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The Relationship between Inflammation, Metabolic Syndrome and Markers of Cardiometabolic Disease among Canadian Adults

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Abstract

Background: The metabolic syndrome (MetS) is a well-established risk factor for cardiometabolic disease. However, the association between MetS, and its components, with the metabolic phenotypes and inflammatory markers that are risk factor for cardiometabolic disease has not been explored in the general population. The present study examines this association among Canadian adults and explores the changes in the profile of a number of metabolic and inflammatory markers associated with cardiometabolic disease at various MetS stages.

Methods: Serum levels of apolipoprotein A1 and B (Apo-A1, -B), total:HDL-cholesterol (HDL-C) ratio, C-reactive protein (CRP), fibrinogen, glycosylated haemoglobin (HbA1c) and homocysteine were determined in 1,818 non-diabetic adults (16-79 years of age) from the Canadian Health Measures Survey (CHMS). The definition of MetS components was based on the National Cholesterol Education Program, Adult Treatment Panel III criteria. Taylor-series expansion methods for complex survey data were used to estimate variances. Generalized linear models adjusted for age, sex, physical activity, smoking status, use of medications and ethnicity were used to quantify the relationship between the metabolic phenotypes and inflammatory markers associated with risk to cardiometabolic disease and the number of MetS components.

Results: The prevalence of the MetS (i.e., with three or more MetS components) among the study subjects was 8.9%, with 31.8% having at least one component. As expected, metabolic markers such as total: HDL-C, Apo-B and HbA1c were all significantly increased as the number of MetS components increased whereas Apo-A was decreased. We also observed a significant association between the number of MetS components and the serum levels of inflammatory biomarkers such as CRP and fibrinogen, but not homocysteine. Mean serum levels of these markers were significantly elevated as the numbers of MetS components increased. Strong correlations were noted between CRP, fibrinogen, and homocysteine and the individual components of the MetS.

Conclusions: There is an apparent profile of metabolic phenotypes and inflammatory biomarkers, known to be related to the cardiometabolic disease risk, that emerges as MetS manifests with increasing the number of its components. These findings may permit proposing a metabolic trait that predisposes to MetS and may permit developing an effective approach for early risk prediction and intervention.

Background

The metabolic syndrome (MetS) is a characteristic clustering of metabolic abnormalities, including abdominal obesity, dysglycemia, hypertension and dyslipidemia, and it is recognized by the World Health Organization (WHO), the National Cholesterol Education Program–Adult Treatment Panel III (NCEP–ATP III) and the International Diabetes Federation (IDF) as a major risk factor for cardiometabolic diseases such as type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) [1]. The NCEP–ATP III has proposed a number of components to identify MetS and the subsequent risk of cardiometabolic disease [2]. The prevalence of MetS is increasing both within Canada [3] and globally [4], and was recently reported to approach 20% in the general Canadian population [5]. Several genetic and lifestyle factors, such as lack of physical activity and calorie-rich diets, have been linked to the development of MetS and an increased risk of T2DM and CVD [6,7].

The link between cardiometabolic disease and certain metabolic phenotypes, such as elevated glycosylated haemoglobin (HbA1c) and markers of lipid metabolism (e.g., apolipoprotein [Apo-] B, apo-A1, total cholesterol:high density lipoprotein cholesterol [HDL-C] ratio), has been well documented [8-10]. Recently, HbA1c levels, which are a measure of plasma glucose over prolonged periods of time, have become an accepted criterion for T2DM diagnosis in the United States [11]. Furthermore, the ratio of Apo-B and Apo-A1, the primary apolipoprotein components of low-density lipoprotein cholesterol (LDL) and HDL, respectively, has been proposed to be more predictive of CVD risk than the total:HDL-C ratio [9].

In addition to these traditional cardiometabolic disease biomarkers, non-traditional markers have been proposed, such as homocysteine, C-reactive protein (CRP), and fibrinogen [8,12,13]. Total levels of homocysteine, an amino acid produced during methionine metabolism, have been associated with cardiovascular events, although

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this association has been inconsistent [12,14]. However, CRP and fibrinogen, which are acute phase proteins that are downstream factors of the innate immunity-related inflammatory pathway, have been strongly associated with cardiometabolic outcomes [8]. Indeed, an impaired innate immune response, characterized by chronic subclinical inflammation and elevated oxidative stress, has been suggested to be involved in the pathogenesis of cardiometabolic disease [8,15,16].

Despite evidence in favor of a relationship between levels of these traditional and non-traditional metabolic phenotypes and cardiometabolic disease outcomes, their association with MetS and its individual components remains poorly explored, particularly in the general population. Elucidating this relationship may enable us to further understand the metabolic changes involved in the early stages of MetS and to define the etiological role of this condition in the risk of cardiometabolic disease. Furthermore, it may provide the basis for developing effective population-based preventive strategies for the range of chronic diseases that are linked to MetS. The objective of the present study was to quantify the association between the number of MetS components and traditional and non-traditional metabolic phenotypes associated with cardiometabolic disease in a representative sample of the general Canadian population.

Methods

The study population

Data from the Canadian Health Measures Survey (CHMS) [17] (cycle 3.1) were used in the present study to examine the association between MetS and metabolic and inflammatory markers related to cardiometabolic disease risk. The CHMS is a population-based survey designed to collect health and wellness indicators in Canadians aged 6-79 years. The 3.7% of the Canadian population who were residents of Indian reserves, Crown lands, certain remote regions, institutions, and full-time members of the Canadian Forces were excluded from the survey [18]. The survey was conducted between 2007 and 2009, using a multi-stage sampling strategy. The CHMS selected 8,772 dwellings and 6,106 agreed to participate (household response rate: 69.6%). From these households, 7,483 people agreed to participate in the survey and 6,604 subjects responded to the study questionnaire (response rate: 88.3%). Of those who responded to the questionnaire, 5,604 agreed to undergo physical measurements (response rate: 84.9%). Nationally, the response rate was 51.7%. Detailed information about the CHMS methodology and protocols for measurement of specific biomarkers has been described elsewhere [19-22]. From the 5,604 subjects available, we excluded persons under the age of 16 years, non-fasting responders, subjects who had fasting serum glucose (FPG) levels >7.0 mmol/L as they may have, or are at risk of, T2DM, and patients who reported to ever being diagnosed with diabetes by a health professional. The final unweighted number of subjects in the present analysis was 1,818 individuals (weighted number = 24,120,330 Canadians).

The metabolic syndrome components

We applied the NCEP ATP III definition [2] to characterize the status of MetS. Under these criteria, an individual is classified as having MetS if he/she has three or more of the following components: waist circumference (WC) >102 cm (male) or >88 cm (female), triglycerides (TGs) ≥1.7 mmol/L, HDL-C <40 mg/dL (1.03 mmol/L) in males or <50 mg/dL (1.29 mmol/L) in females, blood pressure (BP) ≥130/85 mmHg, and FPG ≥6.1 mmol/L (110 mg/dL). Physical activity in this nationally representative population was measured using accelerometers as previously described [23] and was assessed via measuring the average daily energy expended during leisure time activities as reported by the respondent in the past three months. In the CHMS study, smoking was categorized as self-reported type of smoker (daily, occasional, former daily, former occasional and never smoked). For the purpose of this study, we grouped the smoking status categories into ever or never smokers. Ethnicity was divided into 12 different ethnic groups within the CHMS. In the present study, however, to allow for comparisons with adequate numbers across groups, ethnicity was recategorized into 3 main subgroups: Caucasians, Asians (i.e., Koreans, Filipinos, Japanese, Chinese, South Asians, Southeast Asians, Arabs, and West Asians) and Others (i.e., African Canadians, Latin Americans, and mixed). There were 46 participants with missing ethnicity information.

Statistical analysis

As several medications can markedly alter the levels of the metabolic markers examined in this study, we adjusted our analyses for subjects taking cardiac medications (lipid lowering or blood pressure medication, or other drugs with direct effects on the circulatory system), based on subject responses coded using the American Hospital Formulary Service drug code.

The distribution of relevant variables was examined for outliers or aberrant distributions. Generalized linear models were used to quantify the relationship between the biomarkers of interest and the number of MetS components. Models were adjusted for physical activity, smoking, month of interview, age, sex, cardiac medication use, and ethnicity. Survey sampling weights generated by Statistics Canada were applied to the present data sets. Pearson correlation coefficients were estimated between the inflammatory markers of interest and the individual MetS components. Sample weighted data were analyzed by SAS 9.3 software (SAS version 9.3, SAS Institute Inc., Cary, North Carolina) using survey-specific procedures and 11 denominator degrees of freedom. To account for the complex design of the CHMS, variance estimates for all measures were generated using bootstrap weights provided by Statistics Canada.

Results

The unadjusted average levels of metabolic phenotypes and inflammatory biomarkers evaluated in the present study are shown in Table 1, together with the characteristics of the study population. On average, the study population was middle aged (mean age = 42.6 years) and slightly overweight (mean BMI=26.56 kg/m^2) [24]. In the CHMS study, about 36% of Canadian adults aged 20 to 79 who have HDL-C <1.03mmol/L (males) or <1.29mmol/L (females) are obese; by comparison, only about 16% of those with HDL-C >1.03mmol/L

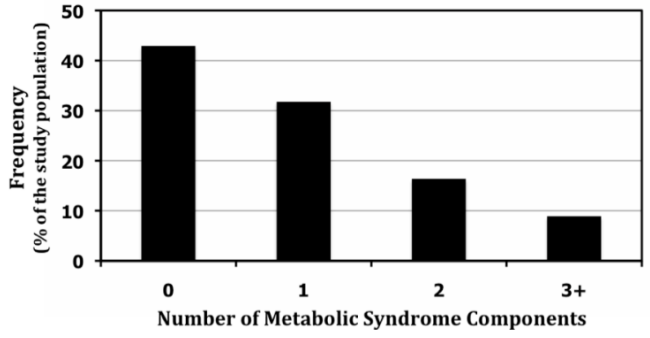

Figure 1: Frequency of the metabolic syndrome components in the study population.

(males) or >1.29mmol/L (females) are obese [25]. Serum levels of the cardiometabolic and inflammatory markers and the components of MetS in the study population fell, on average, within the normal clinical ranges. The population had an even gender distribution and was predominantly Caucasian (82%). Among the 1,818 studied subjects, 42.9% did not exhibit any sign of MetS, 31.8% had at least one MetS component (Figure 1). The prevalence of the MetS condition in the study subjects was 8.9% as indicated by exhibiting three or more MetS components (Figure 1).

We observed a strong association between elevated total: HDL-C ratio, Apo-B, and HbA1c, and lower Apo-A1 with the increasing number of MetS components ($p<0.05$) (Table 2). A positive linear relationship was noted between the MetS components and the elevated levels of serum CRP and fibrinogen but not homocysteine (Table 2). Serum CRP increased by almost 4-fold in subjects with MetS when compared to the levels in the study participants with no MetS factors ($p<0.05$) (Table 2).

The correlations between the three examined inflammatory

Subject Characteristic	n	Mean / % (95%CI)
Age (years)	1,818	42.64 (42.19 - 43.08)
Sex		
Male	869	49.12 (48.55 - 49.69)
Female	949	50.88 (50.31 - 51.45)
Physical Activity Index		
Active	435	21.14 (16.90 – 26.11)
Moderate	466	25.06 (21.69 - 28.76)
Inactive	917	53.80 (46.54 - 60.91)
Smoking status		
Ever	873	48.46 (44.32 - 52.63)
Never	945	51.54 (47.37 - 55.68)
Ethnicity[2]		
Caucasian	1,545	81.92 (71.18 - 89.27)
Asian	146	11.27 (6.04 - 20.06)
Other	81	4.02 (1.94 - 8.15)
Missing	46	2.79 (1.83 – 4.23)
Use of cardiac medication		
No	1,482	84.64 (81.81 - 87.10)
Yes	336	15.36 (12.89 - 18.19)
MetS Components		
BMI (kg/m^2)	1,808	26.56 (26.01 - 27.12)
Waist circumference (cm)	1,805	89.39 (87.68 – 91.04)
HDL-C (mmol/L)	1,818	1.34 (1.29 – 1.39)
FPG (mmol/L)	1,815	4.94 (4.89 – 5.00)
Systolic blood pressure (mmHg)	1,816	110.7 (109.2 – 112.3)
Diastolic blood pressure (mmHg)	1,816	70.7 (69.6 – 71.8)
Triglycerides (mmol/L)	1,816	1.3 (1.2 – 1.4)
Metabolic Markers		
HbA1c (%)	1,776	5.5 (5.4 – 5.6)
Apolipoprotein A1 (g/L)	1,818	1.44 (1.39 - 1.48)
Apolipoprotein B (g/L)	1,814	0.90 (0.88 - 0.93)
Total:HDL-C ratio	1,818	3.84 (3.76 - 3.93)
Inflammatory Markers		
C-reactive protein (mg/L)	1,661	2.16 (1.97 - 2.36)
Fibrinogen (g/L)	1,768	0.029 (0.028 - 0.031)
Homocysteine (μmol/L)	1,807	7.66 (7.27 - 8.05)

[1]Studied subjects were selected between 16-79 years of age from the Canadian Health Measures Survey with sampling weights and bootstrap weights for variance applied. The selected 1,818 subjects (unweighted value) represent a weighted value of 24,120,330 Canadians.
[2]Data with a coefficient of variation from 16.6% to 33.3%

Table 1: Population characteristics and levels of cardiometabolic and inflammatory markers[1].

Biomarker	No. of MetS Components[2] (Biomarker Mean ± SE)				*P*[3]
	0	1	2	3+	
Metabolic Markers					
Total:HDL-C ratio	2.98 ± 0.10	3.62 ± 0.14	4.51 ± 0.13	5.25 ± 0.13	$2.91x10^{-10}$
Apolipoprotein A1 (g/L)	1.57 ± 0.018	1.42 ± 0.018	1.32 ± 0.015	1.23 ± 0.018	$2.22x10^{-8}$
Apolipoprotein B (g/L)	0.81 ± 0.027	0.86 ± 0.031	0.96 ± 0.032	1.03 ± 0.028	0.000047
HbA1c (%)	5.5 ± 0.1	5.6 ± 0.1	5.7 ± 0.1	5.8 ± 0.1	0.00073
Inflammatory Markers					
C-reactive protein (mg/L)	1.40 ± 0.22	2.22 ± 0.23	3.04 ± 0.24	3.91 ± 0.40	$2.69x10^{-8}$
Fibrinogen (g/L)	0.029 ± 0.001	0.031 ± 0.001	0.032 ± 0.001	0.032 ± 0.002	0.00036
Homocysteine (µmol/L)	7.78 ± 0.30	7.84 ± 0.29	7.96 ± 0.27	8.12 ± 0.43	0.435

[1]Measures were evaluated in non-diabetic subjects aged 16 to 79 years from the Canadian Health Measures Survey
[2]Means are adjusted for age, sex, smoking status, physical activity levels, use of cardiovascular related medication and ethnicity
[3]*P* for trend

Table 2: Plasma levels of cardiometabolic and inflammatory markers across the metabolic syndrome components[1].

MetS Component	C-reactive protein (mg/L)			Fibrinogen (g/L)			Homocysteine (µmol/L)		
	n	*r*	*P*[2]	*n*	*r*	*P*	*n*	*r*	*P*
HDL-C (mmol/L)	1,661	-0.10	<0.0001	1,768	-0.01	<0.0001	1,807	-0.02	<0.0001
Waist circumference (cm)	1,649	0.38	0.0001	1,757	0.29	<0.0001	1,795	0.24	0.0007
Systolic blood pressure (mmHg)	1,659	0.15	0.423	1,766	0.14	<0.0001	1,805	0.29	0.095
Diastolic blood pressure (mmHg)	1,659	0.09	0.360	1,766	0.08	<0.0001	1,805	0.22	0.014
FPG (mmol/L)	1,659	0.14	0.297	1,767	0.07	<0.0001	1,806	0.26	0.406
Triglycerides (mmol/L)	1,659	0.26	<0.0001	1,766	0.15	<0.0001	1,805	0.19	<0.0001

[1]Correlation coefficient (*r*) was calculated for *n* number of subjects among non-diabetic individuals aged 16 to 79 years from the Canadian Health Measures Survey
[2]*P* is the level of correlation significance

Table 3: Association between inflammatory markers and metabolic syndrome components[1].

markers (CRP, fibrinogen and homocysteine) and the individual metabolic syndrome components examined in this study (HDL-C, WC, systolic and diastolic BP, FPG, and TGs), shown in Table 3, was performed in an attempt to find the predictive value of these markers in the presence of metabolic syndrome. Indeed, the strength of an association between two markers can be used as an indicator of the predictive value of inflammatory factors for a given metabolic syndrome component. Serum fibrinogen was the only inflammatory marker that was associated with all the MetS components. It was positively correlated with WC, BP, FPG and TGs and inversely with HDL-C ($p<0.05$). Fibrinogen was highly predictive ($p<0.0001$) of WC ($r=0.29$), TGs ($r=0.15$) and systolic BP ($r=0.14$). CRP was significantly inversely associated with HDL-C and directly with WC and TGs ($p<0.05$) where was highly predictive ($p=0.0001$) of WC ($r=0.38$) and TGs ($r=0.26$). No associations were observed between CRP and BP and FPG. The inverse association between HDL-C and CRP and fibrinogen was also evident with homocysteine. The latter was directly associated with higher WC ($r=0.24$, $p<0.0001$) and TGs ($r=0.19$, $p<0.0001$). No association was observed between FPG and homocysteine (Table 3).

Discussion

In this cross-sectional analysis of population-based survey data, we observed associations between traditional and non-traditional cardiometabolic disease biomarkers and MetS as it progresses from none to three or more condition-associated components. Having even one MetS component was associated with increased levels of cardiometabolic disease biomarkers (Table 1). Previous studies have reported a direct relationship between increased MetS components and subclinical [26] and incident coronary heart disease [27]. Our findings suggest that an increasing number of MetS components may reflect a higher risk of cardiometabolic-related dysregulation, even before the manifestation of the MetS. The associations reported here may be of significant public health relevance because, based on our results, one third of Canadian adults without T2D have at least one component of MetS (Figure 1) and may, therefore, be at an increased risk of cardiometabolic disease.

The direction of the associations observed here corroborates

previously reported relationships between cardiometabolic biomarkers and specific cardiometabolic outcomes. For example, we observed a positive association between increasing number of MetS components and total:HDL-C ratio, Apo-B and HbA1c and, in contrast, an inverse association with Apo-A1 (Table 2). These observations suggest a diminished status of glycemic control and enhanced dyslipidemia with increasing MetS components and they are in line with the predictive value of these markers in cardiometabolic disease [11]. These associations were expected, since HbAc1 is influenced by the serum glucose levels, and Apo-A1 and Apo-B are components of HDL-C and LDL-C, respectively [9,11]. Both FPG and HDL-C are components of the MetS that were evaluated in the present study.

The non-traditional inflammatory markers of cardiometabolic disease, CRP and fibrinogen, were also associated with increasing numbers of MetS components, suggesting an increased inflammatory state that is consistent with that observed during the progression of cardiometabolic disease [8,15,16]. An overall trend towards elevated homocysteine was also noted with increased MetS components, but it did not reach statistical significance. In general, the apparent gradual increases in these markers during the progression of MetS to manifestation can be further substantiated from their individual association with the levels of different MetS components (Table 3). Although a causal relationship cannot be concluded from this cross-sectional study, it is possible that elevated serum levels of CRP, fibrinogen and homocysteine may play a role in the increased number of MetS components observed in the present study. Indeed, we recently reported that genetic variants in *CRP* and other inflammatory genes can influence the development of metabolic risk factors related to cardiometabolic disease such as serum insulin, HDL-C and TGs [28].

As the present results suggest, MetS can be characterized by a status of chronic subclinical inflammation. This condition has been proposed to play a role in the pathophysiology of cardiometabolic disease. For example, inflammatory cytokines downregulate major anabolic cascades involved in insulin signaling and trigger insulin resistance in adipose, muscle and hepatic tissues, disrupting whole-body insulin sensitivity and leading to impaired glucose homeostasis [8]. In addition, cytokines also act on the liver to increase the production of very-low density lipoproteins (VLDL) and deactivate the liver X receptors (LXR), resulting in an increased rate of cholesterol accumulation and subsequent elevation of the LDL-C at the expense of HDL-C [29]. In the present study we observed that adverse levels of biomarkers of glucose homeostasis and lipid metabolism were associated with an increased number of MetS components. Although this relationship was expected, when taken together with the parallel gradual increases in inflammatory biomarker levels and the association between serum inflammatory factors and MetS components, it provides additional support for the role of innate immunity-related inflammation in the etiology of cardiometabolic disease. Furthermore, considering inflammatory factors together with the traditional metabolic biomarkers of cardiometabolic disease may provide a more accurate early risk prediction tool for both MetS and its related chronic disorders.

The results presented here are cross-sectional in nature, and additional prospective and interventional data are necessary to further substantiate the potential causal association between inflammation and the early stages of cardiometabolic disease. In addition, the prevalence of MetS in Canada, based on the CHMS data, was reported to be near 20% [5], a figure that is higher than the 8.9% prevalence reported here. This discrepancy reflects our exclusion of those with a previous history of diabetes or FPG levels >7.0 mmol/L. Furthermore, when considering hypertension, we included subjects who were currently hypertensive (rather than only including those with a previous history of hypertension). This approach was sought to permit examining the relationship between cardiometabolic biomarkers and MetS and its components among otherwise healthy individuals. Finally, since our analyses were adjusted for (rather than stratified by) ethnicity, we were unable to assess whether the relationship between the biomarkers presented here and MetS components is similar across different ethnic groups. Given the ethnocultural diversity of the Canadian population and known differences in prevalence of cardiometabolic disease between various ethnic groups, exploring how biomarkers of risk vary in the early disease stages may allow the development of targeted population-based prevention strategies aimed at curbing the increasing rates of a range of chronic diseases related to MetS.

In conclusion, this study is the first analysis of the CHMS data demonstrating a relationship between MetS and traditional cardiometabolic biomarkers, as well as non-traditional inflammatory markers. About one third of the general Canadian population without T2DM has at least one MetS component and may be at increased risk of cardiometabolic disease. Our findings contribute to understanding of the potential mechanisms by which MetS increases risk of cardiometabolic disease, and they may substantiate the use of non-traditional inflammatory biomarkers in the prediction of cardiometabolic disease risk together with traditional metabolic markers. We observed an apparent profile of metabolic phenotypes and inflammatory biomarkers, known to be related to the cardiometabolic disease risk, that emerges with an increasing number of MetS components. These findings allow for the establishment of a composite metabolic trait that predisposes to MetS and may, subsequently lead to the development of improved strategies for early risk prediction and intervention.

Author Contributions

All authors contributed substantially to conception, design and acquisition, and interpretation of data. BRB and PA carried out the data analysis. BG-B drafted the manuscript. All authors critically revised the manuscript for intellectual content and gave final approval of the published version.

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