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Original Article

Comparison of the triglyceride-waist circumference and the C-reactive protein-waist circumference indices in nascent metabolic syndrome

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Abstract: The Hypertriglyceridemia waist (HTGW) appears to be a valid measure of visceral adiposity, metabolic syndrome (MetS), type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD). Since the cut points differ for different race groups recent studies have instead used the simplified product of triglycerides and waist circumference (TG.WC). In our patients with nascent MetS (without the confounding of T2DM, ASCVD, smoking and macro-inflammation) we found that only 41% had an increased HTGW. Since MetS is a pro-inflammatory disorder we compared the product of CRP to WC (CRP.WC) to TG.WC in our patients with nascent MetS as biomarkers. Patients with MetS (n=58) and matched controls (n=44) were recruited. Fasting blood samples were obtained for routine laboratories including the lipid profile, insulin, and adipokines. Both the TG.WC and CRP.WC indices were significantly increased in MetS and both increased with increasing severity of MetS. Whilst both correlated with cardio-metabolic features and insulin resistance, only the CRP.WC correlated significantly with adiponectin, an adipokine largely deriving from visceral adipose tissue. The TG.WC correlated with LDL-cholesterol which was not increased in this group. Receiver Operating Characteristic (ROC) curve analysis showed that both ratios showed good discrimination for MetS with no significant differences between ratios. Thus both the TG.WC and CRP.WC indices are significantly increased in patients with nascent MetS and appear to be valid biomarkers of MetS.

Keywords: Metabolic syndrome, C-reactive protein, triglycerides, waist circumference, adiposity, inflammation, visceral fat

Introduction

Whilst the waist circumference (WC) predicts both morbidity and mortality in a superior fashion to body mass index (BMI) it alone cannot differentiate visceral adiposity from subcutaneous adiposity [1]. Despres and his group from Quebec, Canada proposed the hypertriglyceridemia waist (HTGW), on sound scientific rationale of increase production of triglyceride-rich particles from the liver, as a valid measure of visceral adiposity and confirmed the HTGW as a measure of increased visceral adiposity [1-4]. They also showed it predicted cardio-metabolic risk, metabolic syndrome, type 2 diabetes mellitus (T2DM) and atherosclerotic cardiovascular disease (ASCVD) and these findings were supported by many but not all studies in various parts of the world [5-9]. More recently given the wide variation in waist circumference criteria in different races, investigators have simplified the HTGW to the product of WC and TG (TG.WC) and show essentially similar results to the HTGW [10-12].

Metabolic Syndrome (MetS) is extremely common worldwide and predisposes to both T2DM and ASCVD [13]. In a recent review, the authors catalogued the circulating and cellular biomarkers that qualified MetS as a pro-inflammatory state [14]. Dysregulation in both adipose tissue and monocytes appear to be pivotal [15-20]. Since diabetes, clinical ASCVD, smoking, macro-inflammation (CRP<10 mg/L), hypolipidemic drug therapy were excluded we defined our patients as nascent MetS [15-17].

It has been shown that the prototypic marker of inflammation, high sensitivity (hs) CRP, is also a valid biomarker of MetS and ASCVD in MetS

Table 1. Baseline characteristics in metabolic syndrome stratified by high triglyceride waist (HTGW) category

Variable	HTGW- (n=34)	HTGW+ (n=24)	*P* Value *(- vs +)*
Age (years)	52.8±11.6	53.0±9.0	0.81
Gender Ratio (Female/Male)	22/12	21/3	0.07
BMI (kg/m^2)	36.0±6.2	34.8±5.7	0.51
Waist Circumference (cm)	109.9±13.8	107±13.5	0.37
BP-s (mmHg)	129.8±12.6	132.6±10.3	0.65
BP-d (mmHg)	80.6±9.4	82.9±8.9	0.35
Glucose (mg/dL)	100.1±12.4	100.8±10.9	1.0
Triglycerides (mg/dL)	106 (94, 128)	211 (188, 226)	<0.0001
HDL-C (mg/dL)	41.2±12.2	38.0±8.3	0.45
LDL-C (mg/dL)	125.9±21.5	128.1±22.5	0.75
hsCRP (mg/L)	3.7 (1.1, 5.5)	3.3 (1.9, 6.0)	0.43
HOMA-IR	2.9 (1.9, 5.8)	2.7 (2.1, 5.1)	0.57
Adiponectin (μg/ml)	5.4 (3.9, 7.2)	5.1 (3.6, 12.3)	0.54

Results are presented as mean ± standard deviation or median (25th percentile, 75th percentile).

[21, 22]. Accordingly, we hypothesized that the product of CRP and WC (CRP.WC) might be an equivalent biomarker of MetS compared to the TG.WC product in our patients with nascent MetS.

Patients and methods

This study was approved by the Institutional Review Board of University of California Davis. All volunteers provided informed consent.

We enrolled 58 patients with MetS and 44 controls from the Sacramento area using the harmonized global criteria as recommended by Alberti et al [13]. Furthermore individuals with diabetes (defined by a plasma glucose >125 mg/dl and or HbA1C>6.4%), persons who were smokers or had macro-inflammation defined as an elevated white blood cell count or a high sensitivity (hs) CRP>10 mg/l were also excluded [15-20]. In addition, volunteers with ASCVD were also excluded. Patients were defined as MetS if they had 3 or more cardio-metabolic features and controls if they had 2 or less features. WC was measured at the end of a normal expiration at the midpoint between the lowest rib and the anterior iliac crest.

Routine tests were performed on fasting samples in the clinical laboratory. Plasma insulin, hsCRP, leptin, chemerin and adiponectin were also measured as reported previously [16, 17, 20]. The homeostasis model assessment insulin resistance index (HOMA-IR), a measure of hepatic insulin resistance, was computed from glucose and insulin levels [17]. Adipose tissue insulin resistance (Adipo-IR) was calculated as the product of insulin and free fatty acids [23]. CRP is used as the preferred term in this manuscript for simplicity to connote hs CRP.

SAS version 9.4 (SAS Institute, Cary, NC) was used for statistical analysis and significance was defined as a two-sided *P*-value <0.05. Results are expressed as mean and standard deviation (SD), or as median and interquartile range for skewed variables. Both unpaired t tests and Wilcoxon Rank Sum tests were used to compare MetS and Controls depending on skewness of data. Trend analysis of the products associated with increasing number of characteristics of MetS was evaluated using the Jonckheere-Terpstra test. After combining the control and MetS groups, Spearman rank correlation coefficients were determined to assess the association between both indices and metabolic variables. Logistic regression models were used to compute Receiver Operating Characteristic (ROC) curves. Comparison of areas under correlated ROC curves and 95% confidence intervals (CI) for the ROC area under curve (AUC) for biomarkers (TG.WC and CRP.WC) and biomarker differences were determined. In the MetS group, McNemar's test for paired proportions was used to assess the agreement between presence of hypertriglyceridemia-waist and elevated CRP-waist characteristics.

Results

Despres and his group has suggested based on their studies in Quebec, Canada that their binary definition of hypertriglyceridemia-waist using different cut points for males and females: males TG≥2.0 mmol/l (177 mg/dl) and WC≥90 cm and in females TG≥1.5 mmol/L (133 mg/dl) and WC≥85 cm captures increased visceral adiposity [1-4]. Using their definition in our patients with nascent MetS we showed that only 41% had visceral adiposity by hypertriglyc-

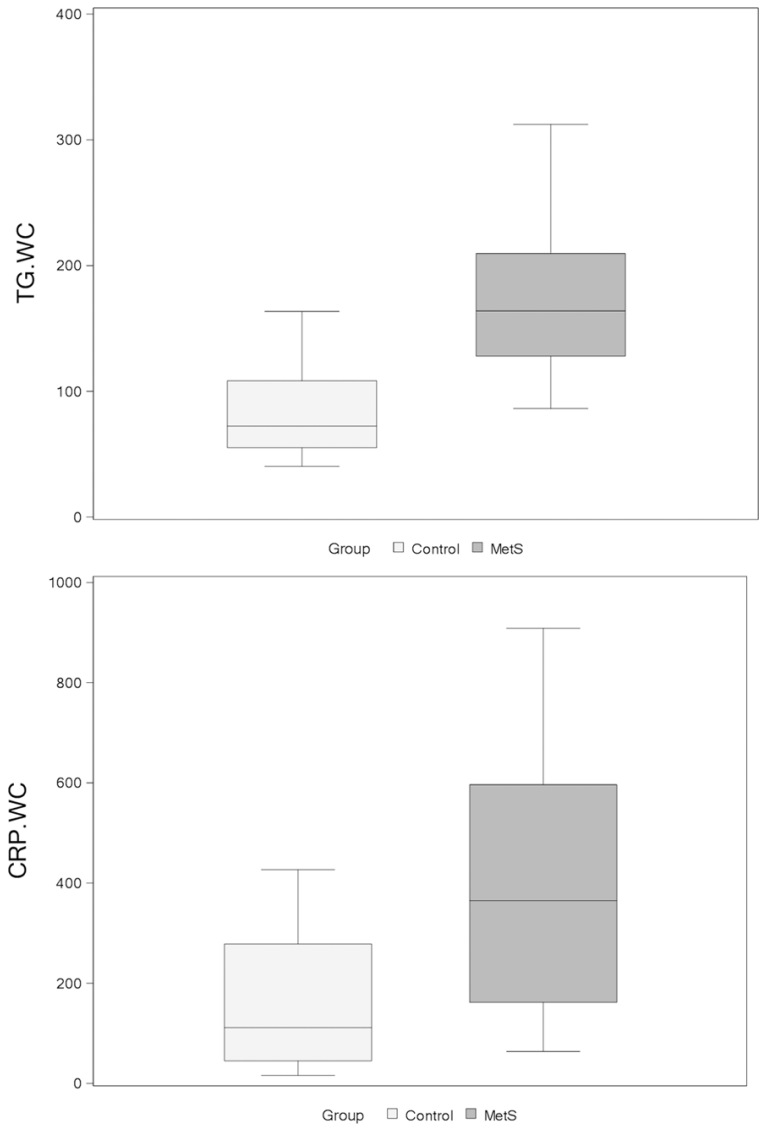

Figure 1. Comparison of TG.WC and CRP.WC in patients with MetS and controls.

eridemia-waist criteria (49% of females and 20% of males). In **Table 1** is depicted the 2 subgroups, HTGW+ and HTGW-. The only variable that was significantly different between the groups was TG levels. The prevalence of HTGW was only 7% in our controls. Given our long standing interest in inflammation and our studies supporting the thesis that MetS is a pro-inflammatory disorder we derived a CRP-Waist using their WC criteria and a CRP≥2.0 mg/L. In our patients with MetS, 67% had an elevated CRP-Waist. The prevalence in controls was 27%. Evaluation of the presence of hypertriglyceridemia-waist and of elevated CRP-waist in paired proportions indicated that 47% of the pairs were discordant and hence agreement between these two criteria is rejected, P=0.006.

This cohort is the same in which we reported on the platelet: HDL-C ratio recently, we refer the readers to **Table 1** with citation to avoid reduplication of the baseline data [24]. Briefly, the patients with MetS whilst matched for age and gender, had significant differences in all cardio-metabolic features and increases in both adipose tissue and hepatic insulin resistance measures, CRP, leptin, adiponectin and chemerin compared to controls.

Given that only 41% of our well curated cohort of nascent MetS has HTGW, to better appreciate this parameter we followed the definition proposed by others: the product of TG (mmol) and WC (cm)-TG.WC [10-12]. According to this criteria there was a significant difference between MetS vs controls in the product of TG and WC (TG.WC) as shown in **Figure 1**, median [25th-75th percentiles] 164 mmol/L.cm [128, 210] vs 72 [55, 108], P<0.0001. We also examined our product of CRP and WC. CRP.WC was also significantly increased in MetS versus controls as depicted in **Figure 1**, 365 mg/L.cm [162, 597] vs 111 [45, 278], P<0.0001.

Also, both products increased significantly with increasing severity (number of features) of MetS using the Jonckheere-Terpstra test for trend; P<0.001 for both.

Correlations between the TG.WC and CRP.WC indices and important variables are shown in **Table 2**. Both indices correlated significantly with features of MetS. Also, CRP, HOMA-IR, Adipo-IR, leptin and chemerin correlated with both indices. Whilst the product of TG and WC correlated significantly with age, adjusting for age did not alter any significant values report-

Table 2. Spearman Rank Correlations between TG.WC and CRP.WC indices and relevant variables

	TG.WC	CRP.WC
Age (yrs)	0.21	0.16
	0.03	0.10
hsCRP (mg/L)	0.34	0.99
	0.0004	<0.0001
BMI (kg/m^2)	0.49	0.61
	<0.0001	<0.0001
Waist (cm)	0.63	0.46
	<0.0001	<0.0001
BP-s (mmHg)	0.39	0.21
	<0.0001	0.03
BP-d (mmHg)	0.38	0.19
	<0.0001	0.05
Glucose (mg/dL)	0.38	0.21
	<0.0001	0.03
Triglycerides (mg/dL)	0.97	0.35
	<0.0001	0.0004
HDL-C (mg/dL)	-0.54	-0.23
	<0.0001	0.02
LDL-C (mg/dl)	0.25	0.16
	0.01	0.11
HOMA-IR	0.28	0.31
	0.006	0.003
Adiponectin (ug/ml)	-0.15	-0.32
	0.21	0.005
Chemerin (mg/ml)	0.44	0.38
	0.001	0.007
Leptin (ng/ml)	0.24	0.57
	0.04	<0.0001
Adipo-IR (uU X mmol/L)	0.68	0.47
	0.0006	0.03

All of these variables were significantly different between controls and MetS[24]. Spearman rho correlation coefficient in row 1 and *P*-value in second row. Adipo-IR connotes adipose tissue insulin resistance.

ed. Also TG.WC index correlated significantly with both Total-cholesterol (r=0.34, P=0.0004) and low-density lipoprotein (LDL-) cholesterol. Surprisingly, only the CRP.WC index correlated significantly in an inverse fashion with adiponectin.

In **Figure 2** is shown the ROC curve analyses. The ROC-AUC for TG.WC was 0.86 with 95% CI between 0.78-0.94 and for CRP.WC of 0.78 with 95% CI of 0.69-0.87. However, there were no significant differences between the two indices (AUC: P=0.11).

Discussion

In our patients with nascent MetS (without the confounding of diabetes, ASCVD, smoking, macro-inflammation and hypolipidemic drug therapy) we demonstrated that the HTGW was only present in 41% of our patients. Thus we decided to compare the TG.WC and CRP.WC as predictors of MetS. Both indices were significantly increased in patients with MetS and increased significantly with severity of MetS defined by the number of cardio-metabolic features. In addition, both indices correlated with cardio-metabolic criteria of MetS. ROC curve analyses showed that both indices displayed good discrimination for MetS, with no significant differences between AUC of both indices.

In previous studies we have delineated subcutaneous adipose tissue (SAT) dysregulation in these patients manifesting as increase adipokine dysregulation, increase in macrophages and pro-inflammatory mast cells and eosinophils, increase fibrosis in SAT and increased NLRP-3 inflammasome activity [14, 16, 18-20]. However we did not obtain visceral adipose tissue for investigation in our patients.

A comparison of CRP.WC index and TG.WC in paired proportions indicated that 47% of the pairs were discordant and hence agreement between these two criteria is rejected, P= 0.006. Thus these indices are providing different measures with respect to MetS. This is understandable since one is a feature of MetS (TG) and the other includes CRP, a marker of inflammation. Also both increased with increased severity of MetS and were good discriminants of MetS as evidenced by ROC-AUC. Whilst the TG.WC correlated significantly with LDL-C it does not appear that LDL-C is increased with HTGW in the present report and published literature [25]. The elevated total cholesterol could be due to increases in VLDL-cholesterol, however this was not reported in that study [25]. An elevated LDL-C is not a characteristic feature of MetS and levels were not significantly different between MetS and controls; 126.8 versus 118.8, P=0.45 [24]. However, LDL-C has relevance to overall cardiometabolic health.

More importantly with respect to visceral adiposity only the CRP.WC index and not the TG.WC correlated significantly with adiponectin which derives largely from visceral adipose tissue [26]. In a previous report from the Despres

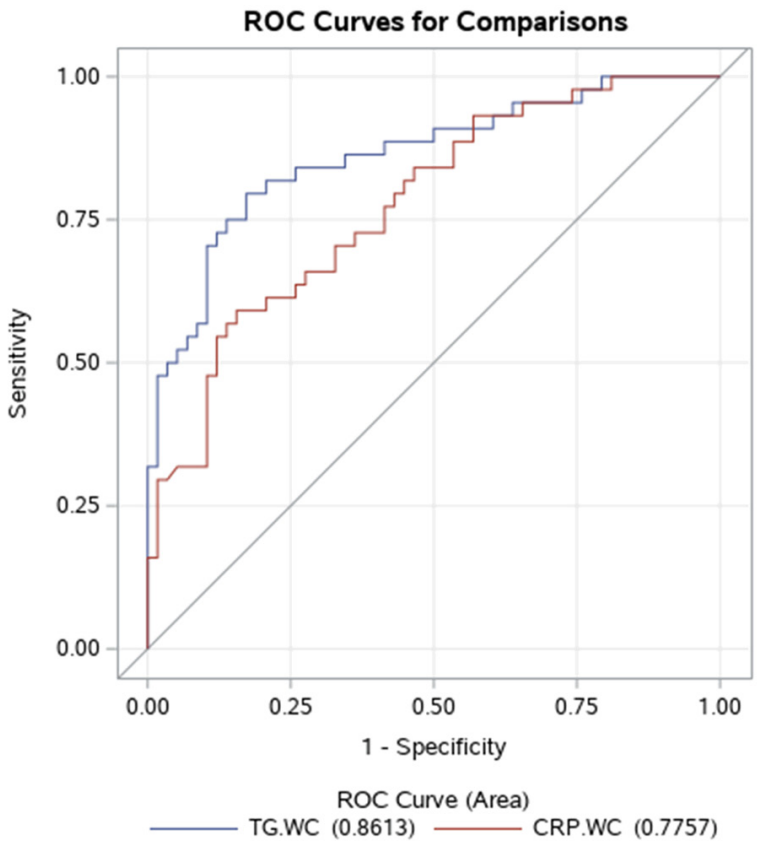

Figure 2. Comparison of Receiver Operating Characteristic (ROC) curves between TG.WC and CRP.WC. There were no significant differences between the AUCs, P=0.11.

group whilst they showed increased CRP and low adiponectin in MetS, they failed to show an increase in CRP but showed a low adiponectin with HTGW [25]. These discrepant findings with respect to adipokine dysregulation need to be probed further since TG.WC is an accepted measure of increased visceral adipose tissue mass.

Importantly, both indices predicted MetS with no significant differences in ROC-AUC between the indices.

In conclusion, our novel observation of an increased CRP.WC index being equivalent to the better studied TG.WC index in predicting nascent MetS supports its validity as a biomarker. This also suggests that inflammation that emanated from both subcutaneous and visceral adipose tissue and phagocytes is also crucial in MetS.

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Disclosure of conflict of interest

None.

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