

# Change in nonhigh-density lipoprotein cholesterol levels in adults with prediabetes

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## Abstract

This study aimed to observe the change in nonhigh-density lipoprotein cholesterol (non-HDL-C) levels and analyzed its related factors in adults with prediabetes (impaired fasting glucose and/or impaired glucose tolerance).

This case-controlled study included 56 adults with normal glucose tolerance (NGT) and 74 adults with prediabetes. The cases and controls were age and gender-matched. Anthropometric measurements including height, weight, waist circumference, and blood pressure were performed. All patients underwent an oral glucose tolerance test (OGTT) after 8 hours of fasting, and the levels of glucose, insulin, lipids, and uric acid were measured.

The levels of non-HDL-C ( $3.63 \pm 0.92$  vs  $3.27 \pm 1.00$  mmol/L) were significantly higher in prediabetic subjects than in NGT subjects ( $P < .05$ ). Non-HDL-C positively correlated with HOMA-IR ( $r = 0.253$ ,  $P = .004$ ), triglyceride ( $r = 0.204$ ,  $P = .020$ ), and uric acid ( $r = 0.487$ ,  $P = .000$ ). After multivariate analysis, uric acid continued to be significantly associated with non-HDL-C ( $\beta = 0.006$ ,  $P = .000$ ).

Non-HDL-C is elevated in adults with prediabetes. A relationship between non-HDL-C and uric acid was observed.

**Abbreviations:** CVD = cardiovascular disease, FPG = fasting plasma glucose, HDL-C = high-density lipoprotein cholesterol, 2-h PG = 2-h plasma glucose, LDL-C = low-density lipoprotein cholesterol, NGT = normal glucose tolerance, OGTT = oral glucose tolerance test, SBP = systolic blood pressure, TC = total cholesterol, TG = triglycerides, WC = waist circumference.

**Keywords:** insulin resistance, non-high-density lipoprotein cholesterol, oral glucose tolerance test, pre-diabetes, uric acid

## 1. Introduction

Cardiovascular disease (CVD) has become the leading cause of death in China. Its incidence has been due to rapid economic growth, increased life expectancy, and changes in lifestyle.<sup>[1]</sup> Diabetes is a major risk factor for CVD, and its prevalence is high and continuously increases in China.<sup>[2]</sup> In the Chinese population, self-reported diabetes has been associated with the doubling of the odds of prevalent CVD.<sup>[3]</sup> Lipid abnormalities in patients with type-2 diabetes are a major problem, and are associated with increased risk of CVD. The most common pattern of dyslipidemia in these patients consists of elevated levels of triglycerides (TG) and low levels of high-density lipoprotein cholesterol (HDL-C).<sup>[4]</sup>

Non-HDL-C (total cholesterol [TC] minus HDL-C) provides a convenient measure of the cholesterol content of all atherogenic lipoproteins, thereby incorporating the potential risk conferred by elevated levels of atherogenic TG-rich remnants, which adds

to the risk associated with low-density lipoprotein cholesterol (LDL-C).<sup>[5]</sup> Non-HDL-C level has been found to be a strong predictor of future cardiovascular risk among patients who exhibit or do not exhibit symptoms of vascular disease, and this has been recommended as a secondary treatment target (after LDL-C) in patients with elevated TG by the National Cholesterol Education Program Adult Treatment Panel III.<sup>[6]</sup>

Type-2 diabetes presents with significantly elevated levels of non-HDL-C when compared with controls, and this can be used as a marker of dyslipidemia and an indicator for predicting the risk of CVD in type-2 diabetes.<sup>[7–9]</sup> In addition, non-HDL-C level is an early predictor for vascular inflammation in type-2 diabetes.<sup>[10]</sup> Non-HDL-C represents the proatherogenic, apo-B-containing lipoprotein fraction of circulating lipids, and represents a secondary target for CVD prevention in people with diabetes.<sup>[11]</sup>

The prevalence of cardiovascular risk factors is high in the Chinese impaired glucose regulation population.<sup>[12]</sup> To our knowledge, few investigators have attempted to evaluate non-HDL-C levels in prediabetic subjects.<sup>[13–14]</sup> In the present study, we attempted to observe the changes in non-HDL-C levels and analyze its related factors in adults with prediabetes (impaired fasting glucose and/or impaired glucose tolerance).

## 2. Materials and methods

### 2.1. Study design

A case-control study of normal glucose tolerance (NGT) and prediabetes adults was performed. All subjects were of Han ethnicity, and each subject underwent oral glucose tolerance test (OGTT) with 75 g of oral anhydrous glucose initiated at 8:00 AM. Peripheral venous blood samples were taken at 0, 60, 120, and 180 minutes after glucose loading. Inclusion criteria were as follows: subjects who were clinically stable with no previous

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medical history of diabetes, hypertension, dyslipidemia, coronary artery diseases, or cerebral stroke; subjects without clinical evidence of endocrinopathy; subjects with fasting plasma glucose (FPG) levels <7.0 mmol/L and 2-hour plasma glucose (2-h PG) levels <11.1 mmol/L after the 75-g OGTT, according to the 2008 diagnostic criteria of the American Diabetes Association; and subjects who did not take medications that are known to affect glucose and lipid metabolism such as statins, glucocorticoids, thyroid hormones, and thiazide diuretics. Exclusion criteria were as follows: subjects with hepatic or renal dysfunction (>1.5-fold elevation of alanine aminotransferase, aspartate aminotransferase, or serum creatinine >115  $\mu\text{mol/L}$ ); subjects with acute and chronic inflammation.

## 2.2. Cases and controls

A total of 74 adults with prediabetes, who visited the First Hospital of Qinhuangdao for health examination in 2011, were enrolled into the study. These subjects were assigned as the case group. A case was defined as an adult with a FPG level  $\geq 5.6$  mmol/L and/or 2-h PG level  $\geq 7.8$  mmol/L after 75-g OGTT, according to the 2008 diagnostic criteria of the American Diabetes Association. During the same period, 56 adults with NGT (with FPG levels <5.6 mmol/L and 2-h PG levels <7.8 mmol/L after 75-g OGTT) were also enrolled into the study. These subjects were assigned as the control group. The cases and controls were age and gender-matched. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Qinhuangdao First Hospital. Written informed consent was obtained from all participants.

## 2.3. Anthropometric measurements

Anthropometric measurements including height, weight, waist circumference, and blood pressure were obtained while the subjects were in light clothing and barefooted. Body mass index was calculated by dividing the weight (kg) by the square of height ( $\text{m}^2$ ). Blood pressure was measured twice using a mercury sphygmomanometer after 10 minutes of rest while the subjects were seated, and the average of 2 measurements was used for analysis.

## 2.4. Laboratory examinations

All subjects underwent OGTT with 75 g of oral anhydrous glucose at 8:00 AM after 8 hours of fasting. Seventy-five gram of anhydrous glucose was dissolved in 250 mL of water. Peripheral venous blood samples were taken at 0, 60, 120, and 180 minutes after glucose loading. Plasma glucose concentration was measured using the glucose oxidase method, and serum uric acid was measured using the uricase method. In addition, serum lipids were measured through enzymatic procedures using an autoanalyzer (Hitachi, Tokyo, Japan). True Insulin was measured using enzyme-linked immunosorbent assay (ELISA) with the model 680 microplate reader (Bio-Rad, USA). ELISA kits were purchased from USCNLIFE (USA). The following equation for the homeostasis model assessment of insulin resistance (HOMA-IR) was used: fasting insulin level ( $\mu\text{U/mL}$ )  $\times$  fasting glucose level (mmol/L)/22.5. Non-HDL-C was calculated as follows: Non-HDL-C = TC – HDL-C.

## 2.5. Statistical analysis

Data were expressed as mean  $\pm$  standard deviation (SD) or medians with interquartile ranges (IQRs). When data were not normally distributed, they were transformed for analysis. Comparisons were conducted between groups using *t* test.  $\chi^2$ -test was used to test for differences in proportions. In order to measure the strength of the association between 2 variables, Pearson correlation coefficient was used. In order to examine the association between non-HDL-C and other variables, multiple linear regression analysis was performed. All analysis was performed using SPSS version 11.5 software (SPSS Inc., Chicago, IL). Statistical significance was established at  $P < .05$ .

## 3. Results

Age and gender between the 2 groups were similar ( $P > .05$ ). Table 1 presents the clinical and laboratory characteristics of the study subjects. Subjects with prediabetes had higher FPG, 2-h PG, TG, non-HDL-C, uric acid, and HOMA-IR levels, compared to subjects with NGT ( $P < .05$ ). Subjects with prediabetes had lower HDL-C levels than subjects with NGT ( $P < .05$ ).

**Table 1**

**Clinical and laboratory characteristics of the subjects in different groups.**

Variable	NGT group (n = 56)	Prediabetes group (n = 74)	<i>t</i> or $\chi^2$	<i>P</i>
Age, y mean (SD)	49.9 (12.8)	50.7 (9.5)	0.395	.694
Sex (male/female)	28/28	38/36	0.023	.879
BMI, $\text{kg/m}^2$ mean (SD)	25.5 (4.5)	25.6 (2.6)	0.095	.925
WC, cm mean (SD)	90.5 (16.1)	92.5 (9.8)	0.823	.413
SBP, mmHg mean (SD)	130.4 (16.8)	131.6 (18.6)	0.383	.702
DBP, (mmHg) mean (SD)	82.1 (10.4)	84.4 (11.3)	1.168	.245
FPG, mmol/L mean (SD)	5.3 (0.1)	6.2 (0.3)	19.479	.000
2-h plasma glucose, mmol/L mean (SD)	6.1 (0.6)	7.7 (1.6)	7.553	.000
TG, mmol/L mean (SD)	1.31 (0.53)	2.11 (1.70)	3.802	.000
TC, mmol/L mean (SD)	4.66 (1.12)	4.87 (0.78)	1.262	.209
HDL-C, mmol/L mean (SD)	1.38 (0.25)	1.24 (0.33)	2.724	.007
LDL-C, mmol/L mean (SD)	2.51 (1.03)	2.74 (0.90)	1.365	.175
Non-HDL-C, mmol/L mean (SD)	3.27 (1.00)	3.63 (0.92)	2.117	.036
Uric acid, $\mu\text{mol/L}$ mean (SD)	263.4 (72.7)	316.8 (70.8)	4.212	.000
HOMA-IR median (IQR)	2.14 (1.58)	3.16 (1.74)	5.653	.000

Data are expressed as mean  $\pm$  SD or medians with IQR. When data were not normally distributed, they were in transformed for analysis. BMI = body mass index, DBP = diastolic blood press, FPG = fasting plasma glucose, HDL-C = high-density lipoprotein cholesterol, HOMA-IR = homeostasis model assessment of insulin resistance, IQR = interquartile range, LDL-C = low-density lipoprotein cholesterol, NGT = normal glucose tolerance, non-HDL-C = nonhigh-density lipoprotein cholesterol, SBP = systolic blood press, SD = standard deviation, TC = total cholesterol, TG = triglycerides, WC = waist circumference.

**Table 2**

**Simple correlations between the nonhigh-density lipoprotein cholesterol and other variables in the study subjects.**

Variable	<i>r</i>	<i>P</i>
Age, y	0.038	.671
BMI, kg/m <sup>2</sup>	0.073	.409
WC, cm	0.128	.147
SBP, mmHg	0.106	.228
DBP, mmHg	0.084	.343
FPG, mmol/L	0.073	.408
2-h plasma glucose, mmol/L	0.145	.100
TG, mmol/L	0.204	.020
Uric acid, μmol/L	0.487	.000
HOMA-IR	0.253	.004

BMI=body mass index, DBP=diastolic blood press, FPG=fasting plasma glucose, HOMA-IR=homeostasis model assessment of insulin resistance, SBP=systolic blood press, TG=triglycerides, WC=waist circumference.

**Table 3**

**Multiple linear regression analyses for nonhigh-density lipoprotein cholesterol (stepwise method).**

Model	Unstandardized coefficients B	Std. error	Standardized coefficients B	<i>t</i>	<i>P</i>	95% CI	<i>R</i> <sup>2</sup>
(Constant)	1.663	0.298		5.578	.000	1.073–2.253	
Uric acid	0.006	0.001	0.487	6.308	.000	0.004–0.008	0.237

Dependent variable: nonhigh-density lipoprotein cholesterol. CI=confidence interval.

Non-HDL-C was positively correlated with HOMA-IR ( $r=0.253$ ,  $P=.004$ ), TG ( $r=0.204$ ,  $P=.020$ ), and uric acid ( $r=0.487$ ,  $P=.000$ ) (Table 2). When non-HDL-C was considered as dependent variables by multiple regression, the analysis with age, gender, body mass index, waist circumference, systolic blood pressure, diastolic blood pressure, TG, FPG, 2-h PG, uric acid, and HOMA-IR were considered as independent variables; and uric acid ( $\beta=0.006$ ,  $P=.000$ ) maintained an independent association with non-HDL-C (Table 3).

#### 4. Discussion

The results of the present study show that non-HDL-C levels increased in adults with prediabetes who were of Han ethnicity. Uric acid continued to be independently associated with non-HDL-C, which explains 23.7% of the total variance.

Liu et al<sup>[13]</sup> found that non-HDL-C levels may be an important indicator in monitoring CVD risk among adolescents with impaired fasting glucose. The data of Banu et al<sup>[14]</sup> indicated the positive association of non-HDL-C levels with the prediabetic and diabetic status of patients. In the present study, changes in non-HDL-C levels in adults with prediabetes were also found. The screening for dyslipidemia poses some challenges. Non-fasting lipid profiles frequently have elevated TG. In addition, in the standard lipid profile, LDL-C is a calculated value rather than a direct measurement. Measuring non-HDL-C levels in type-2 diabetes patients is simple, cost-effective, and convenient, because it does not require 12-hour fasting, allowing clinicians to choose non-HDL-C as a routine measure in clinical practice.<sup>[15]</sup> Based on the present study, we recommend the estimation of non-HDL-C levels in routine clinical practice for prediabetic patients.

Serum uric acid is the final oxidation product of purine metabolism in the circulation. Serum uric acid may accumulate in the body due to increased production or decreased elimination.

High serum uric acid is a prerequisite for gout and is also associated with metabolic syndromes and its components.<sup>[16]</sup> Consequently, it is associated with risk factors for stroke and CVD.<sup>[17,18]</sup> The relationship between lipids and uric acid varied in different populations. A recent study in Nigerians revealed that TC and LDL-C were significantly associated with uric acid,<sup>[19]</sup> but such associations were not found in Iranians.<sup>[17]</sup> In the present study, we found that uric acid was significantly associated with non-HDL-C in prediabetes.

The role of uric acid in the metabolism of lipids remains unclear. It has been believed that uric acid might be involved in either the overproduction or the reduction in clearance of lipids.<sup>[1]</sup> Non-HDL-C incorporates both LDL-C and VLDL-C, which reflects the cholesterol content of all apolipoprotein B-containing lipoproteins.<sup>[21]</sup> An epidemiology survey revealed that serum uric acid level increased and was accompanied by increments of serum LDL-C, TC, and apolipoprotein-B levels.<sup>[22]</sup> This suggests the crucial role of uric acid in the regulation of non-HDL-C.

There are some limitations in the present study. First, it only included adults of Han ethnicity, thereby limiting its ability to apply the result to other ethnic groups. Second, the cross-sectional design of this study precludes the establishment of the causation between events. Third, data on other confounding factors such as diet, alcohol consumption, and physical activity were not considered.

#### 5. Conclusion

In conclusion, the present study demonstrates that non-HDL-C is elevated in adults with prediabetes in real life. We recommend the estimation of non-HDL-C levels in routine clinical practice for prediabetic patients. A relationship between non-HDL-C and uric acid was also observed, which should be examined in future studies.

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