Hypertriglyceridemic-Waist Phenotype and Risk of Type 2 Diabetes: A Prospective Cohort Study Postprint

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Abstract

Background: Hypertriglyceridemic-waist phenotype is a risk factor for type 2 diabetes mellitus (T2DM), and the risk of T2DM onset may vary among different genders, regions, age groups, and overweight/obese populations.

Objective: To investigate the risk of T2DM onset associated with hypertriglyceridemic-waist phenotype in different genders, regions, age groups, and overweight/obese populations, and to provide a scientific basis for diabetes prevention and control.

Methods: This study was a prospective cohort study. In 2010, a stratified cluster random sampling method was used to conduct a baseline survey of 9,280 permanent residents aged 18 years and above in 12 counties (cities, districts) of Guizhou Province as the cohort population. Follow-up was conducted from 2016 to 2020, and 8,163 individuals were followed up. After excluding those with diabetes at baseline, those with missing relevant indicator information, those lost to follow-up, and those who died, 6,743 subjects were finally included. According to baseline waist circumference (WC) and serum triglyceride (TG) levels, the subjects were divided into 4 groups: normal waist circumference and normal serum triglycerides (NWNT) group: male WC <90 cm or female WC <85 cm, serum TG <1.7 mmol/L; normal waist circumference and high serum triglycerides (NWHT) group: male WC <90 cm or female WC <85 cm, serum TG $ $1.7 mmol/L; enlarged waist circumference and normal serum triglycerides (EWNT) group: male WC $ $90 cm or female WC $ $85 cm, serum TG <1.7 mmol/L; enlarged waist circumference and high serum triglycerides (EWHT) group: male WC $ $90 cm or female WC $ $85 cm, serum TG $ $1.7 mmol/L. Cox proportional hazards regression models were used to analyze the relationship between hypertriglyceridemic-waist phenotype groups and incident T2DM.

Results: The median follow-up time was 6.58 years. Among the 6,743 individuals, 706 developed new-onset T2DM, with an incidence rate of 10.47%. After adjusting for relevant confounding factors, Cox proportional hazards regression analysis showed that the risk of T2DM onset in the EWHT group was 1.486 times that of the NWNT group (HR=1.486, 95%CI=1.185-1.865, P=0.001). Subgroup multifactorial Cox proportional hazards regression analysis showed that in males, rural areas, age <45 years, and overweight/obese populations, the risk of T2DM onset in the EWHT group was 1.792 times (HR=1.792, 95%CI=1.297-2.476, P<0.001), 1.483 times (HR=1.483, 95%CI=1.115-1.971, P=0.007), 1.540 times (HR=1.540, 95%CI=1.083-2.190, P=0.016), and 1.614 times (HR=1.614, 95%CI=1.123-2.321, P=0.010) that of the NWNT group, respectively.

Conclusion: After a median follow-up of 6.58 years in a large sample population, hypertriglyceridemic-waist phenotype is a risk factor for T2DM onset in Guizhou Province, which is more pronounced in males, rural areas, age <45 years, and overweight/obese populations. Therefore, health education should be strengthened for these populations, and controlling body weight and reducing serum triglyceride levels through reasonable diet and appropriate exercise are necessary and effective methods for preventing T2DM onset.

Full Text

Hypertriglyceridemic-Waist Phenotype and the Risk of Type 2 Diabetes Mellitus: A Prospective Cohort Study

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Abstract

Background: Hypertriglyceridemic-waist phenotype is a risk factor for type 2 diabetes mellitus (T2DM), though the risk may vary across different genders, regions, age groups, and overweight/obese populations. **Objective:** To explore the risk of T2DM associated with hypertriglyceridemic-waist phenotype across different genders, regions, ages, and overweight/obese populations, and to provide a scientific basis for diabetes prevention and control. **Methods:** This prospective cohort study involved 9,280 permanent residents aged 18 years and older from 12 districts (counties) in Guizhou province, selected through multistage stratified cluster random sampling in 2010. From 2016 to 2020, 8,163 residents were followed up, and 6,743 eligible participants were enrolled after excluding those with baseline T2DM, insufficient clinical data, lost to follow-up, and deaths. Participants were assigned to four groups based on baseline waist circumference (WC) and serum triacylglycerol (TG) levels: Normal WC and TG group (NWNT: WC $<$ 90 cm in men and WC $<$ 85 cm in women, TG $<$ 1.7 mmol/L); normal WC and high TG group (NWHT: WC $<$ 90 cm in men and WC $<$ 85 cm in women, TG $\geq$ 1.7 mmol/L); enlarged WC and normal TG group (EWNT: WC $\geq$ 90 cm in men or WC $\geq$ 85 cm in women, TG $<$ 1.7 mmol/L); and enlarged WC and high TG group (EWHT: WC $\geq$ 90 cm in men or WC $\geq$ 85 cm in women, TG $\geq$ 1.7 mmol/L). Cox proportional hazards regression models were used to analyze the association between hypertriglyceridemic-waist phenotype groups and new-onset T2DM. **Results:** The median follow-up period was 6.58 years. Among 6,743 participants, new-onset T2DM was observed in 706 individuals (10.47%). After adjusting for confounding factors, Cox proportional hazards regression analysis showed that the risk of T2DM in the EWHT group was 1.486 times that of the NWNT group (HR = 1.486, 95% CI = 1.185–1.865, P = 0.001). Subgroup multivariate Cox proportional hazards regression analysis showed that in males, rural residents, individuals aged $<$ 45 years, and overweight/obese populations, the risk of T2DM in the EWHT group was 1.792 (HR = 1.792, 95% CI = 1.297–2.476, P $<$ 0.001), 1.483 (HR = 1.483, 95% CI = 1.115–1.971, P = 0.007), 1.540 (HR = 1.540, 95% CI = 1.083–2.190, P = 0.016), and 1.614 (HR = 1.614, 95% CI = 1.123–2.321, P = 0.010) times higher than the NWNT group, respectively. **Conclusion:** After a median follow-up of 6.58 years in a large cohort, hypertriglyceridemic-waist phenotype was associated with increased T2DM risk in Guizhou Province, with more pronounced effects in males, rural areas, individuals aged $<$ 45 years, and overweight/obese populations. Therefore, health education should be strengthened for these high-risk populations, and weight control through reasonable diet and appropriate exercise to reduce serum triacylglycerol levels are necessary and effective methods to prevent T2DM incidence.

Keywords: Diabetes mellitus, type 2; Triacylglycerols; Waist circumference; Risk of onset; Cohort studies; Prospective studies

Introduction

Globally, more than 500 million adults have diabetes, with over three-quarters living in low- and middle-income countries, and type 2 diabetes mellitus (T2DM) accounts for 91% of cases [1]. In recent years, the prevalence of diabetes among Chinese adults has reached 11.9% and continues to rise [2], making China the country with the largest number of diabetic patients worldwide [1]. In Guizhou Province, diabetes prevalence increased from 5.6% in 2013 to 9.4% in 2018 [3,4]. Diabetes has become a global public health problem, and early identification of risk factors and timely intervention to reduce diabetes incidence are crucial [5].

In 2000, Lemieux et al. [6] proposed hypertriglyceridemic-waist phenotype as a risk factor for atherosclerosis. Hypertriglyceridemic-waist phenotype represents a pathological state of metabolic disorders in proteins, fats, carbohydrates, and other substances, and is a risk factor that can predict diabetes incidence [7]. Currently, cross-sectional studies in China have shown that hypertriglyceridemic-waist phenotype is closely associated with prediabetes and diabetes [8] and is a risk factor for prediabetes and T2DM [9], but comprehensive large-sample studies are lacking. This study used a natural population cohort from across Guizhou Province and Cox regression analysis to explore the risk of T2DM associated with hypertriglyceridemic-waist phenotype, providing a reference basis for diabetes intervention.

Methods

Study Population

This prospective cohort study used stratified cluster random sampling in 2010 to select 9,280 permanent residents aged 18 years and older from 12 counties (districts) in Guizhou Province as the baseline cohort. From 2016 to 2020, all cohort members were followed up. A total of 8,163 individuals were successfully followed up, with 1,117 lost to follow-up (follow-up rate: 87.96%).

Inclusion criteria: (1) Non-diabetic at baseline; (2) Complete examination data (including physical measurements, laboratory tests, and dietary habit surveys); (3) Successfully followed up. **Exclusion criteria:** (1) Diabetic patients at baseline; (2) Incomplete questionnaire data; (3) Lost to follow-up or deceased. A total of 6,743 individuals were included in the final analysis. This study was approved by the Ethics Committee of Guizhou Center for Disease Control and Prevention (Approval No.: S2017-02), and all participants provided informed consent.

Baseline Survey

The baseline survey included: (1) Personal questionnaire: general information including age, gender, ethnicity, urban/rural residence, occupation, and education level, as well as smoking, alcohol consumption, and dietary habits. (2) Physical measurements: height, weight, waist circumference, and blood pressure were measured, and BMI was calculated. Cooking oil and salt intake were converted to daily per capita consumption based on household consumption over one month and the number of family members. (3) Biochemical indicators: after at least 8 hours of fasting, elbow venous blood was drawn to measure fasting blood glucose (FBG), serum triacylglycerol (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), and an oral glucose tolerance test 2-hour glucose (OGTT 2h) was performed.

Follow-up and Outcome Events

Follow-up was conducted from 2016 to 2020, with a median follow-up time of 6.58 years. The 12 county (district) surveillance points of the CDC screened follow-up and death information for participants. The outcome was new-onset T2DM.

Variable Definitions and Grouping

(1) **Diabetes:** Individuals without diabetes at baseline who had fasting blood glucose $\geq$ 7.0 mmol/L or OGTT 2h $\geq$ 11.1 mmol/L at follow-up [10]. (2) **Hypertension:** Defined as blood pressure $\geq$ 140/90 mmHg (1 mmHg = 0.133 kPa) or blood pressure $<$ 140/90 mmHg but with a confirmed diagnosis of hypertension or current use of antihypertensive medication [11]. (3) **Smoking:** Adults who smoked daily or non-daily at the time of survey. (4) **Alcohol consumption:** Adults who had consumed alcohol within the past 12 months at the time of survey. (5) **Dyslipidemia:** TC $\geq$ 6.2 mmol/L (240 mg/dL) or TG $\geq$ 2.3 mmol/L (200 mg/dL) or LDL-C $\geq$ 4.1 mmol/L (160 mg/dL) or HDL-C $<$ 1.0 mmol/L (40 mg/dL) [12]. (6) **BMI:** 24.0 kg/m^2 $\leq$ BMI $<$ 28.0 kg/m^2 was defined as overweight, BMI $\geq$ 28.0 kg/m^2 as obesity, and adult central obesity as WC $\geq$ 90 cm in men and WC $\geq$ 85 cm in women [13]. (7) **Hypertriglyceridemic-waist phenotype grouping:** Normal waist and normal TG group (NWNT): WC $<$ 90 cm in men or WC $<$ 85 cm in women and TG $<$ 1.7 mmol/L; normal waist and high TG group (NWHT): WC $<$ 90 cm in men or WC $<$ 85 cm in women and TG $\geq$ 1.7 mmol/L; enlarged waist and normal TG group (EWNT): WC $\geq$ 90 cm in men or WC $\geq$ 85 cm in women and TG $<$ 1.7 mmol/L; enlarged waist and high TG group (EWHT): WC $\geq$ 90 cm in men or WC $\geq$ 85 cm in women and TG $\geq$ 1.7 mmol/L.

Statistical Methods

Baseline survey data were entered using EpiData 3.1 software with double entry. Follow-up survey data from 2016–2020 were entered using tablets. SPSS 23.0 software was used for statistical analysis. Categorical data were expressed as relative numbers and analyzed using chi-square tests. Non-normally distributed continuous data were expressed as M (Q1, Q3) and compared between groups using Wilcoxon rank-sum tests. The relationship between hypertriglyceridemic-waist phenotype groups and T2DM was analyzed using multivariate Cox proportional hazards regression to calculate hazard ratios (HR) and 95% confidence intervals (CI). The significance level was $\alpha = 0.05$. R 4.0.3 software was used to create sensitivity analysis forest plots.

Results

Comparison of New-Onset T2DM Incidence Across Baseline Characteristics

This study included 6,743 participants with a median follow-up time of 6.58 years. New-onset T2DM occurred in 706 individuals, yielding an incidence rate of 10.47%. Significant differences in new-onset T2DM incidence were observed across different age groups, ethnicities, urban/rural residence, education levels, oil intake > 25 g, and salt intake > 5 g ($P < 0.05$) (Table 1).

The waist circumference, TG, and BMI in the new-onset T2DM group were 77.80 (71.25, 85.20) cm, 1.47 (1.00, 2.21) mmol/L, and 23.00 (20.67, 25.94) kg/m^2, respectively, all significantly higher than those in the non-T2DM group [75.00 (69.70, 81.00) cm, 1.19 (1.00, 2.00) mmol/L, and 22.22 (20.43, 24.46) kg/m^2] (Z_{WC} = 52.073, P_{WC} < 0.05; Z_{TG} = 25.486, P_{TG} < 0.05; Z_{BMI} = 33.016, P_{BMI} < 0.05).

Multivariate Cox Proportional Hazards Regression Analysis of Different Hypertriglyceridemic-Waist Phenotypes and T2DM Incidence

In the total population, without adjusting for confounders (Model 1), the risks of T2DM in the EWNT and EWHT groups were 1.601 and 1.965 times that of the NWNT group ($P < 0.05$). After adjusting for gender and age (Model 2), the risks were 1.563 and 1.806 times higher ($P < 0.05$). After adjusting for gender, age, ethnicity, education level, smoking, alcohol consumption, and other related confounders (Model 3), the EWHT group had a T2DM risk 1.486 times that of the NWNT group ($P < 0.05$) (Table 2).

Subgroup Multivariate Cox Proportional Hazards Regression Analysis

Subgroup multivariate Cox proportional hazards regression analysis showed that in males, rural residents, individuals aged < 45 years, and overweight/obese populations, Model 1 indicated that the EWHT group had T2DM risks 2.004, 1.819, 2.120, and 1.854 times that of the NWNT group ($P < 0.05$), respectively. Model 2 showed risks of 2.029, 1.730, 2.092, and 1.765 times ($P < 0.05$), respectively. Model 3 showed that the EWHT group had T2DM risks 1.792, 1.483, 1.540, and 1.614 times that of the NWNT group, respectively (Table 3).

Sensitivity Analysis

After excluding participants with baseline hypertension, hypercholesterolemia, low HDL-C, and high LDL-C, sensitivity analysis yielded robust results (Figure 1 [Figure 1: see original paper]).

Discussion

Multivariate Cox proportional hazards regression analysis showed that after adjusting for confounders including gender, age, ethnicity, education level, alcohol consumption, smoking, oil intake > 25 g, salt intake > 5 g, fasting blood glucose, and BMI (Model 3), the EWHT group had a T2DM risk 1.486 times that of the NWNT group (HR = 1.486, 95% CI = 1.185–1.865, P = 0.001) in the total population. This is consistent with a national cohort study of middle-aged and elderly Chinese, which found significantly higher T2DM risk in the enlarged waist and hypertriglyceridemia group (HR = 1.61, 95% CI = 1.26–2.06) [14].

In males (Model 3), the EWHT group had a T2DM risk 1.792 times that of the NWNT group (HR = 1.792, 95% CI = 1.297–2.476, $P < 0.001$), better demonstrating that the risk of T2DM associated with hypertriglyceridemic-waist phenotype is gender-related. This aligns with Ike's [15] report that the association between obesity phenotype and type 2 diabetes differs by gender. Hypertriglyceridemic-waist phenotype is a risk factor for increased visceral fat area in male T2DM patients. Abdominal obesity and intra-abdominal fat accumulation are not only characteristic of body fat distribution in diabetes and metabolic syndrome but also initiating factors for various metabolic abnormalities [16,17]. Therefore, in males, attention should be paid to both serum triacylglycerol abnormalities and abdominal obesity.

This study found that in individuals aged < 45 years, the EWHT group had a T2DM risk 1.540 times that of the NWNT group (HR = 1.540, 95% CI = 1.083–2.190, P = 0.016), while in those aged ≥ 45 years, the risk was 1.401 times higher (HR = 1.401, 95% CI = 1.034–1.900, P = 0.030). This may be because younger individuals are more susceptible to electronic products, leading to irregular circadian rhythms and sleep disturbances, as both short and long sleep durations can increase T2DM risk [18,19]. High oil and salt intake increases dyslipidemia risk [20], and different healthy lifestyle patterns affect glucose metabolism regulation, thereby influencing diabetes development [21]. Therefore, differences in T2DM incidence were observed between groups with oil intake > 25 g and salt intake > 5 g.

This study also found that in overweight/obese populations (Model 3), the EWNT group had a T2DM risk 1.614 times that of the NWNT group. Obesity factors and lipid metabolism disorders affect vascular endothelial function, leading to plaque formation and arteriosclerosis. As arteriosclerosis progresses, peripheral microcirculation disorders develop, affecting insulin-mediated muscle perfusion and glucose metabolism, ultimately leading to diabetes development [22–24]. Chen [25] reported that diabetes risk in obese populations is 2.37 times that of non-obese normal populations. Chinese cross-sectional studies have shown that low HDL-C is associated with increased T2DM risk [26], and hypertriglyceridemic-waist phenotype is statistically associated with diabetes in middle-aged and elderly populations [27]. Cohort studies have also found hypertriglyceridemic-waist phenotype to be a major risk factor for T2DM [28]. In rural areas of our province (Model 3), the EWHT group had a T2DM risk 1.483 times that of the NWNT group, consistent with research showing hypertriglyceridemic-waist phenotype is a high-risk factor for T2DM in rural populations [29]. Provincial studies have reported [30] that the risk of comorbid hypertension, diabetes, and dyslipidemia increases with BMI. Therefore, this study conducted sensitivity analysis by excluding participants with hypertension, dyslipidemia, hypercholesterolemia, low HDL-C, and high LDL-C at baseline, making the results more robust and reliable.

This study has several limitations. First, because this study included a natural population from Guizhou Province, the findings may not be generalizable. Second, although many confounders were adjusted for, other potential confounders such as family history, pulse pressure, and sleep-related factors may still exist.

In summary, this prospective cohort study explored the association between hypertriglyceridemic-waist phenotype and diabetes in the entire population of Guizhou Province. In males, rural residents, individuals aged < 45 years, and overweight/obese populations, the EWHT group had T2DM risks 1.792, 1.483, 1.540, and 1.614 times that of the NWNT group, respectively. Based on these findings, future efforts should strengthen monitoring and prevention strategies, and identifying individuals with hypertriglyceridemic-waist phenotype is important for diabetes prevention and control.

Author Contributions: ZHU Ling was responsible for data analysis, conceptualization, and manuscript writing. WANG Jiangtao and DU Yu assisted with data organization. WU Yanli and ZHANG Ji provided guidance on statistical analysis. LIU Tao provided guidance on manuscript quality.

Conflict of Interest: The authors declare no conflict of interest.

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Note: Figure translations are in progress. See original paper for figures.