: All eligible patients provided written informed consent.

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