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Low-grade inflammation in individuals with the hypertriglyceridemic waist phenotype: Another feature of the atherogenic dysmetabolism

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Abstract

The purpose of this study was to explore the possibility that the recently described "hypertriglyceridemic waist" (HTGW) phenotype, a risk for future coronary artery disease, is associated with the presence of low-grade inflammation. This is a cross-sectional study in a cohort of apparently healthy nondiabetic employed individuals in whom the presence of low-grade inflammation was determined by using the Dade Behring high-sensitivity C-reactive protein (hs-CRP) assay. We have presently analyzed the results obtained in 9842 apparently healthy individuals, at a mean (SD) age of 44 (11) years. We identified 1249 individuals (70.0% men) with HTGW phenotype according to the cutoff points of waist girth of at least 90 cm for men and at least 85 cm for women and triglycerides levels of at least 177 mg/dL for men and at least 133 mg/dL for women. In addition, we identified 1164 individuals (69.3% men) with the metabolic syndrome (MetS) according to the updated Adult Treatment Panel III criteria. The mean (SD) of hs-CRP was 1.3 (2.9) mg/L for the 8055 individuals who had neither the HTGW phenotype nor the MetS, 2.1 (2.7) mg/L for those who had the HTGW phenotype and no MetS, and 2.5 (2.7) for 538 individuals with the MetS and no HTGW phenotype, whereas those who had both atherogenic disorders presented an hs-CRP concentration of 2.9 (2.3) mg/L. In this cohort of apparently healthy nondiabetic employed individuals, the HTGW phenotype had a similar prevalence as the MetS and was associated with the presence of low-grade inflammation. This inflammation could be a pathophysiologic link between this dysmetabolism and atherothrombosis. In addition, the HTGW phenotype is relatively prevalent and could be a simple and inexpensive way to single out individuals at risk for future coronary artery disease.

1. Introduction

The hypertriglyceridemic waist (HTGW) phenotype might be an inexpensive clinical method of identifying elevated coronary artery disease (CAD) risk among asymptomatic individuals as well as patients with glucose intolerance and type 2 diabetes mellitus [1-3]. The HTGW phenotype is characterized by the presence of an atherogenic metabolic triad of hyperinsulinemia; elevated apolipoprotein B; and small, dense low-density lipoprotein (LDL) [1,4]. We have presently explored the possibility that the HTGW phenotype is also associated with the presence of low-grade inflammation. The presence of an acute phase response could explain, at least in part, the association between this dysmetabolic and atherogenic metabolism and the risk of developing CAD.

2. Methods

2.1. Study population

In the present study, we analyzed the data collected during the last 5 years in the Tel Aviv Medical Center Inflammation Survey, a registered data bank of the Israeli Ministry of Justice [5-11]. This is a relatively large survey composed of apparently healthy individuals attending a center for periodic health examinations.

Ori Rogowski and Itzhak Shapira should both be considered first authors.

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Table 1
Mean (SD) of the different continuous variables and number (percentage) of cardiovascular risk factors among the groups with and without the MetS and the HTGW phenotype

	No MetS and no HTGW	No MetS and positive HTGW	MetS and negative HTGW	MetS and HTGW	ANOVA
n	8055	623	538	626	
Age (y)	43 (11)	45 (9)	50 (9)	49 (9)	<.001
Male sex	4942 (61%)	465 (75%)	398 (74%)	409 (65%)	<.001
BMI (kg/m^2)	25 (4)	28 (3)	31 (4)	31 (4)	<.001
Diastolic BP (mm Hg)	75 (8)	77 (6)	83 (8)	82 (8)	<.001
Systolic BP (mm Hg)	119 (14)	121 (12)	136 (14)	132 (14)	<.001
Alcohol consumption (glasses/wk)	1.1 (2.0)	1.0 (1.9)	1.0 (1.9)	0.8 (1.8)	.026
Sport intensity (h/wk)	2.3 (2.9)	1.9 (2.2)	1.9 (2.8)	2.0 (2.5)	.007
Current smoker, n (%)	1371 (17%)	126 (20%)	72 (13%)	127 (20%)	<.001
Past smoker, n (%)	1756 (22%)	169 (27%)	162 (30%)	184 (29%)	
Hypertension, n (%)	1064 (13%)	84 (14%)	315 (59%)	295 (47%)	<.001
Family history of CAD, n (%)	1251 (16%)	109 (18%)	103 (19%)	128 (20%)	.002

BMI indicates body mass index; BP, blood pressure.

2.2. Protocol

In the present study, patients attending the Tel Aviv Sourasky Medical Center, Tel Aviv, Israel, for a routine health examination between September 2002 and April 2008 were invited to participate in the Tel Aviv Medical Center Inflammation Survey. All individuals enrolled were recruited during their routine annual health checkup and gave their written consent in accordance with the guidelines of the Institutional Ethics Committee. A total of 13 319 subjects gave their informed consent (male, 8345; female, 4974). Later, 2383 subjects were excluded from the analysis because of known malignancy or immunosuppressive therapy, inflammatory disease (arthritis, inflammatory bowel disease, psoriasis, etc), pregnancy, steroidal or nonsteroidal treatment (except for aspirin at a dose of ≤325 mg/d), or acute infection or invasive procedures (surgery, catheterization, etc) during the last 6 months. An additional 161 subjects were further excluded for having missing high-sensitivity C-reactive protein (hs-CRP) values, 855 for having a history of proven atherothrombotic disease (myocardial infarction, coronary artery bypass graft surgery, cerebrovascular event, or peripheral artery occlusion disease) and/or diabetes mellitus, and finally 78 individuals treated with fibrates because of their potential influence on triglyceride concentrations. After these exclusions, the study group comprised 9842 individuals (6214 men and 3628 women).

2.3. Laboratory methods

Blood was drawn in morning hours after an at least 12-hour fasting period using a standard Vacutainer gel tube (Becton Dickinson, Franklin Lakes, NJ). The hs-CRP was measured by a Behring BN II Nephelometer [12] and CardioPhase reagent (Dade Behring, Marburg, Germany). For hs-CRP cutoff levels less than 15 mg/L, intraassay coefficients of variance (CVs) are in the range of 3.1% to 4.0% (n = 20); and the interassay CVs are in the range of 2.1% to 3.8% (n = 10). Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides were measured using a Bayer Advia 1650 chemistry analyzer and Bayer respective kits (Bayer Healthcare Diagnostics Division, Newbury, United Kingdom). Interassay CVs for

Table 2
Frequency of medications among the groups with and without the MetS and the HTGW phenotype

	No MetS and no HTGW		No MetS and positive HTGW		MetS and negative HTGW		MetS and HTGW		ANOVA
n	8055		623		538		626		
	n	%	n	%	n	%	n	%	
Aspirin	226	2.8	30	4.8	63	11.7	46	7.3	<.001
β-Blockers	157	1.9	9	1.4	68	12.6	61	9.7	<.001
Calcium channel blockers	79	1.0	5	0.8	45	8.4	32	5.1	<.001
ACE inhibitors	123	1.5	7	1.1	50	9.3	44	7.0	<.001
Angiotensin II receptor blockers	36	0.4	1	0.2	11	2.0	10	1.6	<.001
Statins	444	5.5	51	8.2	90	16.7	57	9.1	<.001
Oral contraceptives	480	6.0	26	4.2	4	0.7	8	1.3	<.001
Hormonal replacement therapy	273	3.4	10	1.6	13	2.4	19	3.0	.067

ACE indicates angiotensin-converting enzyme.

Table 3
Mean (SD) of the glucose and lipid concentrations among the groups with and without the MetS and the HTGW phenotype

	No MetS and no HTGW	No MetS and positive HTGW	MetS and negative HTGW	MetS and HTGW	ANOVA
n	8055	623	538	626	
Glucose	90 (9)	91 (8)	102 (10)	99 (10)	<.001
HDL Cholesterol	57 (14)	50 (10)	47 (10)	46 (10)	<.001
LDL Cholesterol	120 (31)	130 (32)	127 (31)	128 (36)	<.001
Triglycerides	89 (2)	217 (1)	126 (1)	228 (1)	<.001

total cholesterol, triglycerides, and HDL are in the range of 4%, 3%, and 3%, respectively. The intraassay variations for these tests are approximately 2%. The LDL cholesterol values given are calculated using the Friedewald formula.

2.4. Definition of atherothrombotic risk factors

Results of the routine health check up were assessed using certain definitions to recognize atherothrombotic risk factors in individuals. These included *diabetes mellitus*, which was defined as an individual displaying blood glucose of at least 126 mg/dL fasting or the intake of insulin or oral hypoglycemic medications. *Hypertension* was defined as displaying blood pressure of at least 140/90 mm Hg in 2 separate measurements or the intake of antihypertensive medications. *Dyslipidemia* was defined as the LDL cholesterol or non–HDL cholesterol concentrations, for individuals displaying elevated triglyceride concentrations of at least 200 mg/dL, greater than the recommended levels according to the risk profile defined by the updated Adult Treatment Panel III recommendations [13] or the intake of lipid-lowering medications. The diagnosis of the metabolic syndrome (MetS) was based on the National Cholesterol Education Program Adult Treatment Panel III criteria [13] with the modified impaired fasting glucose criteria of the American Diabetes Association [14] as proposed by the updated American Heart Association/National Heart, Lung, and Blood Institute scientific statement [15]. The *HTGW phenotype* was defined as waist circumference of at least 90 cm for men or at least 85 cm for women together with triglyceride levels of at least 177 mg/dL for men or at least 133 mg/dL for women [1,16-17]. *Smokers* were defined as individuals who smoked at least 5 cigarettes per day, whereas *past smokers* had quit smoking for at least 30 days before examination.

2.5. Statistical analysis

All data were summarized and displayed as mean (SD) for the continuous variables and as number of patients plus the percentage in each group for categorical variables.

Because hs-CRP and the triglyceride concentrations displayed irregular distributions, we used a logarithmic transformation that converted the distributions to normal ones for all statistical procedures. Therefore, all results of hs-CRP or triglyceride concentrations are expressed as back-transformed geometrical mean and SD. The 1-sample Kolmogorov-Smirnov test was used to assess the distributions.

For all continuous variables, the univariate analysis to compare the various parameters between the different groups with and without the MetS and the HTGW was done using 1-way analysis of variance (ANOVA), with a post hoc pairwise comparison using the Scheffe analysis. For all dichotomous variables, the same comparison was done using the χ^2 analysis.

To control for possible and known confounders with potential influence on the inflammatory profile, estimated marginal means of hs-CRP were calculated for the different groups with and without the MetS and the HTGW with adjustment for sex, age, sport intensity, alcohol consump-

Table 4
Mean (SD) and fully adjusted[a] estimated marginal mean (95% confidence interval [CI]) hs-CRP according to the groups with and without the MetS and the HTGW phenotype

	No MetS and no HTGW	No MetS and positive HTGW	MetS and negative HTGW	MetS and HTGW	ANOVA	Post hoc pairwise comparison	
n	8055	623	538	626			
	0	1	2	3		Group	*P* value
hs-CRP (mg/L)	1.3 (2.9)	2.1 (2.7)	2.5 (2.7)	2.9 (2.4)	<.001	0-1, 2, 3	<.001
						1-2	.043
						1-3	<.001
hs-CRP[a] (mg/L)	1.9 (1.8-2.0)	3.0 (2.7-3.3)	3.5 (3.1-3.9)	4.1 (3.7-4.5)	<.001	0-1, 2, 3	<.001
						1-2	.027
						1-3	<.001

[a] Adjusted for age; sex; sport intensity; alcohol consumption; family history of CAD; smoking status; and use of oral contraceptives, hormonal replacement therapy, or statins.

Table 4a
Mean (SD) and fully adjusted[a] estimated marginal mean (95% CI) hs-CRP according to the groups with and without the HTGW phenotype components just for individuals without the MetS

	Low WC and low TG	Low WC and high TG	High WC and low TG	High WC and High TG	ANOVA	Post hoc pairwise comparison	
N	4129	476	3450	623			
	0	1	2	3		Group	*P* value
hs-CRP (mg/L)	1.0 (2.9)	1.8 (3.1)	1.7 (2.7)	2.1 (2.7)	<.001	0-1,2,3	<.001
						2-3	<.001
hs-CRP[a] (mg/L)	1.5 (1.4-1.6)	2.1 (1.9-2.4)	2.6 (2.4-2.8)	3.1 (2.8-3.5)	<.001	All-all	<.001

WC indicates waist circumference; TG, triglycerides.
[a] Adjusted for age; sex; sport intensity; alcohol consumption; family history of CAD; smoking status; and use of oral contraceptives, hormonal replacement therapy, or statins.

tion, family history of coronary heart disease, smoking status, and use of statins and oral contraceptives or hormonal replacement therapy for women, using analysis of covariance, under a general linear model.

Further evaluation of the partial contribution of the MetS and the HTGW phenotype, as well as the interaction between them, was done using 2-way ANOVA, with adjustment for the same list of confounders.

All of the above analyses were considered significant at *P* less than .05 (2-tailed). The SPSS (Chicago, IL) statistical package was used to perform all statistical evaluations.

3. Results

We have presently analyzed the results obtained in 9842 individuals at a mean (SD) age of 44 (11) years. One thousand two hundred forty-nine (12.7%) had the HTGW phenotype, 1164 (11.8%) had the MetS, whereas 8055 (81.8%) individuals had neither the HTGW nor the MetS. We identified 623 individuals with HTGW and no MetS, 538 with the MetS and no HTGW, and 626 with both the MetS and the HTGW phenotype.

In Table 1, we report the different clinical variables of the different groups, whereas the intake of medication and the laboratory data are given in Tables 2 and 3, respectively. The results of the hs-CRP concentrations are given in Table 4 for the entire cohort of the study. Individuals with the HTGW phenotype have shown increased hs-CRP concentrations but not as high as those seen in those who fulfill the criteria for the MetS. However, the differences in the hs-CRP concentration between those with the HTGW and those who have no MetS and no HTGW are clear and significant.

We have further analyzed the results of the hs-CRP concentrations for individuals who have no MetS and subdivided the HTGW population into its 2 components of waist circumference and hypertriglyceridemia (Table 4a). Both circumference and hypertriglyceridemia might contribute to the elevated hs-CRP concentrations. In fact, each component is associated with CRP increments by itself (Table 4a).

We have further examined the interaction between the above-mentioned 2 definitions of the HTGW phenotype and the MetS and showed a significant correlation (Table 5). This interaction, in which both phenotypes contribute in a significant way but their interaction has an additive affect, is also visualized in Fig. 1.

Finally, we have analyzed the proportion of individuals according to the risk categories of hs-CRP concentrations of less than 1, 1 to 3, and greater than 3 mg/L. The results are shown in Fig. 2 and reveal the sharp drop in the proportion of individuals in the low-risk category of less than 1 mg/L once they fulfill the criteria for the HTGW phenotype.

4. Discussion

Although previously reported in a relatively small (n = 137) group of women [2], the present study is the first to analyze the presence of low-grade inflammation in both

Table 5
Two-way ANOVA table of hs-CRP including the interaction between MetS and HTGW

Parameter	Estimated marginal mean (95% CI) of parameter		*P* value
	No	Yes	
HTGW phenotype	2.8 (2.6-3.0)	3.8 (3.4-4.1)	<.001
MetS	2.6 (2.3-2.8)	4.1 (3.7-4.5)	<.001
Interaction between MetS and HTGW			<.001

Estimated marginal means of the HTGW phenotype and of the MetS are adjusted in addition to the list specified below to the other one, that is, MetS and HTGW, respectively, and to the interaction between those 2. Adjusted for age; sex; sport intensity; alcohol consumption; family history of CAD; smoking status; and use of oral contraceptives, hormonal replacement therapy, or statins.

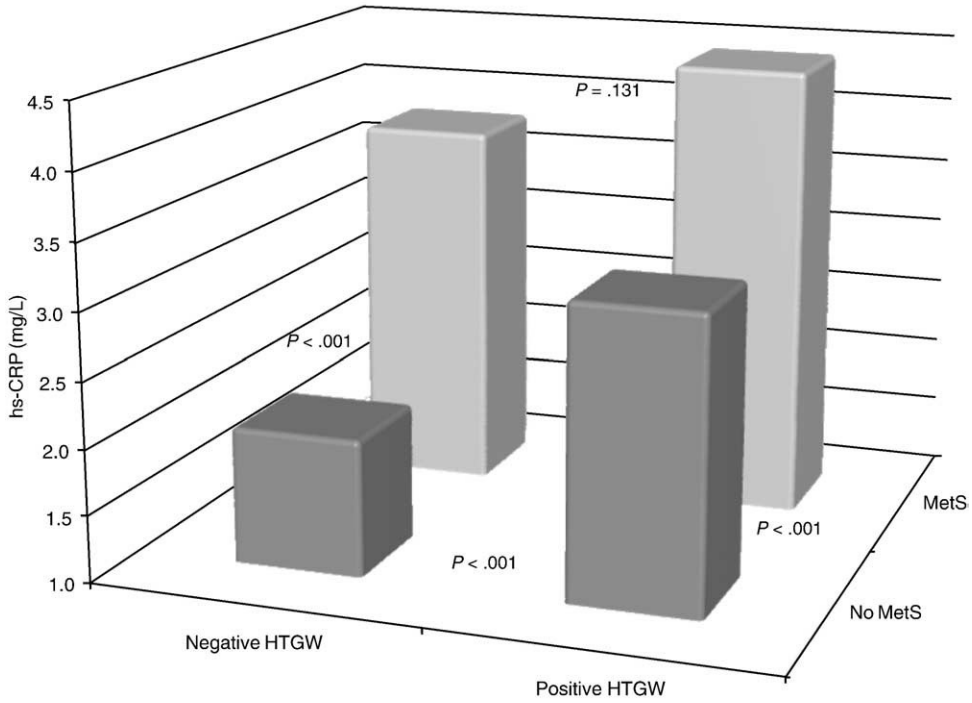

Fig. 1. The concentrations of hs-CRP (in milligrams per liter) in both HTGW phenotype and MetS and the interactions between them.

sexes and in a relatively large number of individuals with the HTGW phenotype. Because both low-grade inflammation [18-21] and the HTGW phenotype [1,3] predict future cardiovascular events, the presence of the acute phase might be one of the mechanisms that associate the HTGW phenotype with these vascular events. In addition, inflammation itself might contribute to the insulin resistance and hyperinsulinemia per se [22].

There are multiple lines of evidence to suggest a role for hs-CRP as an effector of the atherosclerotic [23] and thrombotic [24] disease, suggesting that it might not necessarily be an innocent bystander in the cardiovascular

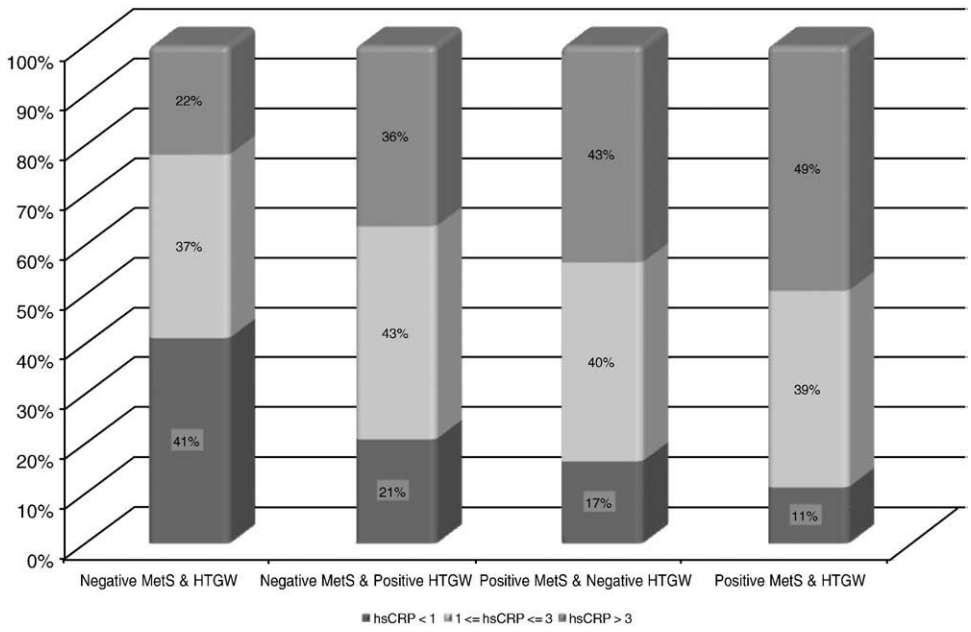

Fig. 2. Proportion of individuals at the hs-CRP risk categories of less than 1, 1 to 3, and greater than 3 mg/L in relation to whether they fulfill the criteria for HTGW phenotype, MetS, or both.

disease. Studies have shown its appearance in patients with the MetS [25], and the present study is the first to document increased hs-CRP concentrations in individuals with the HTGW phenotype without the MetS. However, this observation is not unexpected because elevated concentrations of hs-CRP have been documented in the past in relation to both waist [26] and hypertriglyceridemia [27]. The additional contribution of the present study is by demonstrating the additive effect and the interaction between the 2 phenotypes, namely, HTGW and MetS (Table 5 and Fig. 1). The higher hs-CRP levels observed in individuals with the MetS as compared with individuals with the HTGW phenotype are expected because the waist girth criteria used as cutoff are higher in the MetS (102 vs 90 cm in men, 88 vs 85 cm in women) and the weight (both waist circumference and body mass index) is a very significant determinant of blood levels of hs-CRP.

A relevant observation might be the finding that the HTGW phenotype was as prevalent as the MetS in our cohort. This cohort is composed mainly of employed persons of a relatively higher socioeconomic level. The prevalence in populations of lower socioeconomic status might therefore be even higher because of the fact that they are generally more obese and have less access to preventive medicine and education. Thus, the HTGW phenotype might present a relatively common health problem, the early identification of which might signal out individuals at risk.

The original report of Lemieux et al [1] focused on CAD in men solely. However, the HTGW phenotype has been reported in women as well [3,28,29]. Obviously, its prevalence will depend on the criteria of inclusion that are inconsistent between the articles. The sex differences in hs-CRP concentrations and its impact on MetS variables have been recently reported by our group [30]. Of interest is the observation that, in our cohort, the HTGW phenotype was found mainly in men. At the moment, we do not know whether this is a phenotype that is found mainly in men or a consequence of the criteria used for women. More epidemiologic studies are needed to clarify the sex distribution in relation to the inclusion cutoff values that are used.

Being a simple and inexpensive screening tool, the identification of individuals with the HTGW phenotype might improve the capability of primary care providers to identify populations at risk [16]. In fact, most individuals who have access to primary care physicians have checked their fasting triglyceride concentration once; and it takes only one additional measure (waist circumference) that can be performed by a nurse to establish this atherogenic dysmetabolism. The contribution of the present work is therefore shown by providing an additional pathophysiologic mechanism that might link this phenotype to atherothrombosis on one hand and the finding that it is as prevalent as the MetS, at least in this cohort of apparently healthy individuals. Thus, the HTGW phenotype might present a significant health problem.

During the last decade, CRP became a relevant biomarker for prediction of future cardiovascular events [31]. Moreover, on the basis of data from 27 939 women, plasma concentrations of hs-CRP less than 1, 1 to 3, and greater than 3 mg/L were established as representing lower, average, and higher relative vascular risk added to traditional risk factors [32]. We therefore analyzed our results in relation to these cutoff values (Fig. 2) and demonstrated the sharp drop in the percentage of individuals with hs-CRP concentrations less than 1 mg/L once they fulfilled the criteria for the phenotype. This finding further supports the presence of a worse metabolic profile that these individuals present.

The main limitation of our study at present is its cross-sectional design and the lack of clear cardiovascular end points due to the fact that, currently, our follow-up time is relatively short. However, we are confident that, during the coming years, we will be able to obtain enough information to overcome this limitation. It remains to be seen if the presence of heightened low-grade inflammation in individuals with the HTGW phenotype will have a similar additive value to that recently shown for the MetS [33].

We conclude that the prevalence of the HTGW phenotype in this cohort of apparently healthy nondiabetic employed individuals is similar to that of the MetS and is associated with the presence of low-grade inflammation to which both of its individual components contribute. This inflammation could present a pathophysiologic link between this dysmetabolism and atherothrombosis, supporting the utility of this simple and inexpensive screening measure to single out individuals at risk for future CAD.

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