Association Between Serum Uric Acid to HDL-Cholesterol Ratio as a Novel Indicator of Inflammation and Ischemic Changes on Electrocardiogram: The MASHAD Cohort Study

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Abstract- This study aimed to explore the association between serum uric acid to high-density lipoprotein cholesterol ratio (UHR) and minor and major ischemic electrocardiogram (ECG) changes. The data from the Mashhad Stroke and Heart Atherosclerotic Disorder (MASHAD) cohort study comprised 9035 participants aged 35 to 65 years. A 12-lead resting ECG was recorded at baseline for participants. ECG abnormalities were defined according to the Minnesota coding system and classified into three groups: none, minor, and major ischemic changes. Minor and Major ischemic changes were observed in 6.2% and 14.1% of participants, respectively. Participants in the major ischemic group had higher UHR levels compared to those without ischemic changes on their ECG (odds ratio (OR)=0.023, 95% confidence interval (95% CI)=1.011-1.035, *P*<0.001). UHR remained correlated with major ischemic ECG changes after adjustment for either age (OR=0.019, 95% CI=1.007-1.031, *P*=0.001) or various cardiovascular risk factors (OR=0.018, 95% CI=1.006-1.030, *P*=0.004). UHR was not significantly associated with minor ischemic changes. This research showed, for the first time, that UHR was significantly associated with major ischemic ECG changes. Indeed, the UHR provides additional information for risk stratification of subjects with myocardial ischemia.

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Keywords: Uric acid to HDL-cholesterol ratio; Electrocardiogram; Ischemic ECG abnormalities

Introduction

Cardiovascular disease (CVD) is a main global cause of morbidity and mortality, and ischemic heart disease (IHD) is the most common clinical manifestation of CVD (1). Although death rates are declining in Western countries, CVD morbidity imposes an immense burden on healthcare systems worldwide (2). To decrease morbidity and mortality, cardiovascular risk factors are continually updated and targeted. Prospective research has indicated that the ischemic changes on electrocardiogram (ECG) are associated with an increased risk of CVD (3-5).

Uric acid (UA) is the end product of purine

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metabolism, generated from the breakdown of exogenous (dietary) or endogenous nucleic acid (6). Serum UA is a widely available, inexpensive biomarker that can be obtained in clinical practice (7). UA is a potent scavenger of free radicals, and its antioxidant impacts may prevent cardio-metabolic diseases (8), whereas hyperuricemia can damage several organs by increasing inflammatory response (9). UA can also promote the oxidation of low-density lipoprotein cholesterol, aggravating arterial atherosclerosis and contributing to the progression and development of IHD (10). In addition, emerging studies have reported an independent association between UA and ECG abnormalities, including left ventricular hypertrophy (11), arterial fibrillation (12), and ischemic changes (4).

High-density lipoprotein cholesterol (HDL-C) is a crucial component of lipid metabolism, as it transports cholesterol to the liver (13). It also protects endothelial cells and decreases oxidative conditions in blood vessels (14). Previous studies have found that low serum HDL-C concentrations and hyperuricemia may have synergistic adverse effects on the cardiovascular system by inducing insulin resistance and oxidative injury to endothelial cells (15-17). Although an association between high UA and low HDL-C levels has been observed in metabolic disorders (17-19), the impact of the interaction between UA and HDL-C on the prognosis of subjects with ischemic ECG changes has not been adequately studied.

The UA-to-HDL-C ratio (UHR) is a novel index reflecting inflammation, as well as conditions related to glucose-lipid metabolism and prognosis (20,21). However, to date, no study examined the prognostic value of UHR in patients with ischemic ECG abnormalities. In this study, we aimed to investigate the association between UHR and major and minor ischemic ECG changes.

Materials and Methods

Study population and data collection

This study was derived from the Mashhad Stroke and Heart Atherosclerotic Disorder (MASHAD) study, a 10-year prospective cohort study conducted in Mashhad City, northeast of Iran. The materials and methodology of the MASHAD study were described in detail elsewhere (22). In brief, 9704 subjects aged 35 to 65 years were recruited using a stratified cluster random sampling technique. Socio-demographic, hematologic, anthropometric, biochemical data, and nutritional intake were collected. Informed written consent was obtained from all participants. The study was approved by the Ethics Committee of the Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1399.783).

Electrocardiogram and the Minnesota coding system

A 12-lead ECG was obtained from each participant and was scanned and archived digitally. Among the 9704 subjects, ECGs from 9035 were available and readable according to the Minnesota coding system (23). The details of ECG recording and the results have been previously described and published (24). In the present study, based on the results of reliable and available ECGs, we divided the subjects into two subgroups: participants with major ischemic changes and participants with minor ischemic changes, according to the Minnesota coding standards for ECG classification (23). Major ischemic abnormalities were defined as any of the following: major Q wave abnormalities (Minnesota code 1-1 and 1-2); minor Q wave abnormalities plus ST-T abnormalities (Minnesota code 1-3 plus 4-1, 4-2, 5-1, and 5-2); major isolated ST-T abnormalities (Minnesota code 4-1, 4-2, 5-1, and 5-2). Minor ischemic abnormalities included: minor Isolated Q/QS waves (Minnesota code 1-3); minor ST/T abnormalities: (Minnesota code 4-3, 4-4, 5-3, and 5-4); ST-segment elevation (Minnesota code 9-2). The remaining population was categorized as the participants without ischemic changes group. The flowchart of the study subjects' grouping is outlined in Figure 1.

Statistical analysis

We described the quantitative and qualitative variables as mean±standard deviation (SD) and frequency (%), respectively. A Student's t-test was used to compare quantitative variables, and a chi-square test was used to compare qualitative variables. Mann-Whitney and Kruskal-Wallis tests were used for skewed variables. To determine whether UHR was an independent predictor of ischemic changes, logistic regression analyses were performed across multiple models, with multiple adjustments. The results of logistic regression analyses were expressed as odds ratios (ORs) and their corresponding 95% confidence intervals (CIs). All statistical analyses were carried out using SPSS 26.0 (Armonk, NY: IBM Corp.). $P<0.05$ was considered statistically significant.

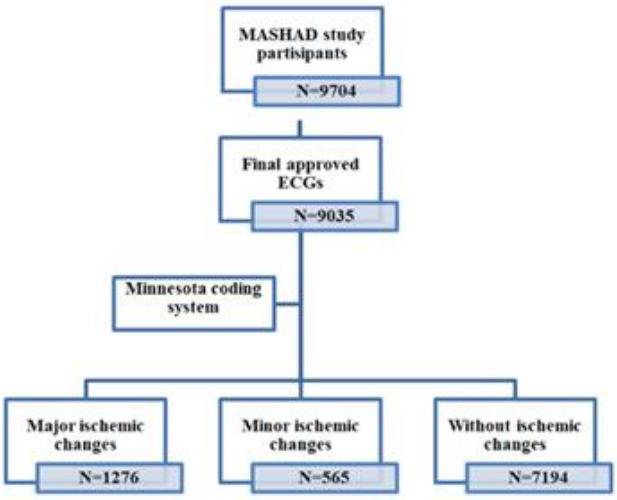

Figure 1. Flowchart of the participants in the present study and their grouping.

Results

This study included 9035 participants aged 35 to 65 years (3615 men and 5420 women). Participants were divided into three groups based on ECG ischemic changes: (1) without ischemic changes, (2) with minor ischemic changes, and (3) with major ischemic changes. The baseline demographic and clinical characteristics of participants in the three groups are presented in Table 1.

The results revealed significant differences between the three groups in terms of sex, age, hypertension (HTN), body mass index (BMI), waist circumference (WC), UHR (P<0.001 for all cases), smoking status (P=0.017), physical activity level (PAL) (P<0.035), triglyceride (TG) (P=0.003), HDL-C (P=0.003), and UA (P=0.001).

The correlation between UHR and major and minor ischemic changes was assessed by logistic regression analysis in non-adjusted and adjusted models (Tables 2 and 3). As shown in Table 2, participants in the major ischemic group had higher UHR levels compared to those without ischemic changes on their ECG (OR=0.023, 95% CI=1.011-1.035, P<0.001). UHR remained correlated with major ischemic changes after adjustment for either age (OR=0.019, 95% CI=1.007-1.031, P=0.001) or various cardiovascular risk factors (OR=0.018, 95% CI=1.006-1.030, P=0.004). UHR was not significantly associated with minor ischemic changes before and after multiple adjustments.

Table 1. Comparison of demographic and clinical characteristics of participants between the three groups

Characteristics	Without ischemic changes (n=7194, 79.60 %)	Minor ischemic changes (n=565, 6.30 %)	Major ischemic changes (n=1276, 14.10 %)	*P**
Sex				
Female	4395 (81.10 %)	251 (4.60 %)	774 (14.30 %)	<0.001
Male	2799 (77.40 %)	314 (8.70 %)	502 (13.90 %)	
Age (year)	47.90±8.19	47.67±8.12	49.57±8.36	<0.001
Marriage status				0.295
Single	47 (85.50 %)	0 (0.00 %)	8 (14.50 %)	
Married	6699 (79.60 %)	538 (6.40 %)	1181 (14.00 %)	
Divorced	98 (80.30 %)	4 (3.30 %)	20 (16.40 %)	
Widow	350 (79.50 %)	23 (5.20 %)	67 (15.20 %)	
Smoking status				0.017
Non smoker	4973 (80.00 %)	364(5.90 %)	881 (14.20 %)	
Ex-Smoker	683 (67.70 %)	61(6.80 %)	147 (16.50 %)	
Current smoker	1538 (79.90 %)	140(7.30 %)	248 (12.90 %)	
Diabetes				0.210
Yes	992 (77.90 %)	82 (6.40 %)	199 (15.60 %)	
No	6109 (77.90 %)	475 (6.20 %)	1058 (13.80 %)	

Cont. table 1

HTN				
Yes	2138 (76.40 %)	160 (5.70 %)	500 (17.90 %)	<0.001
No	5046 (81.10 %)	401 (6.40 %)	773 (12.40 %)	
BMI	27.90±4.74	26.90±4.63	28.33±4.61	<0.001
PAL	1.59±0.28	1.57±0.29	1.58±0.28	0.035
WC (cm)	95.04±12.02	93.99±12.47	96.66±11.86	<0.001
hs-CRP (mg/dl)	4.17±8.85	3.99±8.10	4.32±9.83	0.753
Cholesterol (mg/dl)	191.08±39.37	194.63±40.15	191.39±37.52	0.118
TG (mg/dl)	141.27±91.17	145.46±95.33	150.70±98.03	0.003
LDL-C (mg/dl)	116.41±35.73	116.49±35.21	117.56±33.46	0.562
HDL-C (mg/dl)	42.88±10.00	43.48±10.10	41.97±9.53	0.003
Uric acid (mg/dl)	4.64±1.39	4.78±1.51	4.78±1.41	0.001
UHR	0.11±0.04	0.11±0.04	0.12±0.04	<0.001

Abbreviations: SBP: systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; PAL: physical activity levels; WC: waist circumference; hs-CRP: high-sensitivity C-reactive protein; TG: triglyceride; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; UHR: Uric acid to HDL ratio

**P* was computed based on t-tests for continuous data and the Chi-square test for categorical data

Table 2. Association between UHR and major ischemic changes after multiple adjustments

		B	EXP	95%CI	*P**
UHR	**crude**	0.023	1.023	1.011-1.035	<0.001
	Model 1	0.019	1.019	1.007-1.031	0.001
	Model 2	0.018	1.018	1.006-1.030	0.004

Abbreviations: UHR: uric acid to high-density lipoprotein ratio;
Model 1: after adjustment for age
Model 2: after adjustment for age and DM, SBP, DBP, hs-CRP, smoking status, PAL, and BMI

Table 3. Association between UHR and minor ischemic changes after multiple adjustments

		B	EXP	95%CI	*P **
UHR	**crude**	0.004	1.004	1.011-1.035	0.631
	Model 1	0.005	1.005	0.987-1.023	0.602
	Model 2	-.002	0.998	0.979-1.018	0.858

Abbreviations: UHR: uric acid to high-density lipoprotein ratio;
Model 1: after adjustment for age and sex
Model 2: after adjustment for age and DM, SBP, DBP, hs-CRP, smoking status, PAL, and BMI

Discussion

In the present study, we explored, for the first time, the relationship between UHR, a novel inflammatory factor, and ECG ischemic changes in a large community-based population. We found that elevated UHR levels were significantly correlated with major ECG ischemic changes. After adjusting for several clinical parameters in a general population, UHR levels remained significantly associated with major ECG changes indicative of ischemia. According to the evidence, the most common cause of ST-T abnormalities in the general population is slight-to-moderate myocardial ischemia (3).

UHR has recently been introduced as a novel index of inflammation and metabolism and has attracted considerable attention in current studies due to its potential impact on physiological processes and disease development. UHR was first introduced by Kocak et al. as a strong predictor of metabolic syndrome in patients with type 2 diabetes mellitus among the Turkish population (25). Then, increased UHR levels have been discussed in other metabolic and inflammatory conditions such as metabolic syndrome (26), diabetes mellitus (21), nonalcoholic fatty liver disease (27-29), and poorly controlled hypertension (30).

UHR has also been discussed in the context of CVDs. It has been indicated that an increased level of UHR could predict the increased risk of all-cause and cardiovascular mortality in patients with peritoneal dialysis treatments (17). An observational study demonstrated a nonlinear relationship between serum UHR and brachial-ankle PWV in the Japanese population (31). A longitudinal study found that higher UHR values were positively associated with the incidence of ischemic heart disease in the Korean population without diabetes. This association remained significant after adjustment for potential confounding factors, such as HTN medications (15).

Serum UA is the final product of purine metabolism and is generally regarded as a risk factor for IHD (32). Prior human studies reported that high UA concentrations

are associated with IHD and also its severity and prognosis (33-36). Moshkovits *et al*. showed that the odds of ischemic ECG changes are 80% higher in the high UA tertiles than in the lower UA tertiles (4). At the molecular level, hyperuricemia is accompanied by endothelial injury, thereby enhancing the phosphorylation of endothelial nitric oxide synthase and mediating endoplasmic reticulum stress. When intracellular conditions change, UA becomes a pro-oxidant that enhances IHD progression (37,38).

HDL-C has an important role in stimulating cholesterol efflux in arterial wall cells, decreasing foam cell accumulation, and inhibiting LDL cholesterol oxidation to diminish atherogenicity (39). In addition, HDL-C contains a number of antioxidants and anti-inflammatory components, including apolipoprotein A1 (ApoA1), ApoA2, and paraoxonase, which prevent arteriosclerosis (40). The reconstituted HDL particle infusion was indicated to decrease coronary plaque size in both animal and human models (41). The results of the Framingham Heart study (42) and Prospective Cardiovascular Münster study (43) revealed that a 1 mg/dL (0.026 mmol/L) increase in the HDL-C levels is correlated to a 2-3% reduction in the CVD risk.

As discussed above, the association between UA, HDL-C, and IHD has been broadly recognized. It is indicated that UA and HDL-C may interact to enhance CVD progression by disrupting endothelial cell function and inducing oxidative stress (15).

Aside from the underlying population-based large-scale research strengths, our study must be interpreted in light of its limitations. First, only subjects aged 35-65 years were included in this study. Second, it is a cross-sectional study, so no causal association could be characterized. Therefore, we highly recommend that future researchers conduct multicenter longitudinal research to precisely examine the association between UHR levels and ischemic ECG abnormalities.

This study suggests that UHR is independently associated with major ischemic ECG changes. Accordingly, UHR levels may be a valuable additional measure to assess the risk of myocardial ischemia in the preclinical stage.

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The study protocol was reviewed and approved by the Ethics Committee of Mashhad University of Medical Sciences (IR.MUMS.MEDICAL.REC.1399.783), and written informed consent was obtained from participants.

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