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Circulating Neutrophil and Monocyte Ratios to High Density Lipoprotein-Cholesterol Are Elevated with Increased Triglyceride-Glucose Index

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Abstract: The triglyceride-glucose (TyG) index, is a promising biomarker of Metabolic Syndrome (MetS), Type-2 Diabetes (T2DM) and premature atherosclerotic cardiovascular diseases (ASCVD). Whilst increased inflammation is a crucial mechanism in the pathogenesis of these disorders there is a general paucity of data on the association of the TyG index and inflammation. Accordingly, in the present report we investigated the relationship between tertiles of TyG index and accepted measures of inflammation, the ratios of Neutrophil (PMN):HDL-C and Monocyte(Mono):HDL-C in a cohort of 99 individuals (41 controls and 58 patients with MetS). Both PMN:HDL-C and Mono:HDL-C ratios increased significantly with increasing tertiles of the TyG index and both ratios correlated significantly with the TyG index. Also there was a significant correlation with certain biomarkers of inflammation which also increased over tertiles of PMN:HDL-C and Mono:HDL-C. In conclusion, in this cross-sectional study, we provide further support for a pro-inflammatory phenotype with an increase in the TyG index as manifest by increases in the ratio of the professional phagocytes (neutrophils and monocytes) to HDL-C, as a potential mechanism to explain the increase risk for cardio-metabolic syndromes.

Keywords: triglyceride-glucose index; inflammation; monocytes; neutrophils; insulin resistance

1. Introduction

The triglyceride-glucose (TyG) index is a validated measure of insulin resistance [1–4]. Furthermore the TyG index has been shown to be a reliable biomarker of Metabolic Syndrome (MetS), Type-2 Diabetes (T2DM) and premature atherosclerotic cardiovascular diseases (ASCVD) [1–4]. In all of these disorders inflammation has been suggested to be a crucial pathogenic mechanism [1,2]. In a recent report it was shown that based on circulating and cellular biomarkers of inflammation, the TyG index exhibits a pro-inflammatory phenotype [5]. Both circulating neutrophils (PMN) and monocytes (Mono) are professional phagocytes that possess a rich arsenal of mediators that promote inflammation [6–9]. We have previously shown that both PMN and Mono ratios to high density lipoprotein-cholesterol (HDL-C) are increased in MetS and good predictors of MetS [10]. Accordingly we investigated if these ratios were increased with increasing TyG index and were related to the biomediators of inflammation that we have reported previously to be increased with the TyG index [5] further supporting a pro-inflammatory diathesis.

2. Patients and Methods

Both controls and MetS participants aged 21–72 years were recruited from Sacramento County, CA using the criteria of the Adult Treatment Panel III (ATP III) as detailed previously [5,10,11]. Participants were defined as having MetS, if they had at least three cardio-metabolic features of MetS: increased waist circumference (≥40 inches for men and ≥35 inches for women, elevated triglycerides (≥150 mg/dL), low HDL-cholesterol levels (<40 mg/dL for men and <50 mg/dL for women), high blood pressure (systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mm Hg) and high glucose level (≥100 mg/dL). Important exclusion criteria for all subjects included diabetes defined by fasting blood glucose level >125 mg/dL and HbA1C >6.4%, clinical ASCVD, acute or chronic inflammatory disorders, and history of smoking and lipid lowering therapy. Furthermore all participants in the study had a high-sensitive C-reactive protein (hsCRP) level <10.0 mg/L and a normal white cell count. The study was approved by the institutional review board at the University of California, Davis and informed consent was obtained from all participants.

Fasting blood samples were taken from participants after histories and physical examinations. The details of the different assays have been reported previously. Plasma lipids, lipoprotein profiles, and glucose were assayed by standard laboratory techniques in the Clinical Pathology Laboratory as described previously [5,10,11]. Insulin levels were assayed by ELISA (Linco Biosystems, St. Charles, MO, USA) and homeostasis model assessment insulin resistance index (HOMA-IR) was calculated from glucose and insulin levels as described previously [10,11]. Endotoxin levels were quantitated using reagents from Lonza (Limulus Amebocyte Lysate, QCL 1000; Walkersville, MD, USA) [11]. Chemerin and Interleukin (IL)-6, and were measured using a multiplex cytokine/chemokine array (Bioplex, San Jose, CA, USA). Surface expression of Toll like receptor 4 (TLR4) on monocytes were analyzed by flow cytometry using BD FACS Array as reported previously following activation with endotoxin (LPS) 100 ng/mL [11]. Nuclear factor -Kappa-beta (NFkB) activity and cytosolic phospho-P38-mitogen activated protein (MAP) Kinase activity (P38MAPKinase) were assayed in endotoxin (100 ng/mL) primed monocytes as reported [11].

The triglyceride-glucose (TyG) index was calculated as reported previously:

Ln [fasting triglycerides (mg/dL) × fasting plasma glucose (mg/dL)/2].

Adipose tissue insulin resistance (Adipo-IR) was calculated as the product of FFA and fasting insulin levels as reported previously [5]. The PMN:HDL-C and Monocyte:HDL-C (Mono:HDL-C) ratios were calculated as absolute PMN count and monocyte count (×10) over HDL-C (mg/dL). The details with respect to the other measures reported have been published previously.

Statistical Analysis

SAS version 9.4 (SAS Institute, Cary, NC, USA) was used for statistical analysis and significance was defined as a two-sided p-value < 0.05. Results are expressed as median and interquartile range. Trend analysis of TyG index tertiles, PMN:HDL-C tertiles and Monocyte:HDL-C tertiles in our combined MetS and control participants was evaluated using the Jonckheere-Terpstra (J-T) test for trend. Combining the control and MetS groups, Spearman rank correlation coefficients were also determined to assess the association between TyG index, PMN:HDL-C and Monocyte:HDL-C and relevant variables.

3. Results

As shown in Table 1 there were no significant differences in age or gender across TyG index tertiles. Waist circumference, blood pressure, glucose and triglycerides increased over tertiles of TyG index whist HDL-C decreased significantly. Hence the prevalence of MetS increased over tertiles. In addition, hsCRP, HOMA-IR and Adipo-IR increased over tertiles. Most importantly as portrayed also in Figure 1, both the PMN:HDL-C and Mono:HDL-C ratios increased over the TyG index tertiles.

Table 1. Salient Characteristics across Tertiles of TyG index.

Variable	Tertile 1	Tertile 2	Tertile 3	*p*-Value *
	N = 33	N = 33	N = 33	
Female/Male, n	26/7	26/7	23/10	0.39
Metabolic Syndrome, n	28/5	10/23	3/30	<0.0001
TyG index	7.9 (7.7–8.2)	8.5 (8.5–8.6)	9.1 (8.9–9.3)	<0.0001
PMN:HDL-C Ratio (k/mm^3)	0.06 (0.05–0.07)	0.09 (0.06–0.11)	0.11 (0.09–0.14)	<0.0001
Monocyte: HDL-C Ratio × 10^1 (k/mm^3)	0.08 (0.06–0.11)	0.09 (0.08–0.14)	0.14 (0.10–0.17)	<0.0001
Age (years)	47 (42–56)	54 (45–61)	54 (48–60)	0.06
Waist (cm)	88 (81–98)	103 (95–117)	107 (97–117)	<0.0001
BMI (kg/m^2)	29 (25.8–32.1)	34.7 (32–41)	33.2 (28.5–39.2)	0.0008
Systolic BP (mmHg)	120 (110–132)	132 (116–139)	128 (122–136)	0.02
Diastolic BP (mmHg)	73 (65–82)	81 (74–86)	79 (75–86)	.007
Glucose (mg/dL)	88 (83–95)	95 (90–102)	100 (94–109)	<0.0001
HDL-cholesterol (mg/dL)	53 (43–64)	46 (35–50)	35 (31–41)	<0.0001
Non-HDL cholesterol (mg/dL)	123 (108–149)	153 (136–161)	159 (152–184.5)	<0.0001
Triglycerides (mg/dL)	63 (51–72)	107 (98–122)	174 (156–211)	<0.0001
hsCRP (mg/L)	1 (0.4–2.8)	3.5 (1.5–5.4)	2.5 (1.7–4.6)	0.005
HOMA-IR	1.5 (0.8–2.3)	2.6 (1.6–3.7)	3.8 (2.4–5.7)	<0.0001
ADIPO-IR Index	21.5 (6.8–36)	44.6 (28.5–68.7)	91.2 (55–105.7)	<0.0001

* Jonckheere-Terpstra Test for trend for continuous variables and Cochran-Armitage test for categorical variables. Results are reported as median (25th–75th percentile).

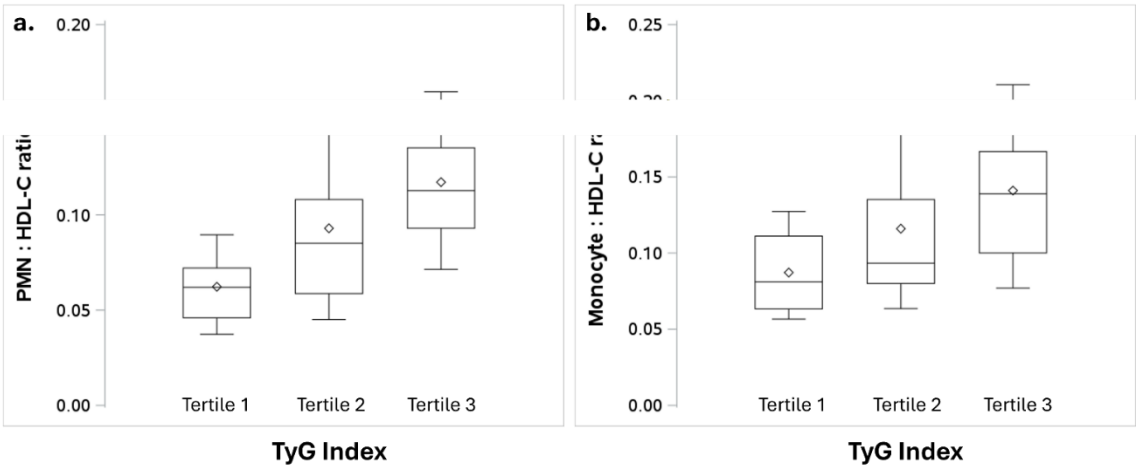

Figure 1. PMN: HDL-C(**a**) and Monocyte:HDL-C. (**b**) ratios over tertiles of the TyG index. The lower and upper limits of the box indicate the 25th and 75th percentiles, the line within the box depicts the median, diamond depicts the mean, and the whiskers (error bars) below and above the box indicate the 10th and 90th percentiles. *p* values < 0.0001 for both a and b (Table 1) and n = 33 per tertile (Table 1).

Since we have shown previously that certain biomediators of inflammation are increased with increasing tertiles of TyG index [5] we also examined these specific biomarkers over tertiles of PMN:HDLC and Mono:HDL-C. In Table 2a, plasma endotoxin, chemerin, IL-6, monocyte TLR4 and both monocyte pP38 MAPkinase and NFkB activity increased over tertiles of PMN:HDL-C. However as depicted in Table 2b only circulating endotoxin, IL-6 , chemerin and monocyte NFkB activity increased with increasing tertiles of Mono:HDL-C ratios. Suprisingly there was no significant increase in monocyte TLR4 abundance or pP38 MAPkinase activity.

Table 2. Relevant biomarkers of inflammation across tertiles of PMN:HDL-C ratio (Table 2a) and Monocyte:HDL-C ratios (Table 2b).

a. Inflammation markers by tertiles of PMN:HDL Ratio				
Variable	PMN:HDL-C Tertile 1	PMN:HDL-C Tertile 2	PMN:HDL-C Tertile 3	*p*-Value *
	N = 33	N = 33	N = 33	
PMN:HDL Ratio (k/mm^3)	0.05 (0.04–0.06)	0.086 (0.07–0.09)	0.13 (0.11–0.16)	<0.0001
Chemerin (ng/mL)	298 (243–338)	320 (273–402)	372 (311–393)	0.04
Endotoxin (EU/mL)	4.1 (3.5–4.3)	10.6 (4.9–12.3)	11.5 (9.4–14.6)	0.002
IL6 (pg/mL)	1197 (510–1784)	1425 (946–1880)	1883 (1396–2179)	0.002
Monocyte TLR-4 ($MFI/10^6$ cells)	23 (18–28)	26 (24–38)	28 (21–37)	0.01
pP38MAPKinase	0.08 (0.04–0.15)	0.13 (0.08–0.27)	0.15 (0.11–0.26)	0.005
NFkB activity	0.06 (0.04–0.16)	0.18 (0.05–0.25)	0.25 (0.1–0.27)	0.003
* Jonckheere-Terpstra Test for trend. Results are reported as median (25th–75th percentile).				
b. Inflammation markers by tertiles of Monocyte:HDL Ratio				
Variable	Monocyte:HDL-C Tertile 1	Monocyte:HDL-C Tertile 2	Monocyte:HDL-C Tertile 3	*p*-Value *
	N = 33	N = 33	N = 33	
Monocyte HDL Ratio × 10^1 (k/mm^3)	0.07 (0.06–0.08)	0.10 (0.09–0.11)	0.16 (0.14–0.18)	<0.0001
Chemerin (ng/mL)	280 (243–330)	314 (290–369)	389 (322–419)	0.0007
Endotoxin (EU/mL)	4.1 (3.5–4.7)	9.8 (3.9–11.5)	11.6 (8.8–16.3)	0.01
IL6 (pg/mL)	1138 (565–1693)	1331 (546–1898)	1775 (1425–2146)	0.001
Monocyte-TLR-4 ($MFI/10^6$ cells)	24 (19–30)	25 (21–31)	29 (25–38)	0.06
pP38MAPKinase	0.09 (0.05–0.26)	0.10 (0.07–0.24)	0.15 (0.11–0.27)	0.18
NFkB activity	0.07 (0.05–0.25)	0.10 (0.05–0.25)	0.24 (0.12–0.28)	0.05
* Jonckheere-Terpstra Test for trend. Results are reported as median (25th–75th percentile).				
MFI Connotes Mean Fluorescence Intensity				

Correlations between PMN:HDL-C and Mono:HDL-C ratios and these biomarkers of inflammation were also undertaken. Most importantly both the PMN:HDL ratio and Mono:HDL-C ratios correlated significantly with the TyG index. The PMN:HDL-C ratio correlated significantly with Mono:HDL-C ratio, and all the biomarkers of inflammation reported in Table 2. In contrast whilst the Mono:HDL-C Ratio correlated with chemerin, endotoxin and IL-6 and Monocyte NFkB activity there were no significant correlations with TLR4 abundance and monocyte pP38 MAPkinase activity. Since in our previous report we have shown significant correlations with cardio-metabolic features, hsCRP and HOMA-IR [10] we are not showing that data to avoid redundancy. Also both PMN:HDL-C and Mono:HDL-C ratios correlated significantly with Adipo-IR, a measure of adipose tissue insulin resistance.

4. Discussion

Whilst the TyG index is a validated and accepted biomarker of cardio-metabolic syndromes there is a paucity of data on mediating mechanisms such as inflammation as highlighted previously [1,5]. Since both the PMN:HDL-C and Mono: HDL-C ratios are accepted measures of inflammation and also predict cardio-metabolic syndromes [10,12–15] we determined if there was a relationship with the TyG index further supporting inflammation as a pathogenic mechanism. In this report we show that in addition to both ratios increasing with increasing TyG index, both ratios correlated significantly with the TyG index. Also there was a strong correlation ($r = 0.73$) between the PMN:HDL-C and Mono:HDL-C ratios. This is expected since both are classical phagocytes that participate in the inflammatory response.

The major focus of this manuscript was to determine if these ratios of circulating phagocytes to the anti-inflammatory protein, HDL [16,17] were increased with an increase in the TyG index as discussed above. Also we wanted to probe if concentrations of biomarkers of inflammation previously reported to be increased with the TyG index [5] provided further plausible support for this thesis. As shown in Table 2a all of these reported biomarkers of inflammation increased over tertiles of PMN:HDL-C ratios including TLR4, p38 MAPkinase and NFkb activity in endotoxin activated monocytes. Furthermore all the correlations with these select biomarkers were also significant as shown in Table 3.

Table 3. Spearman correlations between PMN: HDL-C and Monocyte:HDL-C ratios and relevant variables of inflammation.

	PMN:HDL-C Ratio rho ***p***	**Monocyte: HDL-C Ratio rho** ***p***
TyG index	0.55 <0.0001	0.40 <0.0001
Monocytes:HDL_ratio	0.73 <0.0001	1.00000
Chemerin	0.41 0.003	0.44 0.002
Endotoxin	0.61 0.0001	0.45 0.008
IL 6	0.37 0.0003	0.37 0.0003
Monocyte -TLR 4	0.28 0.01	0.19 0.09
p38MAPKinase	0.31 0.005	0.14 0.23
NFkB activity	0.35 0.002	0.24 0.03
Adipo-IR	0.64 <0.0001	0.49 0.002

However as shown in Table 2b only circulating chemerin, endotoxin, IL-6 levels increased with increasing tertiles of Mono:HDL-C ratios. There were no significant changes with TLR-4, P38Mapkinase and NFkB activity in endotoxin activated monocytes. The correlation analyses largely mirrored these findings except for a significant correlation between Mono-HDL-C and NFkB activity.

Whilst at first glance this appears to be a paradoxical finding it needs to be emphasized that these circulating phagocytes display considerable plasticity [6–9]. Hence we hypothesize that circulating PMNs appear to be predominantly in the pro-inflammatory phenotype rather than the reparative phenotype. Hence if we had studied isolated PMN biology in our cohort this would have been clearly manifest [18,19]. In the same vein, we hypothesize that a significant percentage of circulating monocytes are in the M2 phenotype (alternative/reparative) as opposed to the pro-inflammatory M1 phenotype explaining our findings. In support of this notion we have shown no significant correlation between macrophages and inflammatory markers in adipose tissue in this cohort suggesting they were in the reparative M2 phase [20].

To summarize, we show that both circulating PMN:HDL-C and Mono:HDL-C ratios increase with increasing TyG index and correlate significantly with the TyG index. Furthermore, the studied biomarkers of inflammation showed increases over tertiles and correlate with both PMN:HDL-C and Mono:HDL-C. However the PMN:HDL-C ratio appears superior in this regard. Further support for a pro-inflammatory phenotype with the TyG index is the findings of Wang et al. [21] who showed that the TyG index predicts increasing albuminuria following adjustments for both HOMA-IR and MetS. Inflammation is important in the genesis of dysfunction of podocytes resulting in albuminuria [22].

In conclusion based on the findings in this communication, we provide further support that the TyG index exhibits a pro-inflammatory phenotype explaining in part its ability as a biomarker to predict cardio-metabolic syndromes. Since these studies are cross-sectional, prospective studies should be undertaken to confirm these novel findings supporting a link between the TyG index and inflammation.

Author Contributions

I.J. generated the idea for this publication. B.A.-H. undertook the statistical analyses. Both generated the original version and edited multiple iterations. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

Obtained from UC Davis IRB. This study was approved by UC Davis IRB: 200715074e.

Informed Consent Statement

All volunteers provided written informed consent.

Data Availability Statement

The data is available from the senior author for review on reasonable request.

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Conflicts of Interest

No conflicts of interest, financial or otherwise, are declared by any of the authors.
To avoid any conflict a Guest Editor, Professor Senthil Kumar Venugopal handled this manuscript .

Use of AI and AI-Assisted Technologies

These were not used in this paper.

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