ORIGINAL RESEARCH

Association Between Hypertriglyceridemic Waist Phenotype and Increased Urinary Albumin–Creatinine Ratio in Chinese Adults: The REACTION Study

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Purpose: The hypertriglyceridemic waist (HTGW) phenotype can predict cardiovascular disease (CVD) risk. Additionally, strong evidence indicates that elevated urinary albumin–creatinine ratio (UACR) is associated with increased prevalence of CVD. However, few studies have explored the association between the HTGW phenotype and UACR.

Patients and Methods: In this cross-sectional descriptive study, a total of 40,674 subjects (28,562 women and 12,112 men older than 40 years) were recruited from seven different geographic regional centres. The HTGW phenotype was defined as increased triglyceride levels (triglyceride ≥ 1.5 mmol/L for female and ≥2.0 mmol/L for male) and waist circumference (WC; WC ≥ 85 for female and WC ≥ 90 cm for male). Logistic regression analyses were performed to assess the relationship between UACR and the HTGW phenotype.

Results: Subjects with the HTGW phenotype showed a more significant trend towards increased excretion of UACR [among all subjects, odds ratio (OR) = 1.303, 95% CI: 1.132–1.499, P < 0.001; among men, OR = 1.406, 95% CI: 1.057–1.870, P = 0.019; among women, OR = 1.268, 95% CI: 1.074–1.496, P = 0.005]. Furthermore, the stratified analysis showed that the OR for high-risk significantly increased in individuals in the HTGW group aged below 65 years, with 5.6 ≤ fasting blood glucose < 7.0 or 7.8 ≤ post-load blood glucose <11.1 mmol/L, 120 ≤ systolic blood pressure < 140 or 80 ≤ diastolic blood pressure < 90, 24 ≤ body mass index < 28 kg/m^2, and estimated globular filtration rate > 90 mL/min per 1.73 m^2.

Conclusion: This study has advanced the understanding of visceral obesity and our results supported the fact that the HTGW phenotype is associated with elevated UACR excretion among general Chinese adults.

Keywords: waist circumference, hypertriglyceridemia, chronic kidney disease, urinary albumin-creatinine ratio

Introduction

Recently, the prevalence of visceral obesity has continued to notably rise. Visceral obesity plays an essential role in the occurrence of insulin resistance (IR), metabolic syndrome (MetS), and cardiovascular disease (CVD).[1] Compelling evidence had been detailed in specific prospective studies on the regional adipose tissue distribution,[2] while others have indicated that visceral obesity is closely associated with CVD risk, especially in women.[3,4]

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Moreover, the hypertriglyceridemic waist (HTGW) phenotype is defined as having at-risk triglyceride (TG) values and at-risk waist circumference (WC).[5] Visceral obesity is more closely related to the HTGW phenotype than it is to WC.[6] Increasing evidence has confirmed that the HTGW phenotype is also associated with the onset and prevalence of specific diseases. Specifically, studies have reported that the HTGW phenotype may serve as a strong indicator of atherogenic trends among postmenopausal women.[4] Further, a study in the Chinese population suggests that the HTGW phenotype increases the prevalence of prediabetes;[7] meanwhile, a STROBE compliant study showed that the HTGW phenotype indicates endothelial dysfunction, which can result in hypertension.[8] Furthermore, the HTGW phenotype rather than body mass index (BMI) was recommended as a useful screening tool to predict the risk of CVD and MetS.[9] The HTGW phenotype has also been reported to contribute to a greater risk of coronary artery disease.[10] In fact, the HTGW phenotype can be used as a clinical indicator of atherosclerotic metabolic characteristics in males, with its value in assessing the 7.5-year CVD risk having been confirmed.[11]

The urinary albumin excretion rate can be generally described in terms of the urinary albumin–creatinine ratio (UACR). Elevated UACRs have been described as a symbol for impaired function of kidney and is a crucial risk factor for CVD.[12] Early renal dysfunction is closely associated with a higher incidence of CVD.[13] Furthermore, compared with normal UACR values, diabetic patients with micro- and macro-albuminuria have 1.5- and 3.7-times higher mortality rates associated with CVD, respectively.[14] Hence, considering that visceral obesity is a common risk factor for both CVD and chronic renal disease development,[15] the aim of the present study was to establish if an association exists between the HTGW phenotype and increased UACR.

Materials and Methods
Study Population
This study was drawn from a longitudinal REACTION study, designed to examine the relationship between type 2 diabetes mellitus (T2DM) and cancer risk in a Chinese population. The REACTION study used the multistage random sampling method and was conducted among adults aged over 40 years old from both urban and rural areas with various states of economic development and urbanisation, across mainland China from 2011 to 2012.[16] A total of 47,808 participants, which were representative

of China, were recruited from seven different geographic regional centres (Dalian, Guangzhou, Lanzhou, Luzhou, Shanghai, Zhengzhou, and Wuhan). Participants who used lipid lowering or ACEI/ARB drugs, those who had been diagnosed with primary kidney disease at baseline, and those with incomplete demographic or clinical characteristic data were excluded. A total of 40,674 participants (12,112 men and 28,562 women) were enrolled in the present analysis. The flow chart describing the enrolment of the subjects in this study is presented in Figure 1.

Ethics Approval and Informed Consent
Before data collection, informed consent was acquired from all participants, and the protocols of this study were approved by the Committee on Human Research of Rui-Jin Hospital affiliated with the School of Medicine, Shanghai Jiao Tong University.

Data Collection
According to the standardised procedures, the subjects underwent anthropometric assessments, self-administered questionnaires, blood collection, and a 75 g-oral glucose tolerance test (OGTT). Detailed information of the participants regarding demographic characteristics, clinical medical record, and lifestyle were collected via standard examination questionnaires. The clinical medical record included history of nephritic diseases, hyperlipidaemia, hypertension, T2DM, CVD [including stroke, myocardial infarction (MI), and coronary heart disease (CHD)], and the use of drugs. Smoking practices were also determined based on whether the participant smoked more than once per day. Drinking habits were determined based on whether the frequency of consumption was more than once per week.

The body height, weight, and WC were measured according to the standard protocol. Before measurements were taken, the subjects were asked to remove their hats, coats, and shoes. WC was measured on the ligature's midpoint level between the twelfth rib's inferior margin with anterior superior spine. BMI was calculated as body weight/height^2 (kg/m^2). Blood pressure (BP) was calculated based on three sequential measurements with 1-min intervals each. The three values of systolic BP (SBP) and diastolic BP (DBP) were averaged for analysis. All subjects had specific biochemical parameters assessed, including aspartate transaminase (AST), alanine transaminase (ALT), serum creatinine (Scr), Haemoglobin A1c (HbA1c), fasting blood glucose (FBG), 2 h post-load blood glucose (PBG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein
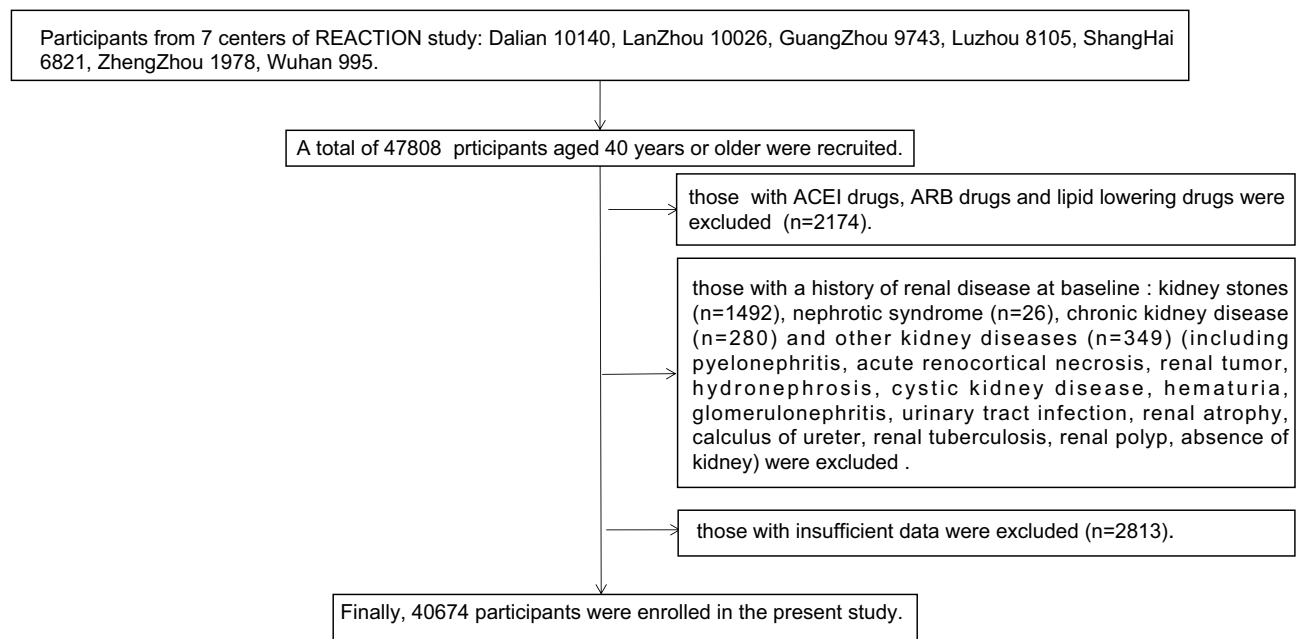
Participants from 7 centers of REACTION study: Dalian 10140, LanZhou 10026, GuangZhou 9743, Luzhou 8105, ShangHai 6821, ZhengZhou 1978, Wuhan 995.

A total of 47808 prticipants aged 40 years or older were recruited.

those with ACEI drugs, ARB drugs and lipid lowering drugs were excluded (n=2174).

those with a history of renal disease at baseline : kidney stones (n=1492), nephrotic syndrome (n=26), chronic kidney disease (n=280) and other kidney diseases (n=349) (including pyelonephritis, acute renocortical necrosis, renal tumor, hydronephrosis, cystic kidney disease, hematuria, glomerulonephritis, urinary tract infection, renal atrophy, calculus of ureter, renal tuberculosis, renal polyp, absence of kidney) were excluded .

those with insufficient data were excluded (n=2813).

Finally, 40674 participants were enrolled in the present study.

Figure 1 The flow chart describing the enrolment of the subjects in this study.
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.

cholesterol (HDL-C), total cholesterol (TC), and TG. Blood samples were collected by venipuncture, and the blood parameters were assessed by quality control procedures. Fasting blood samples were obtained from the subjects following an overnight fast (≥ 10 hours). The 75 g-OGTT or the 100 g-steamed-bread meal test was performed on all subjects regardless of their history of diabetes, and the venepuncture blood specimen was collected to measure PBG after 2 hours. The estimated glomerular filtration rate (eGFR, mL/min per 1.73 m^2) was calculated according to the following formula:

eGFR = 186 × [serum creatinine × 0.011]$^{-1.154}$ × [age]$^{-0.203}$ × [0.742 if female] × 1.233, where serum creatinine is presented as µmol/L. These values were calculated using the Modification of Diet in Renal Disease (MDRD), which was recalibrated for the population of China.[17]

Definition of Variables

According to the questionnaires provided to each participant, self-reported history of diabetes diagnosed by physicians was regarded as history of diabetes. Self-reported history of hypertension by physicians was regarded as history of hypertension. Urinary albumin and creatinine concentrations were tested by the first-void sterile urine samples in the early morning. The UACR was defined as the ratio of the urine albumin concentration to the urinary creatinine concentration. The UACR data were defined as

categorical variables, which were separated into two groups: UACR $\geq$ 30 mg/g or UACR < 30 mg/g. Normal WC was defined as <85 cm for women and <90 cm for men; the normal TG was defined as <1.5 mmol/L for women and <2.0 mmol/L for men. Based on these cut-off values, subjects were separated into the following four groups: normal waist-normal triglycerides (NWNT), normal waist-elevated triglycerides (HTG), enlarged waist-normal triglycerides (EW), and HTGW with elevated triglycerides-enlarged waist.[5]

Statistical Analyses

All statistical analyses were conducted with SPSS version 24.0 (IBM, Chicago, IL, USA). One-way analysis of variance was used to compare the differences among the continuous variables of the four phenotypes. The least significant difference was used as the multiple comparison test, and continuous variables were expressed as means ± standard deviations (SD). The continuous variables that were not normally distributed were expressed as medians (Inter-Quartile Range, IQR). Categorical variables were described as percentages (%). Logistic regression analyses were carried out to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) to explore the associations of the HTGW phenotype with UACR. All analyses were performed by sex. Model 1 was the unadjusted model. Model 2 was adjusted for age, centres, and sex. Model 3

was further adjusted for educational status, smoking habits, drinking habits, and CVD history based on Model 2. Model 4 was further adjusted for diabetes history, hypertension history, and diabetes or hypertension drug usage status. Model 5 was further adjusted for BMI, eGFR, HDL-C, LDL-C, TC, AST, ALT, FBG, PBG, SBP, and DBP. After controlling potential confounders, the relationship between UACR and the HTGW phenotype was also explored within subgroups, which were stratified based on blood pressure (Normal BP: SBP < 120 and DBP < 80 mmHg; Prehypertension: DBP ≥ 80 to < 90 or SBP ≥ 120 to < 140 mmHg; Hypertension: DBP ≥ 90 or SBP ≥ 140 mmHg); blood glucose (Diabetes: FBG ≥ 7.0 or 2-h PBG ≥ 11.1 mmol/L, Prediabetes: FBG ≥ 5.6 to < 7.0 or PBG ≥ 7.8 to < 11.1, mmol/L; Normal: FBG < 5.6 and PBG < 7.8, mmol/L); BMI (Obese: BMI ≥ 28 kg/m^2; General overweight: BMI ≥ 24 to < 28, kg/m^2; Normal weight BMI ≥ 18.5 to <24, kg/m^2; Underweight: BMI < 18.5 kg/m^2); eGFR (eGFR < 60, mL/min per 1.73 m^2; eGFR ≥ 60 to < 90, mL/min per 1.73 m^2; eGFR ≥ 90 mL/min per 1.73 m^2); and age (age < 55 years; age ≥ 55 to ≤ 64; age ≥ 65 years). Analyses of the interactions between the HTGW phenotype and the stratified variables were examined among populations with increased risk of UACR. Two-tailed P < 0.05 were considered to be statistically significant.

Results
Clinical Characteristics of the Study Participants

Ultimately, 40,674 participants (28,562 women and 12,112 men) were recruited. Table 1 shows the clinical and biochemical characteristics of the respective four subject groups. The mean age of the HTGW group was 60.08 ± 9.17 years. Compared with the other three groups, individuals in the HTGW group had higher prevalence of diabetes (NWNT: 6.9%; HTG: 9.3%; EW: 11.6%; HTGW: 15.2%, P < 0.001), hypertension (NWNT: 10.6%; HTG: 17.7%; EW: 21.4%; HTGW: 29.9%, P < 0.001), MI (NWNT: 0.2%; HTG: 0.2%; EW: 0.5%; HTGW: 0.5%, P < 0.001), CHD (NWNT: 2.4%; HTG: 2.8%; EW: 4.4%; HTGW: 5.5%, P < 0.001), and stroke (NWNT: 0.7%; HTG: 0.9%; EW: 1.4%; HTGW: 1.6%, P < 0.001). Additionally, the HTGW group was characterised by higher BMI, LDL-C, AST, ALT, FBG, PBG, SBP, and DBP values, while their eGFR values were lower (P < 0.001).

Association Between UACR and the HTGW Phenotype

Logistic regression analyses were applied to explore the relationship between the HTGW phenotype and UACR after adjusting for confounders. As shown in Table 2, the HTGW and HTG groups showed significant associations with UACR using models 1–5; Table 3 shows an association of the HTGW phenotype with UACR in the respective genders after adjusting for confounders. Furthermore, compared with the other three groups, only the HTGW group was significantly associated with UACR in both sexes after adjusting for confounding factors (OR: 1.303, 95% CI: 1.132–1.499, P < 0.001 in all subjects; OR: 1.268, 95% CI: 1.074–1.496, P = 0.005 in women; OR: 1.406, 95% CI: 1.057–1.870, P = 0.019 in men) (Tables 2 and 3). The association between the HTG phenotype and UACR was significant (OR: 1.182, 95% CI: 1.016–1.376, P = 0.030; Table 3); however, the association between HTG and UACR disappeared in men.

Association Between the HTGW Phenotype and UACR Among Subgroups

To further verify whether the association between UACR and the HTGW was robust, stratified analyses of blood glucose and BP were conducted. As shown in Table 4, among participants aged below 65 years, the HTGW group had a remarkably significant relationship with UACR (age < 55: OR = 1.407, 95% CI = 1.094–1.809, P = 0.008; 55 ≤ age ≤ 64: OR = 1.338, 95% CI = 1.061–1.686, P = 0.014). As for the blood glucose level, a significant association between HTGW and UACR was observed in subjects with prediabetes (5.6 ≤ FBG < 7.0 or 7.8 ≤ PBG < 11.1 mmol/L, OR: 1.425, 95% CI: 1.124–1.808, P = 0.004). A significant result was also found in the HTG group with prediabetes (OR: 1.243, 95% CI: 1.001–1.543, P= 0.049). Additionally, for blood pressure and BMI, similar and significant results were observed in the HTGW group with high-normal BP (120 ≤ SBP < 140 and/or 80 ≤ DBP < 90 mmHg, OR: 1.268, 95% CI: 1.038–1.549, P = 0.020) and overweight (24 ≤ BMI < 28 kg/m^2, OR: 1.268, 95% CI: 1.008–1.595, P = 0.043). Meanwhile, a significant relationship was observed between the HTGW and UACR groups when eGFR ≥ 90 mL/min per 1.73 m^2 (OR: 1.199, 95% CI: 1.047–1.484, P=0.009). A significant interaction between blood glucose and the HTGW phenotype can be seen in Table 4 (P =0.002). To analyse the effect of FBG and PBG on the interaction, the prediabetic subjects were divided into the impaired fasting glucose group (IFG)

Table 1 Baseline Characteristics Based on the Hypertriglyceridemic Waist Phenotype

Variable	NWNT (n=15,250)	HTG (n=6077)	EW (n=10,488)	HTGW (n=8859)	P value
Age, years	56.53±9.13	57.08±8.16	59.63±9.60	60.08±9.17	<0.001[a,b,c,d,e,f]
Male sex, no. (%)	5147(42.5)	1169(9.7)	3825(31.6)	1971(16.3)	<0.001[a,b,c,d,e,f]
Female sex, no. (%)	10,103(35.4)	4908(17.2)	6663(23.3)	6888(24.1)	<0.001[a,b,c,d,e,f]
Waist circumference, cm	77.65±6.36	79.50±5.17	93.82±6.61	94.02±6.95	<0.001[a,b,c,d,e]
Triglycerides, mmol/L	1.00(0.11–1.99)	2.14(1.50–15.93)	1.13(0.23–1.99)	2.26(1.50–15.90)	<0.001[a,b,c,d,e,f]
Body mass index, kg/m2	22.25±2.89	23.20±2.75	26.32±3.25	27.01±3.35	<0.001[a,b,c,d,e,f]
Total cholesterol, mmol/L	4.76±1.12	5.44±1.14	4.87±1.10	5.41±1.10	<0.001[a,b,c,d,f]
LDL-C, mmol/L	2.80±0.88	3.09±0.94	2.98±0.88	3.10±0.91	<0.001[a,b,c,d,f]
HDL-C, mmol/L	1.41±0.37	1.25±0.30	1.32±0.34	1.20±0.26	<0.001[a,b,c,d,e,f]
UACR, mg/g	8.89(5.44–16.64)	11.20(6.53–21.29)	9.47(5.52–18.68)	12.26(6.73–24.53)	<0.001[c,e,f]
ALT, U/L	15.48±0.11	18.61±0.18	18.47±0.15	21.94±0.19	<0.001[a,b,c,e,f]
AST, U/L	20.67±0.10	22.86±0.19	21.84±0.12	24.09±0.13	<0.001[a,b,c,d,e,f]
SBP, mmHg	124.29±0.16	128.63±0.26	135.65±0.21	138.37±0.22	<0.001[a,b,c,d,e,f]
DBP, mmHg	74.26±0.09	76.79±0.14	78.54±0.11	80.23±0.12	<0.001[a,b,c,d,e,f]
Resting heart rate, (beat/min)	78.36±0.10	80.33±0.16	77.99±0.12	80.10±0.13	<0.001[a,b,c,d,f]
FBG, mmol/L	5.64±1.43	5.97±1.70	6.01±1.62	6.43±2.10	<0.001[a,b,c,e,f]
PBG, mmol/L	7.63±3.44	8.83±3.82	8.56±3.95	9.89±4.38	<0.001[a,b,c,d,e,f]
eGFR, mL/min per 1.73m^2	124.31±27.12	115.37±20.41	122.46±26.41	113.71±21.76	<0.001[a,c,d,e,f]
Married, %	88.8%	87.4%	88.7%	85.7%	<0.001
High-school education, %	53.3%	51.1%	45.6%	40.6%	<0.001
Current smoker, %	13.0%	9.2%	12.8%	10.1%	<0.001
Past smoker, %	11.5%	7.1%	13.2%	8.7%	<0.001
Current alcohol drinker, %	6.4%	4.3%	8.4%	5.7%	<0.001
Past alcohol drinker, %	4.8%	3.0%	6.3%	4.2%	<0.001
History of hypertension, %	10.6%	17.7%	21.4%	29.9%	<0.001
History of diabetes, %	6.9%	9.3%	11.6%	15.2%	<0.001
Previous MI, %	0.2%	0.2%	0.5%	0.5%	<0.001
Previous stroke, %	0.7%	0.9%	1.4%	1.6%	<0.001
Previous CHD, %	2.4%	2.8%	4.4%	5.5%	<0.001
Taking diabetic drugs, %	5.8%	8.0%	10.1%	13.0%	<0.001
Taking hypertension drugs, %	1.4%	2.2%	2.1%	2.8%	<0.001

Notes: Data were mean ± SD or median (IQR) for skewed variables or numbers (proportions) for categorical variables: [a, b, c, d, e, f]P < 0.05 for G2 vs G1, G3 vs G1, G4 vs G1, G3 vs G2, G4 vs G2, and G4 vs G3, respectively. G1: NWNT; G2: HTG; G3: EW; G4: HTGW.
Abbreviations: NWNT, normal waist and normal triglyceride; HTG, normal waist with hypertriglyceridemia; EW, enlarged waist circumference; HTGW, hypertriglyceridemic waist; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; eGFR: estimated glomerular filtration rate; MI, myocardial infarction; CHD, coronary heart disease; ALT, alanine aminotransferase; AST, aspartate aminotransferase; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; PBG, 2 h post-load blood glucose; UACR, urinary albumin-creatinine ratio.

(FBG [5.6, 7.0], PBG [0, 7.8], mmol/L) and the impaired glucose tolerance group (IGT) (FBG [0, 7.0], FBG [7.8, 11.1], mmol/L), as seen in Table 5. The association between UACR and HTGW was also significant in the IFG group (OR: 1.407, 95% CI: 1.020–1.941, P = 0.037).

Discussion

Herein, we found that the HTGW phenotype exhibited the most significant association with increased UACR risk, which was nearly 1.92- to 2.23-fold in all participants. In fact, only the association between UACR and the HTGW phenotype retained significance after controlling for confounding factors

in males. For females, increased UACR was observed in both the HTGW and the HTG groups; however, the association with UACR was more significant for the HTGW group. Furthermore, the risk of UACR was significantly increased in the HTGW group aged less than 65 years, with eGFR ≥ 90 mL/min per 1.73 m^2, prediabetes, prehypertension, or borderline values of BMI. Therefore, these results may possibly be proved useful and significative for monitoring populations more likely to benefit from the avoidance and amelioration of the associated factors such as TG and WC. Here, we also first verified a noteworthy association between UACR and the HTGW phenotype.

Table 2 Odds Ratios (95% Confidence Interval) for UACR by HTGW Phenotype Among All Subjects

	NWNT (n=15,250)	HTG (n=6077)	EW (n=10,488)	HTGW (n=8859)
Model 1				
OR(95% CI)	Reference	1.550(1.420–1.693)*	1.344(1.244–1.452)*	2.068(1.920–2.229)*
P value		<0.001	<0.001	<0.001
Model 2				
OR(95% CI)	Reference	1.417(1.308–1.534)*	1.259(1.150–1.378)*	1.830(1.694–1.978)*
P value		<0.001	<0.001	<0.001
Model 3				
OR(95% CI)	Reference	1.395(1.287–1.512)*	1.142(1.133–1.362)*	1.787(1.652–1.933)*
P value		<0.001	<0.001	<0.001
Model 4				
OR(95% CI)	Reference	1.277(1.145–1.424)*	1.110(0.983–1.252)	1.498(1.349–1.665)*
P value		<0.001	0.137	<0.001
Model 5				
OR(95% CI)	Reference	1.243(1.096–1.410)*	1.026(0.898–1.172)	1.303(1.132–1.499)*
P value		<0.001	0.704	<0.001

Notes: *Significant data (P<0.05): Model 1: unadjusted; Model 2: adjusted for age, sex, centres; Model 3: further adjusted for education status, smoking habits, drinking habits, CVD status; Model 4: further adjusted for diabetes history, hypertension history, use of diabetes or hypertension drugs status; Model 5: further adjusted for BMI, eGFR, HDL-C, LDL-C, TC, AST, ALT, FBG, PBG, SBP, DBP.
Abbreviations: NWNT, normal waist and normal triglyceride; HTG, normal waist with hypertriglyceridemia; EW, enlarged waist circumference; HTGW, hypertriglyceridemic waist; UACR, urinary albumin-creatinine ratio.

The association between HTGW phenotype and UACR may be attributable to visceral obesity; however, the underlying mechanism is unclear. In previous studies, the HTGW phenotype was reported to be remarkably associated with visceral obesity, and it was suggested that the combined presence of TG and WC may serve as the optimal indicator for CVD risk among menopausal women.[4] Moreover, it is well established that abdominal adipose tissue serves as an endocrine organ that produces various bioactive substances, affecting the body's metabolic status.[18] The accumulation of fat is likely to be an essential risk factor for kidney injury, and increases in WC and TG indicate accumulation of fat in abdominal adipose tissue. There were other visceral adiposity indices also exploiting WC and TG, such as visceral adiposity index (VAI) and the lipid accumulation product index (LAPI), and it was reported that VAI level is associated with elevated urine albumin excretion and renal dysfunction.[19] The results of this study were consistent with our present findings. In addition, some previous studies showed that prevalence of CKD is significantly associated with both VAI and LAPI.[20,21] Excess fat can indirectly induce kidney damage by increasing the prevalence of atherosclerosis, hypertension, or type 2 diabetes.[22,23] Furthermore, excess fat can directly exacerbate kidney

injury via the inflammatory response, which produces adipokines such as TNF-α and IL-6 leading to change in renal hemodynamics. These changes include an increased demand for renal metabolism and dilation of mesangium, leading to the development of glomerular hypertrophy, excessive filtration, and hypertension. Increased glomerular filtration rates eventually cause proteinuria and glomerulosclerosis.[24–26] Besides, the production of adipokine leptin is also increased, which can subsequently increase the activity of the sympathetic nervous system and the degree of oxidative stress, ultimately leading to glomerulosclerosis, renal fibrosis, and proteinuria.[27]

As seen in Tables 2 and 3, we also determined that the association with UACR was significant in women in Model 5 when the TG level increased, as well as with the HTGW phenotype, a combination of increased WC and TG, had the most significant association with UACR. In men, a significant association was only found between UACR and the HTGW phenotype, which is consistent with previous studies. We showed that especially in postmenopausal women, excessive lipid accumulation, such as hypertriglyceridemia, increased the risk of CVD.[28–30] Increased WC and elevated TG also had a significant cumulative effect on cardiovascular risk.[31,32]

Table 3 Odds Ratios (95% Confidence Interval) for UACR by HTGW Phenotype Among Men and Women

Phenotype groups	Model 1 OR(95% CI)	P value	Model 2 OR(95% CI)	P value	Model 3 OR(95% CI)	P value	Model 4 OR(95% CI)	P value	Model 5 OR(95% CI)	P value
Men										
NWNT(5147)	Reference		Reference		Reference		Reference		Reference	
HTG(1169)	1.537(1.235–1.913)*	0.047	1.524(1.217–1.909)*	<0.001	1.371(1.114–1.688)*	0.044	1.338(1.083–1.652)*	0.007	1.272(0.986–1.639)	0.064
EW(3825)	1.499(1.284–1.750)*	<0.001	1.412(1.204–1.655)*	<0.001	1.342(1.007–1.786)*	<0.001	1.291(0.964–1.730)	0.087	1.292(0.945–1.767)	0.108
HTGW(1971)	2.111(1.810–2.463)*	<0.001	2.011(1.714–2.359)*	<0.001	1.663(1.352–2.045)*	<0.001	1.576(1.274–1.948)*	<0.001	1.406(1.057–1.870)*	0.019
Women										
NWNT(10,103)	Reference		Reference		Reference		Reference		Reference	
HTG(4908)	1.587(1.437–1.753)*	<0.001	1.410(1.283–1.548)*	<0.001	1.395(1.268–1.533)*	<0.001	1.276(1.120–1.453)*	<0.001	1.182(1.016–1.376)*	0.030
EW(6663)	1.315(1.196–1.445)*	<0.001	1.209(1.094–1.336)*	<0.001	1.195(1.079–1.322)*	0.001	1.076(0.941–1.231)	0.284	1.020(0.878–1.186)	0.793
HTGW(6888)	2.073(1.901–2.262)*	<0.001	1.724(1.574–1.888)*	<0.001	1.676(1.529–1.838)*	<0.001	1.459(1.289–1.653)*	<0.001	1.268(1.074–1.496)*	0.005

Notes: *Significant data (P<0.05): Model 1: unadjusted; Model 2: adjusted for age, centres; Model 3: further adjusted for education status, smoking habits, drinking habits, CVD status; Model 4: further adjusted for diabetes history, hypertension history, use diabetes or hypertension drugs status; Model 5: further adjusted for BMI, eGFR, HDL-C, LDL-C, TC, AST, ALT, FBG, PBG, SBP, DBP.
Abbreviations: NWNT, normal waist and normal triglyceride; HTG, normal waist with hypertriglyceridemia; EW, enlarged waist circumference; HTGW, hypertriglyceridemic waist; UACR, urinary albumin-creatinine ratio.

Further, a study among Asian adults showed that CVD was independently associated with high level of albuminuria.[33] These differing results of gender may be partially explained by the difference in the sample ratio of gender. Nevertheless, in the present study, we were unable to identify the actual mechanisms of gender difference. Therefore, possible mechanisms with regard to gender-specific associations of the HTGW phenotype with UACR need to be further explored.

It is interesting to find that the association of HTGW phenotype with UACR in borderline subgroups compared with the two other subgroups was significant, as shown in Table 4. The possible reason, at least in part, might be due to the populations of old age, hypertension, obese and

diabetes possibly had better compliance with medical orders, had more time to exercise, and dietary habits may also improve. Some studies showed that physical activities reduced inflammation which played a key role in the loss of renal function[34,35] and the relationship between HTGW and UACR may attenuate in the abnormal subgroups. Moreover, interaction between HTGW and potential confounders among the UACR group was analysed in the present study. The interaction between the HTGW phenotype and blood glucose was significant. The present result indicated that among the prediabetic population, FBG is more closely related to HTGW and UACR. A Mexican study, whose results were consistent with the findings of our study, suggested that kidney dysfunction was worsened among people with high TG levels, in those with increased WC, and in those who smoke, as well as, most notably, in people with diabetic diseases.[22] Moreover, evidence showed that the glucose abnormality and the functional impairment of β-cell were both caused by the overloaded islets TG content.[36] Furthermore, another study indicated that visceral adiposity was significantly associated with IFG, and isolated IFG had been shown to lead to hepatic IR.[37] Because patients may have undiagnosed IFG for an extended period of time, asymptomatic complications such as diabetic nephropathy can eventually develop.[38] Therefore, the findings of the present study may offer proof for prevention of early diabetic nephropathy via the improvement of the HTGW phenotype.

Our study provides additional evidence for the association between HTGW and UACR in a different population. However, several limitations of this study need to be considered. First, since this research population only included populations over the age of 40 years, our findings may not be applicable to younger individuals. Furthermore, the gender ratio is skewed; thus, the associations obtained in this study should be considered with caution. Second, the selected population excluded those who used lipid lowering and ACEI/ARB drugs but did not exclude the population using other drugs that may affect the association. Therefore, we cannot be certain how the use of other drugs may have affected the results of this study. Third, a limitation to the HTGW phenotype is its dichotomous nature of representation. With cut-off points originated from western populations and not validated in China, using the same cut-off points for HTGW in a Chinese population is a limitation. Finally, due to the cross-sectional nature of the current study, the causal association of UACR and the HTGW phenotype was

Table 4 The Association of the HTGW Phenotype with UACR in Different Subgroups of Age, Blood Glucose and Blood Pressure

Variable	NWNT HTG EW HTGW				P-values
	Reference	OR(95% CI) P value	OR(95% CI) P value	OR(95% CI) P value	For Interaction
Age, year [a]					0.127
<55 (n=15,704)	I	1.260(0.974–1.629) 0.079	1.007(0.790–1.284) 0.954	1.407(1.094–1.809)* 0.008	
55–64 (n=15,264)	I	1.197(0.970–1.476) 0.093	0.938(0.759–1.158) 0.552	1.338(1.061–1.686)* 0.014	
≥65 (n=9706)	I	0.972(0.781–1.210) 0.800	1.208(0.927–1.574) 0.163	1.086(0.836–1.411) 0.536	
Blood glucose, mmol/L [b]					0.002
FBG<5.6 and PBG<7.8 (n=16,035)	I	1.145(0.943–1.390) 0.173	1.038(0.846–1.273) 0.722	1.217 (0.992–1.492) 0.059	
5.6≤FBG<7.0 or 7.8≤PBG<11.1 (n=16,107)	I	1.243(1.001–1.543)* 0.049	1.153(0.923–1.441) 0.209	1.425(1.124–1.808)* 0.004	
FBG≥7.0 or PBG≥11.1 (n=8532)	I	1.017(0.858–1.206) 0.845	1.193(0.988–1.440) 0.067	1.146(0.922–1.407) 0.193	
BP, mmHg [c]					0.234
SBP<120 and DBP<80 (n=13,190)	I	1.236(0.896–1.705) 0.197	0.954(0.714–1.276) 0.751	1.299(0.960–1.756) 0.090	
120≤SBP<140 and/or 80≤DBP<90 (n=15,384)	I	1.128(0.956–1.331) 0.152	1.153(0.960–1.385) 0.127	1.268(1.038–1.549)* 0.020	
SBP≥140 or DBP≥90 (n=12,100)	I	1.048(0.875–1.255) 0.613	1.097(0.890–1.352) 0.388	1.170(0.941–1.456) 0.158	
eGFR, mL/min per 1.73m^2 [d]					0.183
eGFR≥90 (n=37,617)	I	1.108(0.952–1.290) 0.186	1.079(0.932–1.249) 0.311	1.199(1.047–1.484)* 0.009	
60≤eGFR<90 (n=2808)	I	1.253(0.796–1.974) 0.330	1.242(0.831–1.858) 0.291	1.337(0.910–1.946) 0.139	
eGFR<60 (249)	I	0.988(0.617–1.583) 0.961	1.110(0.735–1.678) 0.619	1.131(0.759–1.685) 0.546	
BMI, kg/m^2 [e]					0.136
BMI<18.5 (n=1117)	I	1.305(0.961–1.772) 0.088	0.952(0.747–1.215) 0.695	1.247(0.965–1.610) 0.091	
18.5≤BMI<24 (n=18,097)	I	1.107(0.806–1.519) 0.530	1.007(0.783–1.296) 0.956	1.074(0.842–1.399) 0.598	
24≤BMI<28 (n=15,669)	I	1.002(0.833–1.206) 0.981	1.170(0.948–1.444) 0.143	1.268(1.008–1.595)* 0.043	
BMI≥28 (n=5791)	I	1.019(0.779–1.335) 0.889	0.964(0.746–1.246) 0.779	1.086(0.787–1.499) 0.615	

Notes: *Significant data (P<0.05): [a]For age subgroup: adjusted for sex, centres, ALT, AST, LDL-C, HDL-C, TC, PBG, PBG, SBP, DBP, eGFR, BMI, smoking habits, drinking habits, CVD status, hypertension history, diabetes history, use diabetes drugs and hypertension drugs status: [b]For blood glucose subgroup: adjusted for age, sex, centres, ALT, AST, LDL-C, HDL-C, TC, SBP, DBP, eGFR, BMI, smoking habits, drinking habits, CVD status, hypertension history, use hypertension drugs status: [c]For blood pressure subgroup: adjusted for age, sex, centres, ALT, AST, LDL-C, HDL-C, TC, FBG, PBG, eGFR, BMI, smoking habits, drinking habits, CVD status, diabetes history, use diabetes drugs status: [d]For eGFR subgroup: adjusted for age, sex, centres, ALT, AST, LDL-C, HDL-C, TC, FBG, PBG, SBP, DBP, BMI, smoking habits, drinking habits, CVD status, hypertension history, diabetes history, use diabetes drugs and hypertension drugs status: [e]For BMI subgroup: adjusted for age, sex, centres, ALT, AST, LDL-C, HDL-C, TC, FBG, PBG, eGFR, SBP, DBP, smoking habits, drinking habits, CVD status, hypertension history, diabetes history, use diabetes drugs and hypertension drugs status.
Abbreviations: NWNT, normal waist and normal triglyceride; HTG, normal waist with hypertriglyceridemia; EW, enlarged waist circumference; HTGW, hypertriglyceridemic waist; UACR, urinary albumin-creatinine ratio; FPG, fasting plasma glucose; PPG, postprandial plasma glucose; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure.

Table 5 The Association of the HTGW Phenotype with UACR in Different Subgroups of Prediabetes

Variable NWNT HTG EW HTGW
Reference OR(95%CI) P value OR(95%CI) P value OR(95%CI) P value
IFG (n=6133)
5.6≤FBG<7.0 and I 1.099(0.830–1.456) 0.511 1.012(0.742–1.380) 0.941 1.407 (1.020–1.941)* 0.037
PBG<7.8
IGT (n=9974)
FBG<7.0 and I 0.909(0.750–1.101) 0.329 1.019(0.833–1.247) 0.854 0.878 (0.707–1.091) 0.241
7.8≤PBG<11.1

Notes: *Significant data (P<0.05): Adjusted for age, sex, centres, ALT, AST, LDL-C, HDL-C, TC, SBP, DBP, eGFR, BMI, smoking habits, drinking habits, CVD status, hypertension history, use hypertension drugs status.
Abbreviations: NWNT, normal waist and normal triglyceride; HTG, normal waist with hypertriglyceridemia; EW, enlarged waist circumference; HTGW, hypertriglyceridemic waist; UACR, urinary albumin-creatinine ratio.

undetermined, and prospective studies are surely needed to prove whether the HTGW phenotype could predict increased UACR.

Conclusion

In conclusion, we found a noticeable association between the HTGW phenotype and UACR. When the population belonged to the HTGW group aged less than 65 years with eGFR ≥ 90 mL/min per 1.73 m^2, prediabetes, prehypertension, and a borderline BMI value, the risk for increase of UACR was more likely to be augmented. The present study may supply proofs to suggests that awareness of the HTGW phenotype should be increased, and the HTGW phenotype was associated with increased early renal dysfunction or chronic diseases such as CKD and

CVD. Further prospective epidemiological studies are needed to support the findings of our study.

Data Sharing Statement

All data used to support the findings of this study are available from the corresponding author upon request.

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Author Contributions

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Disclosure

The authors report no conflicts of interest in this work. This study was conducted in accordance with the Declaration of Helsinki.

References

1. Despres JP, Lemieux I, Bergeron J, et al. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. *Arterioscler Thromb Vasc Biol*. 2008;28(6):1039–1049. doi:10.1161/ATVBAHA.107.159228
2. Fujimoto WY, Bergstrom RW, Boyko EJ, et al. Visceral adiposity and incident coronary heart disease in Japanese-American men: the 10-year follow-up results of the seattle Japanese-American community diabetes study. *Diab Care*. 1999;22(11):1808–1812. doi:10.2337/diacare.22.11.1808
3. Nicklas BJ, Penninx BW, Ryan AS, et al. Visceral adipose tissue cutoffs associated with metabolic risk factors for coronary heart disease in women. *Diab Care*. 2003;26(5):1413–1420. doi:10.2337/diacare.26.5.1413
4. Tankó LB, Bagger YZ, Qin G, et al. Enlarged waist combined with elevated triglycerides is a strong predictor of accelerated atherogenesis and related cardiovascular mortality in postmenopausal women. *Circulation*. 2005;111(15):1883–1890. doi:10.1161/01.CIR.0000161801.65408.8D
5. Lemieux I, Pascot A, Couillard C, et al. Hypertriglyceridemic waist: a marker of the atherogenic metabolic triad (hyperinsulinemia; hyperapolipoprotein B; small, dense LDL) in men? *Circulation*. 2000;102(2):179–184. doi:10.1161/01.CIR.102.2.179
6. Sam S, Feinstein S, Haffner S, et al. Hypertriglyceridemic waist phenotype predicts increased visceral fat in subjects with type 2 diabetes. *Diab Care*. 2009;32(10):1916e20. doi:10.2337/dc09-0412
7. Zhao K, Yang SS, Wang HB, et al. Association between the hypertriglyceridemic waist phenotype and prediabetes in Chinese adults aged 40 years and older. *J Diab Res*. 2018;2018:1031939. doi:10.1155/2018/1031939
8. Chen S, Guo X, Yu S, et al. Hypertriglyceridemic waist phenotype and metabolic abnormalities in hypertensive adults: A STROBE compliant study. *Medicine*. 2016;95:49. doi:10.1097/MD.0000000000005613
9. Wang A, Li Z, Zhou Y, et al. Hypertriglyceridemic waist phenotype and risk of cardiovascular diseases in China: results from the Kailuan Study. *Int J Cardiol*. 2014;174(1):106–109. doi:10.1016/j.ijcard.2014.03.177
10. Arsenault BJ, Lemieux I, Despres JP, et al. The hypertriglyceridemic-waist phenotype and the risk of coronary artery disease: results from the EPIC-Norfolk prospective population study. *CMAJ*. 2010;182(13):1427–1432. doi:10.1503/cmaj.091276
11. Czernichow S, Bruckert E, Bertrais S, et al. Hypertriglyceridemic waist and 7.5-year prospective risk of cardiovascular disease in asymptomatic middle-aged men. *Int J Obes*. 2007;31(5):791–796. doi:10.1038/sj.ijo.0803477
12. Amadi CE, Mbakwem AC, Kushimo OA, et al. Prevalence of positive chronic kidney Disease screening in professional male long haul drivers at risk of cardiovascular Disease in Lagos, Nigeria: a cross-section study. *BMC Public Health*. 2019;19(1):1032. doi:10.1186/s12889-019-7328-6
13. J KW X, Devereux RB, Yeh J, et al. Albuminuria within the "normal" range and risk of cardiovascular disease and death in American Indians: the strong heart study. *Am J Kidney Dis*. 2007;49(2):208–216. doi:10.1053/j.ajkd.2006.10.017
14. Resnick HE, Lindsay RS, McDermott MM, et al. Relationship of high and low ankle brachial index to all-cause and cardiovascular disease mortality: the strong heart study. *Circulation*. 2004;109(6):733–739. doi:10.1161/01.CIR.0000112642.63927.54
15. Teixeira da Cunha França AK, Dos Santos AM, Salgado JV, et al. Usefulness of visceral adipose tissue estimation in the prevention of chronic kidney disease in hypertensive patients in primary health care. *Nutr Hosp*. 2018;35(4):948–956. doi:10.20960/nh.1534
16. Ning G. Risk Evaluation of cAncers in Chinese diabeTic Individuals: a lONgitudinal (REACTION) study. *J Diab*. 2012;4(2):172–173. doi:10.1111/j.1753-0407.2012.00182.x

17. Ma YC, Zuo L, Chen JH, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. *J Am Soc Nephrol*. 2006;17(10):2937–2944. doi:10.1681/ASN.2006040368

18. Fortuño ARA, Gómez-Ambrosi J, Frühbeck G, et al. Adipose tissue as an endocrine organ: role of leptin and adiponectin in the pathogenesis of cardiovascular diseases. *J Physiol Biochem*. 2003;59(1):51–60. doi:10.1007/BF03179868

19. Sun K, Lin D, Feng L, et al. Visceral adiposity index is associated with increased urinary albumin excretion: a population-based study. *Clin Nutr*. 2019;38(3):1332–1338. doi:10.1016/j.clnu.2018.05.025

20. Xiao H, Xiong C, Xiaofei S, et al. Visceral adiposity index and Chronic kidney disease in a non-diabetic population: a cross-sectional study. *Diab Metab Syndr Obes*. 2020;13:257–265. doi:10.2147/DMSO.S231656

21. Dai D, Chang Y, Yintao C, et al. Visceral adiposity index and lipid accumulation product index: two alternate body indices to identify chronic kidney disease among the rural population in Northeast China. *Int J Environ Res Public Health*. 2016;13(12):1231. doi:10.3390/ijerph13121231

22. Stenvinkel PZC, Ikizler TA. Obesity in CKD: what should nephrologists know? *J Am Soc Nephrol*. 2013;24:1727–1736. doi:10.1681/ASN.2013040330

23. Wanner CJK. Kidneys do not like excess body fat. *Lancet Diab Endocrinol*. 2015;3:669–671. doi:10.1016/S2213-8587(15)00235-1

24. Mallamaci F, Tripepi G. Obesity and CKD progression: hard facts on fat CKD patients. *Nephrol Dial Transplant*. 2013;28:iv105–108. doi:10.1093/ndt/gft391

25. Spoto B, Zoccali C. Spleen IL-10, a key player in obesity-driven renal risk. *Nephrol Dial Transplant*. 2013;28(5):1061–1064. doi:10.1093/ndt/gft094

26. Stenvinkel P, Ketteler M, Johnson RJ, et al. IL-10, IL-6, and TNF-alpha: central factors in the altered cytokine network of uremia–the good, the bad, and the ugly. *Kidney Int*. 2005;67(4):1216–1233. doi:10.1111/j.1523-1755.2005.00200.x

27. Wolf G, Ziyadeh FN. Leptin and renal fibrosis. *Contrib Nephrol*. 2006;151:175–183.

28. Tanko LB, Bagger YZ, Alexandersen P, et al. Peripheral adiposity exhibits an independent dominant antiatherogenic effect in elderly women. *Circulation*. 2003;107(12):1626–1631. doi:10.1161/01.CIR.0000057974.74060.68

29. Howard BV, Criqui MH, Curb JD, et al. Risk factor clustering in the insulin resistance syndrome and its relationship to cardiovascular disease in postmenopausal white, black, hispanic, and Asian/Pacific Islander women. *Metabolism*. 2003;52(3):362–371. doi:10.1053/meta.2003.50057

30. Bass KMNC, Klag MJ, Bush TL. Plasma lipoprotein levels as predictors of cardiovascular death in women. *Arch Intern Med*. 1993;153:2209–2216. doi:10.1001/archinte.1993.00410190045006

31. Kahn HS, Valdez R. Metabolic risks identified by the combination of enlarged waist and elevated triacylglycerol concentration. *Am J Clin Nutr*. 2003;78(5):928–934. doi:10.1093/ajcn/78.5.928

32. Cheal KL, Abbasi F, Lamendola C, et al. Relationship to insulin resistance of the adult treatment panel III diagnostic criteria for identification of the metabolic syndrome. *Diabetes*. 2004;53(5):1195–1200. doi:10.2337/diabetes.53.5.1195

33. Lim CC, Teo BW, Ong PG, et al. Chronic kidney disease, cardiovascular disease and mortality: A prospective cohort study in a multi-ethnic Asian population. *Eur J Prev Cardiol*. 2015;22(8):1018–1026. doi:10.1177/2047487314536873

34. King DE, Carek P, Mainous III AG, et al. Inflammatory markers and exercise: differences related to exercise type. *Med Sci Sports Exerc*. 2003;35(4):575–581. doi:10.1249/01.MSS.0000058440.28108.CC

35. AbramsonandV.Vaccarino JL. Relationship between physical activity and inflammation among apparently healthy middle-aged and older US adults. *JAMA Intern Cine*. 2002;162(11):1286–1292. doi:10.1001/archinte.162.11.1286

36. Unger RH. Lipotoxicity in the pathogenesis of obesity-dependent NIDDM. Genetic and clinical implications. *Diabetes*. 1995;44(8):780863. doi:10.2337/diab.44.8.863

37. Elizalde-Barrera CI, Rubio-Guerra AF, Lozano-Nuevo JJ, et al. Triglycerides and waist to height ratio are more accurate than visceral adiposity and body adiposity index to predict impaired fasting glucose. *Diab Res Clin Pract*. 2019;153:49–54. doi:10.1016/j.diabres.2019.05.019

38. de Simone G, Wang W, Best LG, et al. Target organ damage and incident type 2 diabetes mellitus: the strong heart study. *Cardiovasc Diabetol*. 2017;16(1):64. doi:10.1186/s12933-017-0542-6