

Non-HDL-Cholesterol and Total Cholesterol to HDL-C Ratio in Abdominally Obese Adults in Phitsanulok

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ABSTRACT

Objective: To compare non-HDLc and the TC/HDLc ratio in men and women with and without abdominal obesity (AO). To evaluate the association of non-HDLc and the TC/HDLc ratio with the other risk factors and to estimate the non-HDLc and TC/HDLc ratio level in both men and women with AO to establish the cutoff point by using ROC curve analysis.

Methods: Data (n=533) was used from adult Phitsanulok participants (aged ≥ 40 years) who came for their health check ups in the service project. AO was defined as waist circumference (WC) of ≥ 90 cm for men and ≥ 80 cm for women. The *t*-test was used to compare the difference in non-HDLc and the TC/HDLc ratio and other risk factors. The Pearson bi-variate correlation analysis was used to quantify the association of non-HDLc and the TC/HDLc ratio with blood pressure (BP) and other lipids.

Results: Both non-HDLc and the TC/HDLc ratio levels were elevated in men and women with AO. However in men neither two variables were significantly different, both non-HDLc and TC/HDLc ratio levels were elevated in men with and without AO. Non-HDLc and the TC/HDLc ratio were significantly higher in women with AO than without AO. We used the ROC curve to estimate cutoff values for non-HDLc and TC/HDLc ratio levels and also other lipids in our Thai subjects. The area under the curve of ROC of triglycerides may be superior to other risk markers for men and women in the present study.

Conclusion: Both non-HDLc and the TC/HDLc ratio were elevated in men and women with AO. WC and BP may be better associated markers for non-HDLc and the TC/HDLc ratio for men participants. The combination of elevated non-HDLc, the TC/HDLc ratio, BP, and WC may identify a group of participants with more marked risk of CVD, metabolic syndrome, and type 2 diabetes.

Keywords: Abdominal obesity, Non-HDLc, TC/HDLc ratio

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Obesity has recently become so prevalent across the world that it is replacing undernourishment and infectious diseases as the most significant contributor to poor health.¹ In particular, obesity is part of the metabolic syndrome with several abnormalities, including dyslipidemia, insulin resistance, elevated blood pressure (BP), and high plasma glucose.² The measures commonly used for assessing obesity are body mass index (BMI) and waist circumference (WC). BMI is not considered to be a good estimate of obesity in the

Asian population as they have a characteristic obesity phenotype with relatively lower BMI but with AO. A large body of epidemiologic evidence links AO with increased risk of many cardiovascular diseases (CVD).^{3,4} Elevated total cholesterol and lipoproteins through atherogenic and thrombotic processes have been hypothesized in the association of AO with CVD.⁵ Among the conventional lipids, non-high density lipoprotein-cholesterol (non-HDLc), and the ratio of total cholesterol (TC) to high density lipoprotein-cholesterol (TC/HDLc) ratio are reliable predictors of CVD often employed in epidemiological investigations. Non-HDLc is simply defined as the difference between TC and HDLc,

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thus, representing the cholesterol carrier on all of the potentially proatherogenic apoB-containing particles [primarily VLDL, IDL, and LDL as well as chylomicron remnants and lipoprotein (a)]. Non-HDLc provides estimates of circulating atherogenic particles. The National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) has acknowledged the importance of the atherogenic role of non-HDLc in diabetes and recommends it as the secondary target of cholesterol-lowering therapy in individuals with type 2 diabetes after the primary target of reducing elevated LDL-C and triglycerides (TG) (≥ 200 mg/dl). Although the mechanism of action of the TC/HDLc ratio is not well understood, some investigators have suggested the action of this lipoprotein phenotype in CVD is linked to visceral or abdominal adiposity by atherogenic and thrombotic mechanisms.^{5,6} The TC/HDLc ratio has been speculated to be linked to CVD by its thrombotic action.

In this study, we aimed to compare non-HDLc and the TC/HDLc ratio levels in both men (WC ≥ 90 cm) and women (WC ≥ 80 cm) with and without AO⁷ and to compare non-HDLc and the TC/HDLc ratio levels in AO men (WC ≥ 90 cm) with AO women (WC ≥ 80 cm) as well as to determine the association of non-HDLc and the TC/HDLc ratio with the other conventional CVD risk markers (such as blood pressure, TC, TG, HDL-C, LDL-C, age, and obesity) in the AO adults in Phitsanulok.

MATERIALS AND METHODS

Subjects

A total of 533 adults from Phitsanulok aged ≥ 40 years who came for their health check ups in our service project on the Celebration of His Majesty the King Bhumibol Adulyadej's 80th Birthday and the grand celebration of the 60th anniversary of his accession to the throne participated in this study. The Ethics Committee of Naresuan University approved this study. All participants provided written informed consent.

Data collection and measurement

Data were collected from the residents of Phitsanulok. We administered a questionnaire, including age, sex, and health status. WC was measured at the mid-point between the rib cage and the top of the lateral border of the iliac crest during minimal respiration. The blood pressure measurements were obtained with the participants in the seated position after 5 minutes of rest. Two measurements were made on all participants at 5 minutes intervals. The average of the two measurements was used in data analysis. Blood samples were collected from participants in the morning after an overnight fasting. Participants who had not fasted for at least 8 hours did not have their blood drawn. Blood specimens were processed and assayed at the central laboratory of the Department of Medical Technology on the same day. All biochemical examinations (fasting glucose (Glu), total cholesterol (TC), TG, and HDL-C) were performed using the enzymatic method on a Hitachi 912 autoanalyzer (Roche Diagnostic, Switzerland). The intra- and inter assay coefficients of variance (CV) of Glu, UA, TC, TG, and HDL-C levels were 1.2%, 0.5%, 0.8%, 1.5%, 0.95%, and 1.7%, 1.7%, 1.7%, 1.8%, 1.3% respectively. Low density lipoprotein-

cholesterol (LDL-C) was calculated by using Friedewald's formula,⁸ which is valid for TG values less than or equal to 400 mg/dl.

Abdominal obesity

According to the World Health Organization's revised definition and IDF definition, the WC cut-off values in Asians are 90 cm for men and 80 cm for women.⁷

Statistical analysis

All data are expressed as mean (\pm SD). Data from blood pressure, fasting plasma Glu, TC, TG, and HDL-C were categorized according to the WC as defined by IDF for AO. All data were expressed as mean and standard deviation. We excluded the participants aged less than 40 years. The *t*-test was used to estimate differences between groups. The Pearson correlation was used to assess the correlation of non-HDLc and TC/HDLc with the conventional CVD risk factors. Tests were two-tailed and a *P*-value of < 0.05 was considered significant. We used the Receiver Operating Characteristic (ROC) curve analysis to calculate areas under the ROC curve expressed as standard errors (SE) and estimated the non-HDLc, TC/HDLc, LDL-C, TG, and TC optimal cut-off values [as sensitivity – (1-specificity)] for those participants who had AO in the present study. All data were analyzed using the SPSS version 11.0 computer program.

RESULTS

There were a total of 533 individuals age ≥ 40 years in the study area after exclusion of the incomplete and age lower than 40 years patient cases. In regard to the health status of our participants, 60.3% of men and 23.1% of women consumed alcohol, 51.1% of men and 3.0% of women were smokers, and 33.6% of men and 2.2% of women consumed both tobacco and alcohol. Forty-three (8.1%, M/F: 11/32) participants were previously diagnosed and treated for type 2 diabetes, 72 (13.5%, M/F: 12/60) participants were previously diagnosed and received drug treatment for hyperlipidemia, and 116 (21.8%, M/F: 29/87) of participants were previously diagnosed and received treatment for hypertension. The basic anthropometric and clinical characteristics of the 533 eligible participants with and without AO are shown in Table 1 and 2.

A total of 76 (58.0%) men and 294 (73.1%) women had AO (WC ≥ 90 cm in men and ≥ 80 cm in women). Fifty-two (68.42%) of the AO men had elevated TG levels (≥ 150 mg/dl), 49 (64.47%) had elevated TC levels (≥ 200 mg/dl), 54 (71.05%) had elevated LDL-C levels (≥ 100 mg/dl), 5 (6.58%) reduced HDL-C levels, 57 (75%) had elevated BP (≥ 130 and/or 85 mmHg), and 42 (55.26%) had elevation of both TG and BP. One hundred seventy-one (58.16%) of these AO women had elevated TG levels (≥ 150 mg/dl), 235 (79.93%) had elevated TC levels (≥ 200 mg/dl), 243 (82.65%) had elevated LDL-C levels (≥ 100 mg/dl), 63 (21.43%) with reduced HDL-C levels, 187 (63.61%) with elevated BP (≥ 130 and/or 85 mmHg), and 102 (34.69%) with both elevated TG and BP.

In men, non-HDLc, TC/HDLc ratio and other lipid profiles were not significantly different with and without AO. However, WC, systolic BP, and diastolic BP were

TABLE 1. The characteristics of men participants aged ≥ 40 years with and without AO in Phitsanulok.

Variables	Men with AO (76) mean (SD)	Men without AO (55) mean (SD)	P-value
Age (years)	60.82 (8.97)	60.80 (9.48)	0.992
Non-HDLc (mg/dl)	167.95 (42.84)	161.21 (47.09)	0.396
TC/HDLc ratio	4.10 (0.99)	3.98 (1.19)	0.520
Waist circumference (cm)	97.38 (7.60)	80.43 (9.78)	<0.001
Systolic BP (mmHg)	137.36 (18.78)	129.65 (19.33)	0.024
Diastolic BP (mmHg)	82.76 (12.22)	75.55 (13.36)	0.002
Triglycerides (mg/dl)	190.83 (85.79)	179.38 (123.38)	0.532
HDL-C (mg/dl)	56.71 (12.89)	58.76 (15.77)	0.537
Fasting Glu (mg/dl)	94.05 (16.04)	93.22 (21.46)	0.799
Total cholesterol (mg/dl)	224.66 (44.31)	219.47 (49.43)	0.530
LDL-C (mg/dl)	129.79 (40.44)	125.34 (47.37)	0.564

TABLE 2. The characteristics of women participants aged ≥ 40 years with and without AO in Phitsanulok.

Variables	Women with AO (294) mean (SD)	Women without AO (108) mean (SD)	P-value
Age (years)	59.66 (8.93)	53.62 (12.38)	<0.001
Non-HDLc (mg/dl)	176.94 (47.09)	160.28 (45.92)	0.002
TC/HDLc ratio	4.10 (1.18)	3.43 (0.99)	<0.001
Waist circumference (cm)	90.22 (8.38)	74.56 (6.27)	<0.001
Systolic BP (mmHg)	132.2 (21.64)	120.31 (18.44)	<0.001
Diastolic BP (mmHg)	80.57 (12.24)	75.51 (10.31)	<0.001
Triglycerides (mg/dl)	183.18 (93.36)	152.02 (59.89)	0.001
HDL-C (mg/dl)	60.87 (15.01)	70.14 (16.62)	<0.001
Fasting Glu (mg/dl)	92.30 (28.03)	83.17 (10.84)	0<.001
Total cholesterol (mg/dl)	237.81 (47.50)	230.43 (47.42)	0.168
LDL-C (mg/dl)	140.30 (44.12)	129.88 (44.26)	0.037

significantly higher in men with AO than in men without AO (Table 1). Both with and without AO men were elevated in lipid and lipoprotein profile, they may in the same risk. In women, WC, BP, non-HDLc, TC/HDLc ratio, TG, and HDLc were significantly different in with and without AO (Table 2). Both with and without AO women were elevated in lipid and lipoprotein profile, and higher in AO. They may have the same risk. We examined the Pearson bi-variate correlation analysis of non-HDLc and the TC/HDLc ratio with age, WC, BP, and other lipids. The non-HDLc was significantly correlated with TC/HDLc, age, diastolic BP, TC, TG, and LDL-C in men with AO ($P < 0.05$, Table 3). The TC/HDLc ratio was significantly correlated with TC, TG, LDL-C, and HDL-C in men with AO ($P < 0.05$, Table 3). In women, non-HDLc and the TC/HDLc ratio, age, WC, systolic BP, diastolic BP, Glu, TG, LDL-C, and HDLc were significantly higher in women with AO than women without AO ($P < 0.05$, Table 2). The non-HDLc was significantly correlated with TC/HDLc, WC, TC, TG, LDL-C, and HDL-C in women with AO ($P < 0.05$, Table 3). The TC/HDLc ratio was significantly correlated with TC, TG, LDL-C, and HDL-C in women with AO ($P < 0.05$, Table 3).

We plotted the ROC curves for non-HDLc, the TC/HDLc ratio, TC, TG, and LDL-C for analysis of the area under the ROC curves for AO men and women with non-HDLc, TC/HDLc ratio and other lipid profiles. The largest area under the ROC curve in men with AO was TG ($0.586 \pm \text{SE } 0.051$). This area was not significantly greater than those of the other 4 markers because the same comparable variables were seen in men without AO. Whereas, the largest area under the ROC curve in women with AO was the TC/HDLc ratio ($0.698 \pm \text{SE } 0.030$), and this area was significantly greater than

those of the other 4 markers. It may indicate that the TC/HDLc ratio is a superior marker for women with AO in this study. Using the ROC curve, the estimated cutoff value [as sensitivity – (1-specificity)] for non-HDLc was 165 mg/dl in men with AO and 160 mg/dl in women with AO. The estimated cutoff value [as sensitivity – (1-specificity)] for the TC/HDLc ratio was 4.0 in men with AO and 3.5 in women with AO in the present study.

DISCUSSION

AO is now recognized in the third report of the NCEP ATP III and by the World Health Organization as a component of the metabolic syndrome,^{2,9} which is associated with the development of diabetes, cardiovascular disease, kidney disease, and an increased risk for mortality from cardiovascular disease and all causes.¹⁰ The WC directly reflects abdominal fat mass and has been suggested as an index of AO,^{2,11} which is an independent predictor for cardiovascular disease. WC correlated stronger with visceral adiposity than waist-to-hip ratio or BMI.¹² Visceral adiposity is the component of body composition that is most highly associated with many metabolic abnormalities such as hypertension, glucose intolerance, hyperinsulinemia, hypercholesterolemia, hypertriglyceridemia, and high levels of LDL-C.^{13,14} Visceral adiposity is clearly associated with insulin resistance and is a definite risk factor for CVD events. Prospective studies have shown that the atherogenic metabolic profile of persons with visceral obesity contributes substantially to their increased risk of premature CHD. The International Diabetes Federation (IDF) proposed that central obesity is a prerequisite risk factor for diagnosing the metabolic syndrome. Non-HDLc,

TABLE 3. Correlation of non-HDLc and TC/HDLc with conventional CVD risk factors.

Variables	Non-HDLc		TC/HDLc ratio	
	Men (P-value)	Women (P-value)	Men (P-value)	Women (P-value)
Age	r = -0.231 (0.045)	NS	NS	NS
WC	NS	r = 0.121 (0.039)	NS	NS
Systolic BP	NS	NS	NS	NS
Diastolic BP	r = 0.351 (0.002)	NS	NS	NS
Glu	NS	NS	NS	NS
TG	r = 0.336 (0.003)	r = 0.352 (<0.001)	r = 0.527 (<0.001)	r = 0.633 (<0.001)
LDL-C	r = 0.917 (<0.001)	r = 0.918 (<0.001)	r = 0.576 (<0.001)	r = 0.549 (<0.001)
Non-HDLc	1	1	r = 0.755 (<0.001)	r = 0.766 (<0.001)

NS = non significant

TABLE 4. The area under curves of the ROC analysis for AO men and women in the present study.

Anthropometric indicators	Area	Standard error	95% CI	
			Lower bound	Upper bound
Men				
Non-HDLc (mg/dl)	0.541	0.052	0.439	0.644
TC/HDLc ratio	0.541	0.052	0.438	0.643
TC (mg/dl)	0.536	0.052	0.434	0.639
TG (mg/dl)	0.586	0.051	0.485	0.686
LDL-C (mg/dl)	0.522	0.052	0.420	0.625
Women				
Non-HDLc (mg/dl)	0.618	0.032	0.555	0.681
TC/HDLc ratio	0.698	0.030	0.638	0.758
TC (mg/dl)	0.549	0.033	0.484	0.614
TG (mg/dl)	0.600	0.031	0.539	0.660
LDL-C (mg/dl)	0.586	0.033	0.521	0.651

TABLE 5. The optimal cut-off values for BMI and waist circumference indicators along with their sensitivity and specificity in this study.

Anthropometric indicators	Cut-off values	Sensitivity	Specificity
Men			
Non-HDLc (mg/dl)	164.65	50.0%	50.9%
TC/HDLc ratio	3.945	53.9%	50.9%
Women			
Non-HDLc (mg/dl)	160.50	62.7%	55.9%
TC/HDLc ratio	3.51	66.3%	64.7%

represents cholesterol carried on all of the potentially proatherogenic apolipoprotein B- containing particles [primarily VLDL, IDL, and LDL as well as chylomicron remnants and lipoprotein (a)]. The TC/HDLc ratio was shown to exhibit resistance to insulin-stimulated glucose disposal in non-diabetic individuals who were normal weight or obesity.¹⁶ In the present study, the overall prevalence of metabolic syndrome according to the IDF-definition⁷ was 237 (44.5%), 67 (51.2%) in men and 170 (42.3%) in women (data not shown). In both groups, most dyslipidemic men did not have reduced HDL-C levels. While these men may not meet the IDF criteria for the metabolic syndrome, it does not mean that they are free from the metabolic syndrome and CHD risk associated with elevated non-HDLc, TC/HDLc ratio, and other lipid profiles. These demonstrated that WC may be a good predictor for CHD risk in our Thai men with dyslipidemia and elevated non-HDLc and TC/HDL ratio.

The non-HDLc ratio had a stronger association with CVD risk and was a better predictor of CVD risk than LDL-C in the metabolic syndrome, diabetes, and obesity.^{17,18} The use of only LDL-C ignores the significant contribution of atherogenic VLDL-C and IDL-C to

CVD. In addition, in the present study, men had higher levels of the non-HDLc level. The ability of the TC/HDLc ratio to predict CVD compared with single lipid markers is of particular clinical relevance and may possibly be explained by the association of the lipid ratio with a cluster of cardiovascular risk factors that are at least in part unrelated to cholesterol metabolism.¹⁹ The TC/HDLc ratio was shown to correlate negatively with rates of insulin-stimulated glucose disposal in a small group of healthy individuals.²⁰ An increase in the TC/HDLc ratio was shown to exhibit resistance to insulin-stimulated glucose disposal and to have a higher BP, elevated TG levels, and hyperinsulinemia. Each of these factors is part of the metabolic syndrome and is an independent risk factor for CVD.¹⁹ The TC/HDLc ratio is mathematically equivalent to the ratio of non-HDLc. Non-HDLc and the TC/HDLc ratio can be easily calculated from the TC and HDL-C levels without the limitation of hypertriglyceridemia, thus also eliminating the cost for additional lipid measurements.

The women with AO (59.66 ± 8.93 years) were significantly older than women without AO (53.62 ± 12.38 years) with significantly higher levels of non-HDLc, TC/HDLc ratio, other lipid profiles and BP. These

may suggest more prevalence of AO in older women and after menopause. The CHD risk is associated with having elevated non-HDLc, TC/HDLc ratio, other lipid profiles and BP. Whereas, the TC/HDLc ratio was not associated with BP in AO women. Only non-HDLc was correlated with diastolic BP in AO men. The recent guidelines have emphasized the importance of non-HDLc and the TC/HDLc ratio as stronger predictors of cardiovascular risk than LDL-C in the metabolic syndrome, diabetes mellitus, and obesity.^{2,21-23} The Lipid Research Clinics Program Follow-up Study in subjects without initial cardiovascular disease showed that the risk of cardiovascular mortality was increased by more than 2 fold in both men and women with the highest non-HDLc levels.²¹

We calculated the area under the ROC curve to compare the non-HDLc, TC/HDLc, TC, TG, and LDL-C abilities in discriminating between men and women with and without AO.²⁴ The greater the area under the ROC curve, the better the predictive power of the variables. In general, an area under the ROC curve of 0.5 suggests no discrimination, whereas a maximal ROC of 1 suggests outstanding discrimination. The largest AUC of the ROC curve in the AO men was TG (0.586), this area was not significantly greater than those of the other 4 markers possibly because both men with and without AO had elevated lipid profiles. Hence, TG may be better than non-HDLc and the TC/HDLc ratio in this study, and it may be included in the concept of the hypertriglyceridemia waist phenotypes. Our finding of the non-HDLc level for discrimination of the abnormalities was 165 mg/dl for men and 160 mg/dl for women, and the TC/HDLc ratio was 4.0 for both men and women. The greatest area under the ROC curve of women was the TC/HDLc ratio. These women may be insulin resistant or have hyperinsulinemia. Once the characteristics of patients identified as being at increased risk for CVD on the basis of the ratio of TC/HDLc have been identified, it can be seen that they share the cluster of abnormalities that were initially demonstrated to be secondary to resistance to insulin-mediated glucose disposal.^{25,26} Insulin resistance is not a predictor of CVD, but rather the cluster of abnormalities associated with insulin resistance may be very important in this context. Initially,²⁵ the abnormalities associated with insulin resistance were said to include some degree of glucose intolerance, hyperinsulinemia, and dyslipidemia characterized by increases in VLDL-cholesterol and TG and decreases in HDL-C, along with a tendency for increased BP.

The common underlying aetiological factor is abdominal visceral fat²⁶ and WC is considered the best indicator, which may be used in the community as a screening tool.²⁷ Clinical implications of AO are the same as the metabolic syndrome and are self-evident. Excess adiposity and physiological inactivity are the major lifestyle variables. When weight loss and increased physical activity are appropriately initiated, insulin sensitivity will be enhanced and the associated CHD risk factors will be decreased.

CONCLUSION

Both non-HDLc and the TC/HDLc ratio were elevated in men and women with AO. However, in men with and without AO both non-HDLc and the TC/HDLc

ratio were elevated. Serum non-HDLc levels, TC/HDLc ratio, and other lipid profiles could not discriminate the different abnormalities. These men may have the same risk. WC and BP may be markers for OA which associate better than non-HDLc and the TC/HDLc ratio and other lipid profiles in both sexes. The combination of elevated non-HDLc and TC/HDLc ratio along with elevated WC and BP may identify a group of participants with more marked risk of CVD, metabolic syndrome, and type 2 diabetes mellitus.

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