Hypertriglyceridemia Is Associated With White Blood Cell Count and Red Cell Distribution Width: A Gender Stratified Analysis in a Population-Based Study

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Abstract- Hypertriglyceridemia is a common form of dyslipidemia and is associated with several comorbidities, such as increased risk of pancreatitis and cardiovascular diseases (CVD). The white blood cell (WBC) count is a non-specific inflammatory marker associated with a wide variety of diseases such as diabetes, hypertension, and atherosclerotic cardiovascular disease. The objective of this study was to perform a gender-stratified examination of the association between hypertriglyceridemia and hematological parameters in a large sample of Iranian population. The triglyceride (TG) levels and hematological parameters were measured in 9,780 participants (40% males and 60% females) aged 35-65 years, enrolled in a population-based cohort (MASHAD) study in northeastern Iran. Participants were stratified into three groups based on the definition of hypertriglyceridemia: TG<150 mg/dl (n=6521), TG=150-199 mg/dl (n=1597), and TG≥200 mg/dl (n=1662). A complete blood count (CBC) was obtained for all the subjects. The mean WBC count increased with increasing severity of hypertriglyceridemia among both men and women. Participants with high and very high TG levels had significantly higher WBC count, RBC count, platelet count, hemoglobin, hematocrit, and mean corpuscular hemoglobin concentration and significantly lower RDW. After performing multivariate logistic regression, WBC count and RDW were independently related to hypertriglyceridemia. In conclusion, hypertriglyceridemia is associated with elevated WBC count which may partly explain the observed association between hypertriglyceridemia and CVD.

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Keywords: Hypertriglyceridemia; White blood cell count; Cardiovascular disease

Introduction

Hypertriglyceridemia is a common form of dyslipidemia with multifactorial characteristics, including genetic and environmental factors (1-4). A plasma triglyceride (TG) concentration equal or above 150 mg/dl (1.7 mmol/l) is a defining component of metabolic syndrome (5) and is associated with several

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comorbidities, such as increased risk of pancreatitis (6,7) and cardiovascular diseases (CVD) (8,9). It has been reported that 1 mmol/l increase in serum triglycerides is independently related to 14% and 37% increased the risk of coronary heart disease in men and women, respectively (9). Environmental factors such as obesity, inactivity, excessive alcohol intake, smoking, hormone dysfunctions, use of certain medications, and diseases such as diabetes mellitus are described in the literature to be associated with hypertriglyceridemia (10-12). According to a systematic review and meta-analysis of population-based studies and national surveys conducted in subjects aged ≥15 years, the prevalence of hypertriglyceridemia (≥150 mg/dl) in Iranian population was estimated to be 46.0% (43.3-48.7) among both sexes and in both rural and urban areas (13).

The white blood cell (WBC) count, a non-specific inflammatory marker, is usually measured as part of the complete blood count (CBC) panel. Increased WBC count is an available measure of inflammation which is associated with a wide variety of diseases such as diabetes, hypertension, and atherosclerotic cardiovascular disease (14,15). Moreover, several studies have indicated that an elevated WBC count is significantly associated with all-cause cardiovascular and cancer mortality (16). It has been suggested that combined exposure to both high WBC count and triglyceride level is related to more than three-fold risk of cardiovascular mortality, independent of traditional risk factors (17). Red cell distribution width (RDW), another routinely reported parameter in CBC test, is a quantitative measure of anisocytosis, the variability in size of the circulating erythrocytes (18). It has been reported that increased RDW is associated with negative clinical outcomes in patients with cardiovascular diseases independent of hemoglobin values (19,20).

There are limited reports of the positive association between hypertriglyceridemia and WBC count (21-24). Huang *et al*., found a positive correlation between serum TG level and total leukocyte count and counts of all subtypes except eosinophils (21). Nagasawa *et al*., also found a significant and independent association between serum TG level and WBC count (22). In another study, after controlling for potential confounders, the adjusted means of WBC count were significantly higher in patients with each feature of the metabolic syndrome such as hypertriglyceridemia (23). Alipour *et al*., reported that acute hypertriglyceridemia is a leukocyte activator most likely by direct interaction between TG-rich lipoproteins (TRLs) and leukocytes and uptake of fatty acids. The authors also suggested that TG-mediated leukocyte activation is an alternative proinflammatory and pro-atherogenic mechanism of hypertriglyceridemia which is associated with the generation of oxidative stress (25).

The primary objective of the present study was to perform a gender-stratified examination of the association between hypertriglyceridemia and hematological parameters in a sample of 9,780 subjects who took part in the Mashhad stroke and heart atherosclerotic disorder (MASHAD) study.

Materials and Methods

Study population

A total sample of 9,780 subjects [3913 (40%) men and 5867 (60%) women], were recruited from Mashhad, a city in northeastern of Iran, using a stratified-cluster method and derived from the MASHAD study (26). The MASHAD study is a 10-year cohort study that aims to evaluate the impact of various genetic, nutritional, environmental, and psychosocial risk factors on the incidence of cardiovascular events among a general urban population aged 35-65 years in north-eastern Iran (26). The mean age of men and women were 48.8±8.4 y and 47.5±8.0 y, respectively (unshown data). The overall inclusion and exclusion criteria of MASHAD study and the general characteristics of the study sample such as marriage status, education level, job status, comorbid conditions, medication use, biochemical and anthropometric measurements have been reported earlier (26). Of the original, 9908 individuals recruited, 128 participants were excluded due to missing data or taking medication for hypertriglyceridemia. All participants gave informed, written consent to contribute to the survey, which was approved by the Ethics Committee of Mashhad University of Medical Sciences.

Demographic, anthropometric and metabolic data

For all subjects that participated in the study, height (in cm), weight (in kg), body mass index (in kg/m^2), and waist circumference were measured. Body weight was measured to the nearest 0.1 kg with electronic scales, and height and waist circumference (WC) was measured to the nearest millimeter with a tape measure. The systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by sphygmomanometer twice in exactly the same manner. It was measured on the left arm when the participants remained seated at rest for 15 minutes. We took the third measurement and averaged the two closest readings if the first two readings differ by more than 15 mm Hg in diastolic or more than 25 mm Hg in

systolic blood pressure.

Samples of fasting blood were collected after a 12-hour overnight fast to determine fasting blood glucose (FBG), uric acid and a full fasted lipid profile, consisted of high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), total cholesterol, and TG, as described previously (27-29). Serum hs-CRP concentration was estimated using an immunoturbidimetry method, with detection limit of 0.06 mg/L (Pars Azmun, Karaj, Iran) (30).

Definition of hypertriglyceridemia

The definition of hypertriglyceridemia was based on the National Cholesterol Education Program-Adult Treatment Panel III (NCEP ATPIII), which defined normal TG level as <150 mg/dl, borderline high as 150-199 mg/dl, high as 200-499 mg/dl and very high TG as ≥500 mg/dl (31).

Measurements of hematological parameters

A complete blood count including white blood cell (WBC) count, red blood cell (RBC) count, hemoglobin (HGB), hematocrit (HCT), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), and estimated of platelet (PLT) count, were determined in all the individuals, as described previously (29).

Statistical analysis

Data analysis was carried out using SPSS-18 software (SPSS Inc., IL, USA). The normality of data was evaluated using Kolmogorov-Smirnov test. Data were expressed as the mean±standard deviation (SD) for variables with normally distribution or median (interquartile range) for not normally distributed variables. For normally distributed variables, analysis of variance (ANOVA) was performed. The Mann-Whitney U test was used for serum hs-CRP since it was a continuous non-normal variable even after logarithmically transformed. All the analyses were two-sided and $P<0.05$ was considered as significant. Chi-square tests were used to compare the qualitative variables. TG levels were divided into categories according to the definition of hypertriglyceridemia and participants in the first group (normal TG level) were considered as a reference group. Multivariate analyses were used to estimate the risk, as approximated by the odds ratio (OR). The odds ratios, with 95% confidence intervals (CI), were obtained using multivariate logistic regression, to determine the influence of potential confounding factors, e.g., age, WC, SBP, DBP, LDL-C, HDL-C, TC, FBG, uric acid, and hs-CRP.

Results

Among the 9,780 adults, the average age was 48.0±8.2 y, with 60% being female. Participants were stratified into three groups: those with normal TG level (TG<150 mg/dl, n=6521), those with borderline high TG level (TG=150-199 mg/dl, n=1597), and those with high and very high TG levels (group≥200 mg/dl, n=1662). Demographic and biochemical characteristics of participants in groups of hypertriglyceridemia are presented in Table 1. Subjects with normal TG levels were significantly younger than subjects with borderline high and high TG levels. A higher percentage of males were observed in the high and very high group ($P<0.001$). BMI, WC, SBP, DBP, TC, FBG, uric acid, and hs-CRP were significantly lower among subjects with normal TG levels. Moreover, individuals with normal TG levels had significantly higher HDL-C levels (Table 1).

As reported in table 2, WBC count, RBC count, PLT count, HGB, and HCT were significantly higher in men and women with high and very high TG levels. There were no significant differences between different groups of hypertriglyceridemia in terms of MCV and MCH. Subjects with normal TG levels had significantly lower MCHC. Moreover, RDW was significantly higher among subjects with normal TG levels (Table 2).

In all our multivariate analyses, the group who had normal TG levels served as a reference group. Multivariate analysis showed that in the borderline high and high and very high groups compared with the reference group, WBC count and RDW were the strongest determinants of the severity of hypertriglyceridemia (Table 3). Even after adjusting for age, WC, SBP, DBP, LDL-C, HDL-C, TC, FBG, uric acid, and hs-CRP, WBC count and RDW had a significant impact on the severity of hypertriglyceridemia (Table 4).

Table 1. Demographic and biochemical characteristics of participants in groups of hypertriglyceridemia

	Triglyceride level		
	Normal (N=6521) <150 mg/dl	**Borderline high (N=1597) 150-199 mg/dl**	**High and very high (N=1662) ≥200 mg/dl**
Sex (male) n (%)	2495 (38.3%)	655 (41.0%)	763 (45.9%)***
Age (y)	47.4±8.2	49.0±8.1	49.6±8.0***
BMI (kg/m^2)	27.2±4.7	29.0±4.6	29.2±4.3***
WC (cm)	93.5±12.1	97.9±11.7	99.2±10.5***
SBP (mmHg)	120.0±18.7	124.8±19.4	126.2±19.2***
DBP (mmHg)	78.1±11.8	80.9±11.4	81.4±11.4***
LDL-C (mg/dl)	115.6±32.2	121.7±38.7	115.0±42.2***
HDL-C (mg/dl)	44.4±10.0	40.9±8.8	38.6±8.8***
TC (mg/dL)	182.8±35.0	202.8±37.5	213.7±43.9***
FBG (mg/dL)	88.2±33.2	95.7±40.5	107.4±53.6***
Uric acid (mg/dL)	4.4±1.2	5.0±1.5	5.3±1.5***
hs-CRP (mg/L)	1.5 (0.93-3.24)	1.92 (1.13-3.99)	1.97 (1.16-4.11)***

Values are expressed as mean±SD for variables with normal distribution, and median (interquartile range) for hs-CRP as a non-normally distributed variable. BMI: body mass index; WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; LDL-C: low density lipoprotein-cholesterol; HDL-C: high density lipoprotein-cholesterol; TC: total cholesterol; FBG: fasting blood glucose; hs-CRP: high sensitivity C-reactive protein. *P<0.05; **P<0.01; ***P<0.001

Table 2. Hematological parameters in groups of hypertriglyceridemia

		Triglyceride level		
		Normal (N=6521) <150 mg/dl	**Borderline high (N=1597) 150-199 mg/dl**	**High and very high (N=1662) ≥200 mg/dl**
WBC (10^9/L)	**Male**	6.0±1.6	6.4±1.8	6.6±1.6***
	Female	5.8±1.4	6.2±1.5	6.3±1.5***
RBC (10^{12}/L)	**Male**	5.1±0.5	5.2±0.5	5.2±0.4***
	Female	4.6±0.4	4.7±0.4	4.7±0.4***
HGB (g/dl)	**Male**	14.7±1.3	14.9±1.1	15.0±1.2***
	Female	12.9±1.3	13.1±1.2	13.3±2.9***
HCT (%)	**Male**	43.7±3.4	44.2±3.2	44.3±3.0***
	Female	39.2±5.6	39.9±3.6	39.9±3.5***
MCV (fl)	**Male**	85.6±5.7	85.2±4.8	85.1±5.7
	Female	84.4±6.5	84.7±6.0	84.5±5.2
MCH (pg/cell)	**Male**	28.8±2.7	28.8±2.4	28.9±2.1
	Female	27.9±2.8	28.0±2.5	28.0±2.1
MCHC (g/dl)	**Male**	33.5±1.9	33.8±1.7	33.7±1.6**
	Female	32.9±1.5	33.0±1.4	33.1±1.3***
RDW (fl)	**Male**	41.8±3.2	41.1±3.3	40.9±3.1***
	Female	41.8±3.0	41.6±3.2	41.0±3.5***
PLT (10^9/L)	**Male**	210.8±52.8	214.1±52.8	217.9±53.5**
	Female	238.8±63.0	247.4±62.9	247.1±65.8***

Values are expressed as mean±SD. WBC: white blood cell; RBC: red blood cell; HGB: hemoglobin; HCT: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width; PLT: platelet. *P<0.05; **P<0.01; ***P<0.001

Table 3. The odds ratio of having normal, borderline high or high triglyceride level associated with hematological parameters among men and women

		Triglyceride level	
		Reference group and 2nd group	Reference group and 3rd group
WBC (10^9/L)	**Males**	1.12 (1.06-1.20)***	1.20 (1.14-1.27)***
	Females	1.14 (1.08-1.20)***	1.21 (1.15-1.27)***
RBC (10^{12}/L)	**Males**	0.75 (0.23-2.45)	0.62 (0.34-1.12)
	Females	1.08 (0.55-2.09)	1.01 (0.47-2.18)
HGB (g/dl)	**Males**	0.94 (0.73-1.22)	1.02 (0.83-1.26)
	Females	1.22 (0.95-1.56)	1.38 (1.00-1.9)
HCT (%)	**Males**	1.1 (0.94-1.28)	1.1 (1.00-1.22)
	Females	0.99 (0.97-1.02)	0.96 (0.90-1.03)
MCV (fl)	**Males**	1.04 (0.95-1.14)	0.98 (0.96-1.01)
	Females	1.01 (0.98-1.04)	1.03 (0.99-1.07)
MCH (pg/cell)	**Males**	0.81 (0.62-1.06)	1.00 (0.94-1.07)
	Females	0.96 (0.85-1.08)	0.91 (0.78-1.06)
MCHC (g/dl)	**Males**	1.3 (0.98-1.66)	1.01 (0.94-1.09)
	Females	0.95 (0.85-1.08)	0.98 (0.85-1.14)
RDW (fl)	**Males**	0.92 (0.89-0.96)***	0.88 (0.85-0.91)***
	Females	0.97 (0.94-1.00)*	0.91 (0.88-0.94)***
PLT (10^9/L)	**Males**	1.00 (0.99-1.00)	1.00 (1.00-1.00)
	Females	1.00 (1.00-1.00)	1.00 (1.00-1.00)

Odds ratios with 95% confidence intervals (95% CI) obtained from multiple logistic regression tests. WBC: white blood cell; RBC: red blood cell; HGB: hemoglobin; HCT: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width; PLT: platelet. **P*<0.05; ***P*<0.01; ****P*<0.001.

Table 4. The odds ratio of having normal, borderline high or high triglyceride level associated with hematological parameters adjusted for potential confounders

		Triglyceride level	
		Reference group and 2nd group	Reference group and 3rd group
WBC (10^9/L)	**Males**	1.07 (1.008-1.14)*	1.12 (1.03-1.21)**
	Females	1.11 (1.05-1.18)**	1.15 (1.07-1.24)***
RBC (10^{12}/L)	**Males**	0.84 (0.25-2.77)	0.80 (0.31-2.04)
	Females	1.32 (0.60-2.86)	1.09 (0.52-2.31)
HGB (g/dl)	**Males**	0.84 (0.64-1.09)	0.89 (0.62-1.27)
	Females	0.94 (0.70-1.25)	1.07 (0.97-1.17)
HCT (%)	**Males**	1.07 (0.91-1.25)	1.04 (0.89-1.21)
	Females	1.00 (0.97-1.03)	0.94 (0.87-1.02)
MCV (fl)	**Males**	1.05 (0.95-1.15)	0.98 (0.93-1.04)
	Females	1.03 (1.00-1.07)	1.06 (1.01-1.10)
MCH (pg/cell)	**Males**	0.82 (0.63-1.07)	1.05 (0.96-1.13)
	Females	0.95 (0.81-1.12)	0.91 (0.76-1.09)
MCHC (g/dl)	**Males**	1.33 (1.02-1.73)	1.06 (0.92-1.22)
	Females	1.05 (0.92-1.21)	1.08 (0.91-1.28)
RDW (fl)	**Males**	0.94 (0.91-0.98)**	0.92 (0.88-0.96)***
	Females	0.99 (0.96-1.02)	0.95 (0.91-0.98)**
PLT (10^9/L)	**Males**	1.00 (0.99-1.00)	1.00 (1.00-1.00)
	Females	1.00 (1.00-1.00)	1.00 (0.99-1.00)

Odds ratios with 95% confidence intervals (95% CI) obtained from multiple logistic regression tests adjusted for potential confounders (i.e. age, WC, SBP, DBP, LDL-C, HDL-C, TC, FBG, uric acid, and hs-CRP). WBC: white blood cell; RBC: red blood cell; HGB: hemoglobin; HCT: hematocrit; MCV: mean corpuscular volume; MCH: mean corpuscular hemoglobin; MCHC: mean corpuscular hemoglobin concentration; RDW: red cell distribution width; PLT: platelet. *P<0.05; **P<0.01; ***P<0.001.

Discussion

Current results suggest that higher TG levels are associated with an enhanced inflammatory state, as assessed by higher WBC count. There was also a significant negative association between TG levels and RDW.

There is limited number of studies which attempted to investigate the association between hypertriglyceridemia and WBC count (21-24). A cross-sectional study of 3,594 Japanese men aged 34–69 years showed that TG level, as well as BMI, HDL-C, SBP, and FBG, have a significant

and independent association with WBC count (22). Another study on 5275 Japanese male office workers aged 23-59 years also reported significantly higher WBC count in subjects with each feature of the metabolic syndrome including hypertriglyceridemia, hypercholesterolemia, obesity, hypertension, high fasting plasma glucose levels, low high-density lipoprotein cholesterol levels, and hyperuricemia) (23). Similarly, Rong *et al*., found an association between increased WBC count and components of metabolic syndrome (24). By multivariate regression analysis, Huang *et al*. also found a positive correlation between serum TG level and total leukocyte count and counts of all subtypes except eosinophils (21).

Alipour *et al*., reported that acute hypertriglyceridemia is a leukocyte activator most likely by direct interaction between TRLs and leukocytes and uptake of fatty acids in the bloodstream associated with the generation of oxidative stress (25,32). The ability of triglycerides to induce leukocyte activation has also been observed in *in-vitro* studies (33,34). For instance, Wanten *et al*., showed that various lipid emulsions are involved in neutrophil activation through effects on calcium mobilization and protein kinase C activation (34). Van Oostrom and colleagues found a leukocyte increment after fat ingestion which was suggested to be related to the postprandial TG increase (35). This neutrophil increase during postprandial lipemia and glycemia was suggested to be associated with the production of proinflammatory cytokines and oxidative stress which may contribute to endothelial dysfunction (36). Moreover, it has been reported that postprandial lipemia is associated with the upregulation of leukocyte activation markers CD66b and CD11b in healthy individuals and in patients with premature coronary sclerosis (37, 38). Previous studies also showed that the biomarkers of oxidative stress are elevated in the serum of humans with high plasma TG-rich lipoproteins (39,40). Cardona *et al*., reported greater oxidative status as reflected by increased levels of serum lipoperoxides (LPO), carbonylated proteins, and oxidized glutathione (GSSG) and lower levels of antioxidant enzymes in hypertriglyceridemic patients, with or without metabolic syndrome (41).

Hypertriglyceridemia is a risk factor for atherosclerosis and CVD (42,43) and is also associated with higher leukocyte count as shown in this study. Since higher peripheral total leukocyte count is associated with a higher risk of CVD (44,45), it seems that the association of hypertriglyceridemia with a higher CVD risk can partly be explained by higher counts of leukocytes. In agreement with this hypothesis, Bae *et al*., found that postprandial hypertriglyceridemia can cause endothelial dysfunction via increased leukocyte superoxide anion radical production which may pave the way for the development of atherosclerosis (46). Another study showed that hypertriglyceridemia is associated with higher soluble and cellular cell adhesion molecule (CAM) levels which can highlight the inflammatory process as a key event in atherogenesis (47).

In the present study, we also found a negative association between TG levels and RDW. In contrast to our results, Vaya *et al*., found an association between RDW and components of metabolic syndrome except for abdominal obesity (48). In another study, 1,111 healthy subjects were classified into RDW-quartiles, and the authors observed no changes in plasma lipids with increasing RDW-quartiles (49). In a study conducted on 217,567 workers who underwent a routine medical checkup, Sánchez-Chaparro found a significant association between high RDW and metabolic syndrome (50). Further studies are needed to better understand the relationship between TG levels and RDW.

A major strength of the present study is that it was a large population-based study and the gender-stratified examination provided a new insight regarding the relationship between hematological markers and risk of hypertriglyceridemia in a representative sample of Iranian adults. We acknowledge the limitations in our study, including (a) the greater percent of the study sample was women (60%), and (b) the fact that we had measured both TG levels and hematological parameters at baseline.

In summary, we found that TG levels are associated with elevated WBC count which may partly explain the observed association between hypertriglyceridemia and CVD. There was also a significant negative association between TG levels and RDW which needs further investigation.

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