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Is measurement of non-HDL cholesterol an effective way to identify the metabolic syndrome?

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Abstract

Background and Aims—The metabolic syndrome (MetS) has been shown to predict coronary heart disease (CHD). Non-high-density lipoprotein cholesterol (non-HDL-C) is also known to predict CHD, and recent evidence indicated non-HDL-C was able to predict MetS in adolescents. The study aim was to determine whether non-HDL-C serves as a useful metabolic marker for MetS in adults.

Methods and Results—Fasting non-HDL-C measurements were obtained in 366 non-diabetic adults not on lipid-lowering therapy. In addition to traditional non-HDL-C cut-points based on Adult Treatment Panel III guidelines, receiver-operating characteristic curve analysis was used to identify an optimal cut-point for predicting MetS. A secondary goal was to assess the relationship between non-HDL-C and insulin resistance, defined as the upper tertile of steady-state plasma glucose concentrations measured during the insulin suppression test. Prevalence of MetS was 40% among participants. Those with MetS had higher mean non-HDL-C (4.17 ± 1.0 vs 3.70 ± 0.85 mmol/L, $p < 0.001$), and the upper vs lower tertile of non-HDL-C concentrations was associated with 1.8-fold increased odds of MetS ($p < 0.05$). Traditional non-HDL-C cut-points 4.14 and 4.92 mmol/L demonstrated respective sensitivities 46% and 24% (specificities 72% and 89%) for identifying MetS. The optimal non-HDL-C cut-point 4.45 mmol/L had sensitivity 39% (specificity 82%). Comparable results were observed when non-HDL-C was used to identify insulin resistance.

Conclusion—While MetS was associated with increased non-HDL-C, an effective non-HDL-C threshold to predict MetS in adults was not identified. Dyslipidemic nuances may explain why non-HDL-C may be less useful as a metabolic marker for MetS and/or insulin resistance than for CHD.

Keywords

non-high-density lipoprotein cholesterol; coronary heart disease risk; insulin resistance; metabolic syndrome; obesity

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Introduction

Epidemiologic studies [1, 2] have shown that non-high-density lipoprotein cholesterol (non-HDL-C) concentration is at least equivalent to concentration of low-density lipoprotein cholesterol (LDL-C) in the prediction of coronary heart disease (CHD). Lowering of non-HDL-C is recommended in the Adult Treatment Panel (ATP) III Report as a secondary target in heart disease prevention after low-density lipoprotein cholesterol (LDL-C) targets have been achieved [3]. In this context, recent studies have examined the relationship between non-HDL-C concentration and the metabolic syndrome (MetS) [4, 5]. In the case of children and adolescents, it has been suggested that measurement of non-HDL-C might also serve as a simple and useful way to identify individuals at high risk to have MetS, and specific non-HDL-C cut-points have been provided for this purpose [5]. Given the importance of the MetS as a risk factor for type 2 diabetes and CHD [6], the ability of a non-fasting measurement to identify individuals at increased risk to develop this cluster of abnormalities would be of considerable clinical benefit. In view of the encouraging results in children and adolescents [5], it seemed reasonable to pursue the putative relationship between non-HDL-C and MetS in a population of apparently healthy adults, without diabetes and not taking prescription lipid-lowering drugs. Furthermore, since the cluster of abnormalities that comprise the MetS may involve “insulin resistance as a linking factor” [6], a secondary goal was to evaluate the relationship between non-HDL-C concentration and insulin resistance.

Methods

The study population consisted of 366 adult volunteers recruited from the San Francisco Bay area who had responded to advertisements for our research studies on the role of insulin resistance in human disease. All subjects gave informed consent, and the study protocols were approved by the Stanford Human Subjects Committee. Participants were in general good health, without evidence of heart, kidney, or liver disease. All subjects were non-diabetic as defined by the American Diabetes Association [7], and none reported taking prescription lipid-lowering drugs. Body mass index (BMI) was calculated (kg/m^2) based on height and weight measured while subjects wore light clothing and no shoes. Waist circumference was measured as the midpoint between iliac crest and rib cage at end-expiration [8]. Plasma samples for fasting glucose and lipid/lipoprotein concentrations were measured after an overnight fast by methods as described previously that were consistent over the study period [9]. Non-HDL-C was calculated by subtracting HDL-C from total cholesterol concentration.

MetS was defined using the recent “harmonious” criteria [6], of which 3 of the 5 following conditions must be met: fasting plasma glucose ≥ 5.56 mmol/L; systolic blood pressure ≥ 130 mmHg or diastolic blood pressure ≥ 85 mmHg; triglycerides (TG) ≥ 1.70 mmol/L; HDL-C < 1.30 mmol/L in women or HDL-C < 1.04 mmol/L in men. Abdominal obesity was present if waist circumference was ≥ 88 cm in women or ≥ 102 cm in men, which are criteria used for individuals in the United States [6, 10].

Insulin-mediated glucose disposal was directly quantified by a modification [11] of the insulin suppression test as originally described and validated by our research group [12, 13]. After an overnight fast, subjects were infused for 180 minutes with octreotide ($0.27 \mu\text{g}/\text{m}^2/\text{min}$), insulin ($32 \text{ mU}/\text{m}^2/\text{min}$), and glucose ($267 \text{ mg}/\text{m}^2/\text{min}$). Plasma glucose and insulin were measured every 10 minutes during the final half hour and averaged to determine steady-state plasma glucose (SSPG) and insulin (SSPI) concentrations. Because SSPI is similar for all individuals, SSPG provides a direct measure of the ability of insulin to mediate disposal of an infused glucose load; the higher the SSPG, the more insulin-resistant

the individual. Measurements of insulin-mediated glucose uptake using the insulin suppression test were shown to be highly correlated ($r > 0.9$) with those obtained using the hyperinsulinemic euglycemic clamp method [12]. We have shown previously that individuals in the upper tertile of SSPG concentrations are at increased risk for clinical events such as type 2 diabetes and CHD [14, 15]. Insulin resistance was defined as the upper tertile of SSPG concentrations (corresponding with the cut-point, SSPG 10.3 mmol/L) in this study population, based on the results of prospective, outcome studies [14, 15].

Two cut-points for non-HDL-C concentration were used to identify subjects at increased risk for MetS or insulin resistance: 4.14 mmol/L (160 mg/dL in traditional units) and 4.92 mmol/L (190 mg/dL in traditional units). As outlined in the ATP III Report [3], these non-HDL-C goals were formulated to be 0.78 mmol/L (30 mg/dL) higher than low-density lipoprotein cholesterol (LDL-C) goals for individuals in the intermediate and low risk levels for CHD events, respectively, consistent with the composition of our study population. The study population was also divided into tertiles of non-HDL-C for purposes of comparison. Tertiles of non-HDL-C corresponded with: non-HDL-C 3.37 mmol/L (Tertile 1, $n = 121$), non-HDL-C 3.38 – 4.20 mmol/L (Tertile 2, $n = 123$), and non-HDL-C 4.21 mmol/L (Tertile 3, $n = 122$).

Statistical analyses were conducted using SPSS software 19.0 (Chicago, IL, USA). Student's unpaired t test was used to compare characteristics between those with and without MetS in our study population. Area under the receiver-operating characteristic (ROC) curve and its 95% confidence interval (CI) were calculated to evaluate the predictive value of non-HDL-C for MetS. Area under the curve (AUC) values range from 0.5 (indicating random test) to 1.0 (indicating perfect test). The maximum value as calculated by the Youden index (sensitivity + specificity – 1) was used to identify the optimal cut-point for non-HDL-C concentration in relation to MetS. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated. Pearson's correlation coefficients were also calculated between metabolic variables.

Logistic regression was conducted to evaluate odds ratios of MetS and insulin resistance across tertiles of non-HDL-C, and then adjusted for age, sex, and BMI. Age was arbitrarily divided into categories defined as: < 39 years, 40–54 years, and ≥ 55 years. Categories of BMI were based on conventional groups including normal weight (BMI < 25 kg/m²), overweight (BMI 25 – 29.9 kg/m²), and obese (BMI ≥ 30 kg/m²). $P < 0.05$ was taken to indicate statistical significance.

Results

Table 1 summarizes the demographic and clinical characteristics of the study population. There were more women than men, and subjects were mostly Caucasian (70%), with smaller proportion of Latinos, Asians, and Blacks. While the range of BMI was broad (18.8 – 39.7 kg/m²), the majority were overweight (49%) or obese (42%). Insulin sensitivity as assessed by SSPG concentration varied considerably, with the mean SSPG of the upper third of the study population roughly equivalent to 3-fold the value of the third with the lowest SSPG concentrations (12.9 vs 4.11 mmol/L, respectively). Mean non-HDL-C was 3.89 mmol/L (median=3.78 mmol/L). Approximately 40% of individuals met the criteria for MetS, a prevalence comparable to that recently reported by Ford et al using the updated “harmonious” criteria for MetS [16].

Comparison of individuals with and without MetS is seen in Table 2. Those with MetS were slightly older and proportionately more were men. Mean non-HDL-C was higher in those with MetS, 4.17 ± 1.0 mmol/L vs 3.70 ± 0.85 mmol/L ($p < 0.001$). As expected, those with

MetS were heavier, more insulin-resistant, and differed in the metabolic variables that comprise MetS. However, there were no differences in total or LDL cholesterol between the 2 groups.

Table 3 summarizes the ability of the 2 non-HDL-C concentration cut-points based on ATPIII criteria to identify MetS or insulin resistance. The top panels (Table 3a) present the results for the ability of non-HDL-C concentration to predict MetS. Using the cut-point non-HDL-C 4.14 mmol/L, it can be seen that only slightly more than half (67 vs. 62) of those with values above the cut-point met the MetS criteria (PPV 52%), while approximately one-third of those with non-HDL-C <4.14 mmol/L also had the MetS (80/237). Overall a small proportion of our total study population had non-HDL-C concentrations ≥ 4.92 mmol/L, but among those, 60% (35/58) of individuals met criteria for MetS. As before, a not insignificant number of individuals below the non-HDL-C cut-point of 4.92 mmol/L had MetS (112/308 or 36%). The relatively reasonable specificity (89%) of this higher non-HDL-C cut-point can be attributed to the overall small number of individuals with non-HDL-C ≥ 4.92 mmol/L.

Comparable findings were observed in identification of insulin resistance (Table 3b). Insulin resistance was present in 54 of 129 (PPV 42%) individuals whose non-HDL-C concentrations exceeded 4.14 mmol/L. Of those with non-HDL-C <4.14 mmol/L, 29% (69/237) were insulin-resistant. These data are reflected in the overall low sensitivity and PPV observed for the non-HDL-C cut-point of 4.14 mmol/L in prediction of insulin resistance. Values for specificity and NPV fared somewhat better. Using the cut-point of 4.92 mmol/L, less than half (27/58) of those with non-HDL-C concentration ≥ 4.92 mmol/L met criteria for insulin resistance, and 31% (96/308) of those with non-HDL-C concentrations below 4.92 mmol/L were insulin-resistant.

The low values for calculated sensitivity and PPV using the above non-HDL-C cut-points led us to identify the optimal non-HDL-C cut-point by calculating AUC for the association between non-HDL-C and Met S (0.64, 95% CI 0.58 – 0.70). The optimal non-HDL-C cut-point was found to be 4.45 mmol/L, with calculated sensitivity of 39% (57/147) and specificity 82% (180/219). Respective PPV and NPV were 59% (57/96) and 67% (180/270).

Table 4 presents data on unadjusted and adjusted (for age, BMI, and sex) odds ratios for the MetS and insulin resistance across tertiles of non-HDL-C. The odds of MetS were increased in Tertile 3 as compared with Tertile 1 of non-HDL-C in unadjusted (2.7-fold) and adjusted (1.8-fold) analyses ($P < 0.05$). A difference in unadjusted odds (1.7-fold) of MetS was seen between Tertile 3 and Tertile 2 of non-HDL-C, but this difference was abrogated once adjusted for confounders. In the lower panels pertaining to insulin resistance, the only statistically significant result was in the unadjusted comparison between Tertile 3 vs Tertile 2 of non-HDL-C, exhibiting 1.7- fold increased odds for insulin resistance. However, statistical significance was eliminated after adjustment for confounders.

Correlation coefficients for the individual components of MetS, non-HDL-C, and SSPG are shown in Table 5. All components of MetS were correlated with non-HDL-C and SSPG, with the exception of diastolic blood pressure and SSPG. The relationship between non-HDL-C and SSPG was $r = 0.15$ ($p = 0.004$), and after adjustment for age, BMI, and sex, $r = 0.083$ ($p = 0.11$).

Finally, the subset of our study population with TG ≥ 200 mg/dL (2.26 mmol/L) was examined, since ATP III identified these persons to benefit most from non-HDL-C lowering. Among the 61 subjects in our study with TG ≥ 2.26 mmol/L, mean non-HDL-C concentration was not different between those with and without MetS (4.59 ± 1.24 vs 4.91 ± 0.79 mmol/L, $P = 0.39$).

Discussion

To the best of our knowledge, this is the first study to evaluate the ability of non-HDL-C concentrations to identify adults with MetS in an apparently healthy population, without diabetes, and not taking lipid-lowering agents. The MetS is acknowledged to be a predictor of both CHD and type 2 diabetes [6]. Use of one plasma measurement such as non-HDL-C to identify such individuals would be of significant clinical utility. Given the close relationship between insulin resistance and the MetS [6], it also seemed valuable to evaluate the ability of non-HDL-C concentrations to identify insulin-resistant individuals. Unfortunately, the results presented here do not support the use of simple measurement of non-HDL-C concentration as an effective means to predict MetS, or the presence of insulin resistance. These results are in contrast to data [5] reporting the ability of non-HDL-C thresholds to identify adolescents at increased risk for MetS, suggesting that this relationship may not be generalizable or comparable to our adult population. Absence of a standardized pediatric MetS definition [17] with variable adaptation from adult MetS definitions may account for this difference, as well as disparities in lipid measurements between children and adults. Another study [4] reporting a close association between non-HDL-C and MetS included a mixed population of adults with and without diabetes, and without information about use of lipid-lowering therapy which may have led to confounding.

The reason why non-HDL-C concentration is such an effective predictor of CHD may help to explain why it is less effective in identifying subjects with the MetS or insulin resistance [2]. Specifically, non-HDL-C includes the cholesterol in all of the apolipoprotein B-containing lipoproteins, including LDL-C, as well as other atherogenic lipoprotein particles such as TG-rich chylomicrons and chylomicron remnants, and very-low density lipoprotein (VLDL) and VLDL remnants. Thus, elevated non-HDL-C concentrations could identify three different groups at high risk for CHD: 1) individuals whose primary metabolic abnormality is an increase in LDL-C; 2) persons who are insulin-resistant, and whose major lipid abnormality is an increase in TG-rich lipoproteins [18] and 3) individuals with both lipoprotein abnormalities [19]. Only the last two groups are insulin-resistant, and would demonstrate the individual components of the MetS. Nonetheless, even among a small subset of individuals with high TG (≥ 200 mg/dL) in our study, non-HDL-C was not an effective predictor of MetS.

Our results do indicate that being in the upper tertile of non-HDL-C conferred increased odds of MetS when compared to individuals in the lowest tertile of non-HDL-C, after adjustment for confounders (Table 4). Incidentally, those in Tertile 3 of non-HDL-C had non-HDL-C levels nearly identical to that of the non-HDL-C cut-point 4.14 mmol/L, corresponding with the recommended goal per ATP III guidelines for individuals with intermediate level risk of CHD. Nonetheless, when tested for practicality (as shown in Table 3), use of the non-HDL-C cut-point of 4.14 mmol/L in clinical practice would miss a substantial proportion of individuals with MetS, as well as incorrectly identify a number of individuals as being at risk for MetS. Based on these findings it is apparent that application of traditional non-HDL-C cut-points to identify MetS cannot be recommended. Use of the optimal non-HDL-C cut-point 4.45 mmol/L did not improve sensitivity substantially and further underscored the inadequacy of non-HDL-C as a metabolic marker for MetS.

The major strength of our study was the inclusion of a relatively large number of apparently healthy, non-diabetic individuals, who were not taking any lipid lowering drug. A weakness was that the vast majority was Caucasian, and the results may not be relevant to other ethnic/racial populations. The study population was also predominantly overweight to obese; therefore the findings may not be generalizable to a leaner group of individuals. Nonetheless that prevalence of MetS in our population was similar to that found in a larger representative

sample of the U.S. adult population [16] suggests that our findings are at least, applicable to a significant proportion of Americans. Data on physical activity and smoking were not available, which may affect the results.

In conclusion, it should be emphasized that although our results do not support the view that a simple measurement of non-HDL-C concentration is an effective way to identify adults at high risk for MetS and/or insulin resistance, they do not diminish the role of non-HDL-C in CHD prediction in any way. Rather they underscore the still unmet need for a simple approach by which to identify adults at high risk for MetS and/or insulin resistance for the prevention of CHD.

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Table 1Characteristics of the study population ($n = 366$).

Variable	Mean	Range
Age (years)	50 $\pm$ 9	22 – 70
Number of women/men	223/143	
Number by race ^a	258C/33L/47A/23B/5O	
Body mass index (kg/m ²)	29.4 $\pm$ 4.0	18.8 – 39.7
Waist circumference (cm)	98.7 $\pm$ 11.8	67.5 – 133.5
Systolic blood pressure (mmHg)	123 $\pm$ 16	89 – 169
Diastolic blood pressure (mmHg)	74 $\pm$ 9	48 – 102
Fasting glucose (mmol/L)	5.33 $\pm$ 0.56	3.89 – 6.94
Steady-state plasma glucose (mmol/L)	8.28 $\pm$ 3.89	2.11 – 17.2
Total cholesterol (mmol/L)	5.1 $\pm$ 0.96	2.75 – 10.5
Low-density lipoprotein cholesterol (mmol/L)	3.21 $\pm$ 0.83	0.28 – 9.12
Triglycerides (mmol/L)	1.51 $\pm$ 1.08	0.17 – 9.04
High-density lipoprotein cholesterol (mmol/L)	1.22 $\pm$ 0.36	0.28 – 2.59
Non-high-density lipoprotein cholesterol (mmol/L)	3.89 $\pm$ 0.96	2.02 – 10.2
Number with metabolic syndrome (%)	147 (40.2)	

Data are expressed as mean $\pm$ S.D. unless otherwise indicated.^aC = Caucasian; L = Latino; A = Asian; B = Black or African-American; O = Other or mixed race

Table 2

Comparison of subjects without and with metabolic syndrome.

Variable	Without metabolic syndrome (n = 219)	With metabolic syndrome (n = 147)	p
Age (years)	49 ± 9	52 ± 9	0.005
Gender (% female)	67.6	51	0.002
SSPG (mmol/L)	6.75 ± 3.32	10.5 ± 3.54	<0.001
BMI (kg/m ²)	28.3 ± 3.9	31.2 ± 3.5	<0.001
Waist circumference (cm)	95 ± 11	105 ± 10	<0.001
Systolic blood pressure (mm Hg)	118 ± 14	129 ± 15	<0.001
Diastolic blood pressure (mm Hg)	72 ± 9	77 ± 8	<0.001
Fasting glucose (mmol/L)	5.50 ± 0.59	5.81 ± 0.40	<0.001
Total cholesterol (mmol/L)	4.80 ± 0.84	4.66 ± 0.84	0.11
LDL-cholesterol (mmol/L)	2.90 ± 0.58	2.75 ± 0.74	0.54
HDL-cholesterol (mmol/L)	1.45 ± 0.26	1.13 ± 0.25	<0.001
Triglycerides (mmol/L)	1.08 ± 0.52	1.72 ± 0.85	<0.001
Non-high-density lipoprotein cholesterol (mmol/L)	3.70 ± 0.85	4.17 ± 1.0	<0.001

Data are expressed as mean± S.D. unless otherwise specified.

SSPG = steady-state plasma glucose

Table 3

Non-HDL cholesterol	4.14 or	4.92 mmol/L to predict (a) metabolic syndrome or (b) insulin resistance.

(a)	Non-HDL-C < 4.14, no MetS	Non-HDL-C < 4.14, with MetS	Non-HDL-C	4.14, no MetS	Non-HDL-C	4.14, with MetS	Sensitivity, %	Specificity, %	PPV, %	NPV, %
	(N = 237)									
<i>n</i>	157	80	62	67	67	67	46	72	52	66
	(N = 129)									
	Non-HDL-C < 4.92, no MetS	Non-HDL-C < 4.92, with MetS	Non-HDL-C	4.92, no MetS	Non-HDL-C	4.92, with MetS	Sensitivity, %	Specificity, %	PPV, %	NPV, %
	(N = 308)									
<i>n</i>	196	112	23	35	35	35	24	89	60	64
	(N = 58)									
(b)	Non-HDL-C < 4.14, non-IR	Non-HDL-C < 4.14, IR	Non-HDL-C	4.14, non-IR	Non-HDL-C	4.14, IR	Sensitivity, %	Specificity, %	PPV, %	NPV, %
	(N = 237)									
<i>n</i>	168	69	75	54	54	54	44	69	42	71
	(N = 129)									
	Non-HDL-C < 4.92, non-IR	Non-HDL-C < 4.92, IR	Non-HDL-C	4.92, non-IR	Non-HDL-C	4.92, IR	Sensitivity, %	Specificity, %	PPV, %	NPV, %
	(N = 308)									
<i>n</i>	212	96	31	27	27	27	22	87	47	69
	(N = 58)									

Insulin resistance defined as the upper tertile of steady-state plasma glucose concentrations in the study population. IR = insulin-resistant; MetS = Metabolic syndrome; Non-HDL-C = non-HDL-cholesterol; Non-IR = non-insulin resistant; NPV = negative predictive value; PPV = positive predictive value.

Table 4
Odds ratios for metabolic syndrome and insulin resistance across tertiles of non-HDL cholesterol.

Metabolic syndrome	Unadjusted OR (95% CI)	p (vs. Tertile 1)	Unadjusted OR (95% CI)	p (vs. Tertile 2)	Adjusted ^a OR (95% CI)	p (vs. Tertile 1)	Adjusted ^a OR (95% CI)	p (vs. Tertile 2)
Non-HDL-C								
Tertile 1	1 [Ref]							
Tertile 2	1.57 (0.92 – 2.68)	0.097	1 [Ref]		1.29 (0.72 – 2.3)	0.40	1 [Ref]	
Tertile 3	2.71 (1.60 – 4.61)	<0.001	1.72 (1.04 – 2.87)	0.035	1.84 (1.03 – 3.30)	0.04	1.43 (0.83 – 2.47)	0.20
Insulin resistance								
	Unadjusted OR (95% CI)	p (vs. Tertile 1)	Unadjusted OR (95% CI)	p (vs. Tertile 2)	Adjusted ^a OR (95% CI)	p (vs. Tertile 1)	Adjusted ^a OR (95% CI)	p (vs. Tertile 2)
Non-HDL-C								
Tertile 1	1 [Ref]							
Tertile 2	0.98 (0.56 – 1.69)	0.93	1 [Ref]		0.93 (0.51 – 1.68)	0.80	1 [Ref]	
Tertile 3	1.70 (0.99 – 2.88)	0.051	1.74 (1.02 – 2.95)	0.041	1.43 (0.79 – 2.58)	0.24	1.54 (0.88 – 2.71)	0.13

Insulin resistance defined as the upper tertile of steady-state plasma glucose concentrations in the study population.

^a Adjusted for age, sex, and BMI. Non-HDL-C = non-HDL cholesterol; OR = odds ratio; CI = confidence interval.

Table 5

Correlation coefficients (r) between components of metabolic syndrome (MetS), non-HDL-C, and steady-state plasma glucose (SSPG).

MetS components	Non-HDL-C	SSPG
Waist circumference (cm)	0.25 *	0.40 *
Systolic blood pressure (mm Hg)	0.24 *	0.17 *
Diastolic blood pressure (mm Hg)	0.21 *	0.069 [‡]
Fasting glucose (mmol/L)	0.13 [‡]	0.34 *
HDL-cholesterol (mmol/L)	-0.19 *	-0.35 *
Triglycerides (mmol/L)	0.46 *	0.30 *

Data are expressed as mean± S.D. unless otherwise specified.

* $p < 0.001$;

[‡] $p < 0.05$,

[‡] Not significant.