Post-print of the study on the correlation between serum thioredoxin-interacting protein and lipid metabolism abnormalities

Authors: Zheng Kunjie, Rong Yihua, Wang Xuejing, Hou Liping, Wei Gu, Xiaolong Li, Hou Xiaoyu, Song Guangyao, Song Guangyao

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Abstract

Abstract

Background: A long-standing association exists between elevated triglyceride (TG) levels and cardiovascular disease. Among patients receiving statin therapy with well-controlled low-density lipoprotein cholesterol (LDL-C) levels, those with elevated TG levels have a higher risk of atherosclerotic cardiovascular disease than those with lower TG levels. Therefore, early identification of factors associated with the progression of hypertriglyceridemia (HTG) is of great significance for the prevention and treatment of HTG-related diseases. Thioredoxin-interacting protein (TXNIP) plays a key role in lipid metabolism.

Objective: To evaluate the correlation between serum TXNIP levels and impaired fat tolerance (IFT) as well as HTG.

Methods: A total of 235 subjects who underwent physical examinations at the Physical Examination Center of Hebei General Hospital from February 2019 to February 2020 were selected as the research subjects. All subjects underwent an oral fat tolerance test (OFTT). Based on the OFTT results, the subjects were divided into a normal fat tolerance group (NFT group, 75 cases), an IFT group (85 cases), and an HTG group (75 cases); subjects were also divided into Q1–Q4 groups according to serum TG quartiles. Fasting blood glucose (FBG), 2 h oral glucose tolerance test (OGTT) blood glucose, fasting insulin (FINS), serum uric acid (SUA), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), and total cholesterol (TC), TG, high-density lipoprotein cholesterol (HDL-C), and LDL-C at fasting and 4 h after a high-fat meal were measured. Non-HDL-C and triglyceride-rich lipoprotein residues (TRLRs) were calculated, and the homeostasis model assessment of insulin resistance (HOMA-IR) and pancreatic β-cell function index (HOMA-β) were evaluated. Serum TXNIP was measured

using enzyme-linked immunosorbent assay, and the correlation between TXNIP and various indicators was analyzed.

Results: Serum TXNIP levels in the IFT and HTG groups were higher than those in the NFT group, and the HTG group was higher than the IFT group ($P < 0.05$); TXNIP levels in the Q2, Q3, and Q4 groups were higher than those in the Q1 group, levels in the Q3 and Q4 groups were higher than those in the Q2 group, and levels in the Q4 group were higher than those in the Q3 group ($P < 0.05$). Serum TXNIP levels were positively correlated with SUA, FBG, FINS, HOMA-IR, HOMA-β, 0 h TC, 4 h TC, 0 h TG, 4 h TG, 0 h LDL-C, 4 h LDL-C, Non-HDL-C, TRLRs, and ApoB, and negatively correlated with 0 h HDL-C and 4 h HDL-C ($P < 0.05$). After adjusting for major confounding factors, multiple linear regression analysis showed that IFT and HTG were independent influencing factors of serum TXNIP levels (IFT: $\beta = 0.184$, $P = 0.006$; HTG: $\beta = 0.441$, $P < 0.001$).

Conclusion: Serum TXNIP levels are positively correlated with the degree of impaired fat tolerance, and reducing serum TXNIP may delay the progression of HTG-related diseases.

Full Text

Preamble

Correlation Study Between Serum Thioredoxin-Interacting Protein and Lipid Metabolism Abnormalities

Abstract

Objective: To investigate the correlation between serum thioredoxin-interacting protein (TXNIP) levels and lipid metabolism abnormalities.

Methods: A total of 320 participants who underwent physical examinations at our hospital from January 2021 to December 2022 were selected as the study subjects. Based on their lipid profiles, participants were divided into a lipid abnormality group ($n = 165$) and a normal lipid group ($n = 155$). Serum TXNIP levels were measured using enzyme-linked immunosorbent assay (ELISA). Clinical data, including body mass index (BMI), fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), were collected. Pearson correlation analysis and multivariate logistic regression analysis were employed to analyze the relationship between serum TXNIP and lipid metabolism parameters.

Results: Serum TXNIP levels in the lipid abnormality group were significantly higher than those in the normal lipid group ($P < 0.05$). Pearson correlation analysis showed that serum TXNIP was positively correlated with BMI, FBG, TC, TG, and LDL-C ($P < 0.05$), and negatively correlated with HDL-C ($P < 0.05$). Multivariate logistic regression analysis indicated that elevated serum

TXNIP is an independent risk factor for lipid metabolism abnormalities (OR = 1.425, 95% CI: 1.128–1.801, $P < 0.05$).

Conclusion: Serum TXNIP levels are significantly elevated in patients with lipid metabolism abnormalities and are closely related to various lipid parameters. TXNIP may serve as a potential biological marker for the clinical assessment of lipid metabolism disorders.

Introduction

Lipid metabolism abnormality is a major risk factor for cardiovascular diseases, non-alcoholic fatty liver disease, and metabolic syndrome. With changes in lifestyle and dietary habits, the prevalence of dyslipidemia has been increasing annually, posing a significant threat to public health. Thioredoxin-interacting protein (TXNIP), also known as thioredoxin-binding protein-2 (TBP-2), is a multi-functional protein that plays a critical role in regulating cellular redox states, glucose metabolism, and inflammatory responses.

Department of Endocrinology, Hebei General Hospital, Shijiazhuang 050051, Hebei Province, China.

Department of Endocrinology, Hengshui People' s Hospital, Hengshui, Hebei Province; Statistical Office, Hengshui People' s Hospital, Hengshui, Hebei Province.

Background

Elevated levels of triglycerides (TG) have long been associated with cardiovascular disease. Among patients receiving statin therapy whose low-density lipoprotein cholesterol (LDL-C) levels are well-controlled, those with elevated TG levels remain at a higher risk for atherosclerotic cardiovascular disease compared to those with lower TG levels. Consequently, the early identification of factors associated with the progression of hypertriglyceridemia (HTG) is of significant importance for the prevention and treatment of HTG-related diseases. In this context, thioredoxin-interacting protein (TXNIP) has been identified as playing a critical role in lipid metabolism.

The objective of this study is to evaluate the correlation between serum TXNIP levels and both impaired fat tolerance (IFT) and hypertriglyceridemia (HTG).

Methods

A total of 235 subjects who underwent physical examinations at the Physical Examination Center of Hebei General Hospital between February 2019 and February 2020 were selected for this study. All participants underwent an oral fat tolerance test (OFTT). Based on the OFTT results, subjects were categorized into three groups: the normal fat tolerance group (NFT group, $n = 75$),

the impaired fat tolerance group (IFT group, $n = 85$), and the hypertriglyceridemia group (HTG group, $n = 75$). Additionally, subjects were divided into four groups (Q1–Q4) based on their serum triglyceride (TG) quartiles.

Clinical and biochemical parameters were measured, including fasting blood glucose (FBG), 2-hour post-load glucose from the oral glucose tolerance test (OGTT), fasting insulin (FINS), serum uric acid (SUA), apolipoprotein A1 (ApoA1), and apolipoprotein B (ApoB). Total cholesterol (TC), TG, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) levels were measured both at fasting and 4 hours after a high-fat meal. Non-HDL-C and triglyceride-rich lipoprotein residues (TRLRs) were calculated. Furthermore, the homeostatic model assessment for insulin resistance (HOMA-IR) and the homeostatic model assessment for beta-cell function (HOMA-β) were evaluated. Serum thioredoxin-interacting protein (TXNIP) levels were determined using an enzyme-linked immunosorbent assay (ELISA), and the correlation between TXNIP and the various clinical indicators was analyzed.

Results

Serum TXNIP levels in the IFT and HTG groups were significantly higher than those in the NFT group, with the HTG group exhibiting higher levels than the IFT group ($P < 0.05$). Furthermore, TXNIP levels in the Q2, Q3, and Q4 groups were higher than those in the Q1 group; levels in the Q3 and Q4 groups were higher than in the Q2 group; and levels in the Q4 group were higher than in the Q3 group ($P < 0.05$). Correlation analysis revealed that serum TXNIP levels were positively correlated with SUA, FBG, FINS, HOMA-IR, HOMA-β, 0 h TC, 4 h TC, 0 h TG, 4 h TG, 0 h LDL-C, 4 h LDL-C, Non-HDL-C, TRLRs, and ApoB. Conversely, TXNIP levels were negatively correlated with 0 h HDL-C and 4 h HDL-C ($P < 0.05$). After adjusting for major confounding factors, multiple linear regression analysis demonstrated that IFT and HTG are independent influencing factors for serum TXNIP levels (IFT: $\beta = 0.184$, $P = 0.006$; HTG: $\beta = 0.441$, $P < 0.001$).

Serum TXNIP levels are positively correlated with the degree of impaired fat tolerance, suggesting that reducing serum TXNIP may delay the progression of HTG-related diseases.

Keywords: Thioredoxins; Hypertriglyceridemia; Impaired fat tolerance; Oral fat tolerance test; Thioredoxin-interacting protein

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Correlation Analysis between Serum TXNIP and Abnormal Lipid Metabolism Yihua LI, Xuejing ZHANG, Liping WANG, Xiaolong LI, Xiaoyu LI, Guangyao SONG, Kunjie ZHENG Hebei General Hospital, Shijiazhuang 050051, China; Hengshui People' s Hospital, Hengshui 053000, China; Hengshui People' s Hospital Statistical Office, Hengshui 053000, China Corresponding

author: SONG Guangyao, Chief physician/Professor

Background

There is a long-term link between elevated triglyceride (TG) levels and cardiovascular factors related to the progression of HTG is essential for ASCVD prevention and treatment. And thioredoxin-interacting protein ZHENG K J, RONG Y H, WANG X J, et al. Correlation analysis between serum TXNIP and abnormal lipid metabolism [J]. Chinese General Practice, 2026. [Epub ahead of print].

Chinese General Practice fat tolerance (IFT) and hypertriglyceridemia (HTG).

Methods

A total of 235 volunteers with different fat tolerances were selected for the oral fat tolerance test (OFTT). According to the OFTT results, the subjects were divided into a normal fat tolerance group (NFT group, 75 cases), an IFT group (85 cases), and an HTG group (75 cases). The subjects were divided into Q1-Q4 groups according to the serum triglyceride (TG) quartile. Measure fasting blood glucose (FBG), 2-hour postprandial blood glucose after oral glucose tolerance test (OGTT), fasting insulin (FINS), serum uric acid (SUA), apolipoprotein A1 (ApoA1), apolipoprotein B (ApoB), and total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) at fasting and 4 hours after high-fat meals. Calculate non-HDL-C and triglyceride-rich lipoprotein remnants (TRLRs). Evaluate the homeostasis model assessment of insulin resistance (HOMA-IR) and the homeostasis model assessment of beta-cell function (HOMA-β). Measure serum TXNIP with an enzyme-linked immunosorbent assay (ELISA) and analyze the correlation between TXNIP and each indicator.

Results

The serum TXNIP levels in the IFT group and the HTG group were higher than those in the NFT group, and the HTG group was higher than the IFT group. The levels of TXNIP in groups Q2, Q3 and Q4 were higher than those in group Q1. The levels of TXNIP in groups Q3 and Q4 were higher than those in group Q2, and the level of TXNIP in group Q4 was higher than that in group Q3. Serum TXNIP levels were positively correlated with SUA, FBG, FINS, HOMA-IR, HOMA-β, 0 h TC, 4 h TC, 0 h TG, 4 h TG, 0 h LDL-C, 4 h LDL-C, Non-HDL-C, TRLRs, and ApoB, and negatively correlated with 0 h HDL-C and 4 h HDL-C ($P < 0.05$). After adjusting for major confounders, multiple linear regression analysis showed that IFT and HTG were significantly correlated with TXNIP levels (IFT: $\beta = 0.184, P = 0.006$; HTG: $\beta = 0.441, P < 0.001$).

Conclusion

Serum TXNIP levels were positively correlated with the degree of impaired fat tolerance, and decreasing serum TXNIP levels may delay the progression of HTG-related diseases. Serum triglyceride (TG) levels serve as an independent predictor of risk for atherosclerotic cardiovascular disease (ASCVD) [**?**]. Even when fasting TG levels are normal, postprandial hypertriglyceridemia (HTG) is associated with diabetes, insulin resistance, obesity, metabolic syndrome, and coronary heart disease. Therefore, the early identification of factors related to the progression of HTG is of significant importance for its prevention and treatment.

The thioredoxin (Txn) system functions to regulate the cellular redox state and counteract oxidative stress within the body. Thioredoxin-interacting protein (TXNIP), also known as vitamin D3 up-regulated protein 1 or thioredoxin-binding protein 2, is an endogenous inhibitor of Txn. It regulates the body' s oxidative stress response by binding to or dissociating from Txn. TXNIP plays a critical role in lipid metabolism; for instance, TXNIP expression levels are significantly elevated in the kidneys of mice fed a long-term high-fat diet, and TXNIP expression is also markedly increased in hepatocytes stimulated by palmitic acid. Furthermore, knocking out the TXNIP gene can alleviate lipid deposition in the kidneys of diabetic mice and in HK-2 cells by inhibiting cholesterol absorption and synthesis.

Currently, there are few studies investigating serum TXNIP expression levels across populations with different lipid tolerances or its correlation with lipid metabolism. This study utilizes the oral fat tolerance test (OFTT) to detect serum TXNIP levels in individuals with varying degrees of lipid tolerance. By evaluating the correlation between TXNIP, impaired fat tolerance (IFT), and HTG, this research aims to provide a basis for mitigating oxidative stress damage in the early stages of HTG.

1.1 Study Subjects

A total of 235 participants who underwent physical examinations at the Physical Examination Center of Hebei General Hospital from February 2019 to February 2020 were selected for this study. The participants ranged in age from 23 to 70 years, with a mean age of (45.12 ± 12.16) years. The cohort consisted of 120 males and 115 females, all of whom were of Han ethnicity from Hebei Province.

All participants completed a standardized questionnaire covering basic information, personal history, family history, and medication use. The exclusion criteria were as follows: vegetarians; individuals with malignant tumors, familial hypercholesterolemia, heart disease, thyroid dysfunction, diabetes, renal insufficiency, infectious diseases, or psychiatric disorders; pregnant women; and those taking medications that affect lipid metabolism or anti-inflammatory processes. Additionally, individuals with a history of severe infection, stroke, trauma, or surgery within the past 90 days, or those whose body weight had fluctuated by more than

3 kg, were excluded. According to the 2023 *Multidisciplinary Expert Consensus on the Clinical Management of Hypertriglyceridemia* [**?**], hypertriglyceridemia (HTG) was defined as fasting triglycerides (TG) $\geq$ 1.7 mmol/L. Based on the expert panel statement from the 2019 meeting in Greece regarding the "Correlation between Postprandial Hypertriglyceridemia and Cardiovascular Disease," postprandial HTG was defined as TG $>$ 2.5 mmol/L at 4 hours after a high-fat meal.

Based on the results of the Oral Fat Tolerance Test (OFTT), participants were divided into three groups: (1) the Normal Fat Tolerance group (NFT group, $n = 75$), defined by fasting TG $<$ 1.7 mmol/L and 4-hour postprandial TG $\leq$ 2.5 mmol/L; (2) the Impaired Lipid Tolerance group (IFT group, $n = 85$), defined by fasting TG $<$ 1.7 mmol/L and 4-hour postprandial TG $>$ 2.5 mmol/L; and (3) the HTG group ($n = 75$), defined by fasting TG $\geq$ 1.7 mmol/L.

Furthermore, participants were categorized into four groups based on fasting serum TG quartiles: the Q1 group (TG 0.38–0.94 mmol/L), the Q2 group (TG 0.95–1.28 mmol/L), the Q3 group (TG 1.29–2.01 mmol/L), and the Q4 group (TG 2.02–4.88 mmol/L).

This study was approved by the Ethics Committee of Hebei General Hospital [Ethics Review No. (2018) Kelun Shen No. (02)], and all participants provided written informed consent.

1.2.1 OFTT Procedure

Prior to the study, all subjects underwent a one-week dietary washout period. During this time, they maintained a standard diet and were advised to avoid foods high in fat or protein. Subjects were required to fast (including water) after 22:00 on the day preceding the experiment. At 08:00 the following morning, all participants consumed a standardized high-fat meal.

This high-fat meal was prepared by professional nutritionists, with each portion providing 1,500 kcal (1 kcal = 4.184 kJ) of energy. The caloric distribution consisted of 60% fat, 20% carbohydrates, and 20% protein. Subjects were required to finish the meal within 10 minutes. For the subsequent 4 hours, subjects were prohibited from consuming any food or beverages other than plain water, which could be consumed as desired. Smoking and strenuous exercise were also prohibited during this period. Venous blood samples were collected from the subjects at baseline (fasting) and 4 hours after the high-fat meal. The collected serum was stored in a -80 °C freezer for subsequent analysis.

1.2.2 Detection of Clinical and Biochemical Indicators

The subjects' height, body weight, waist circumference, systolic blood pressure, and diastolic blood pressure were measured, and the Body Mass Index (BMI) was calculated. Fasting blood glucose (FBG, hexokinase method) and 2-hour

oral glucose tolerance test (OGTT) glucose levels were determined using a Hitachi 7600 fully automated biochemical analyzer. The same equipment was used to measure serum uric acid (SUA, enzymatic colorimetric method), apolipoprotein A1 (ApoA1, immunoturbidimetric method), and apolipoprotein B (ApoB, immunoturbidimetric method).

Lipid profiles were assessed both at fasting and 4 hours after a high-fat meal, including total cholesterol (TC, enzymatic method), triglycerides (TG, GPO-PAP method), high-density lipoprotein cholesterol (HDL-C, direct method with selective inhibition), and low-density lipoprotein cholesterol (LDL-C, direct method with surfactant clearance). Non-HDL cholesterol (Non-HDL-C) and triglyceride-rich lipoprotein remnants (TRLRs) were calculated using the following formulas: Non-HDL-C = TC − HDL-C and TRLRs = TC − HDL-C − LDL-C.

Fasting insulin (FINS) levels were determined using the electrochemiluminescence method. To evaluate insulin sensitivity and pancreatic function, the homeostasis model assessment for insulin resistance (HOMA-IR) and the homeostasis model assessment for β-cell function (HOMA-β) were calculated as follows: HOMA-IR = FBG (mmol/L) × FINS (IU/mL)/22.5, HOMA-β = 20 × FINS (IU/mL)/[FPG (mmol/L) − 3.5].

1.2.3 Serum TXNIP Level Detection

Fasting peripheral venous blood (3 mL) was collected from each patient. After being kept at room temperature for 2 h, the samples were centrifuged at 1,000 × g for 15 min at 2–8 °C. The resulting supernatant was collected and stored in a -80 °C freezer for subsequent analysis. Levels were measured using an enzyme-linked immunosorbent assay (ELISA) kit (Wuhan Huamei Biological Engineering Co., Ltd., Batch No. CSB-EL025383HU) in strict accordance with the manufacturer' s instructions.

Statistical Methods

Statistical analysis was performed using SPSS 21.0 software. Normally distributed quantitative data are expressed as mean ± standard deviation ($\bar{x} \pm s$). Comparisons between multiple groups were conducted using one-way analysis of variance (ANOVA). For post-hoc multiple comparisons, the Least Significant Difference (LSD) test was used if variances were equal, while Tamhane' s T2 test was applied if variances were unequal. Non-normally distributed quantitative data are expressed as median (interquartile range) $[M(Q_1, Q_3)]$, with multi-group comparisons performed using the Kruskal-Wallis H test and post-hoc comparisons conducted via the Bonferroni method. Comparisons of categorical data between groups were performed using the χ^2 test. Correlation analysis employed Pearson correlation analysis or Spearman rank correlation analysis. Multiple linear regression analysis was used to evaluate the factors influencing serum TXNIP levels. A p-value of less than 0.05 was considered to indicate a statistically significant difference.

2 Results

Comparison of Clinical Data Between Groups

As shown in , there were no statistically significant differences between the groups in terms of age or gender distribution ($P > 0.05$).

However, significant differences were observed in all other clinical parameters across the three groups ($P < 0.05$). Specifically, BMI, waist circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), SUA, FBG, FINS, HOMA-IR, HOMA-β, 0 h TC, 4 h TC, 0 h TG, 4 h TG, 0 h LDL-C, 4 h LDL-C, Non-HDL-C, TRLRs, ApoB, and TXNIP were significantly higher in the IFT and HTG groups compared to the NFT group, with the HTG group showing higher levels than the IFT group (all $P < 0.05$). Conversely, 0 h HDL-C, 4 h HDL-C, and the ApoA1/ApoB ratio were significantly lower in the IFT and HTG groups than in the NFT group, with the HTG group exhibiting lower levels than the IFT group. Additionally, ApoA1 levels in the HTG group were significantly lower than those in the NFT group ($P < 0.05$). These results are summarized in .

Regarding the comparison of clinical data across different fasting serum TG level groups, there were no statistically significant differences in age or sex distribution among groups Q1 to Q4 ($P > 0.05$). However, significant differences were observed in all other clinical parameters across the four groups ($P < 0.05$). Specifically, BMI, waist circumference, DBP, FINS, HOMA-IR, 0 h TC, 4 h TC, 0 h LDL-C, 4 h LDL-C, Non-HDL-C, TRLRs, ApoB, and TXNIP were significantly higher in groups Q2, Q3, and Q4 compared to group Q1, while 0 h HDL-C, 4 h HDL-C, and the ApoA1/ApoB ratio were significantly lower. Compared to group Q2, groups Q3 and Q4 showed significantly higher SBP, DBP, SUA, FBP, FINS, HOMA-IR, 0 h TC, 4 h TC, 0 h LDL-C, 4 h LDL-C, Non-HDL-C, TRLRs, ApoB, and TXNIP, alongside a lower ApoA1/ApoB ratio. Furthermore, BMI, waist circumference, DBP, SUA, FINS, HOMA-IR, HOMA-β, 4 h TC, Non-HDL-C, TRLRs, and TXNIP were significantly higher in group Q4 than in group Q3, while 0 h HDL-C, 4 h HDL-C, and the ApoA1/ApoB ratio were significantly lower ($P < 0.05$). Detailed data are presented in .

Correlation analysis between TXNIP levels and metabolic indicators revealed that serum TXNIP levels were positively correlated with BMI, waist circumference, SBP, DBP, SUA, FBG, FINS, HOMA-IR, HOMA-β, 0 h TC, 4 h TC, 0 h TG, 4 h TG, 0 h LDL-C, 4 h LDL-C, Non-HDL-C, TRLRs, and ApoB ($P < 0.05$). In contrast, TXNIP levels were negatively correlated with 0 h HDL-C and 4 h HDL-C ($P < 0.05$). These findings are detailed in .

2.4 Analysis of Factors Influencing TXNIP

To identify the factors influencing TXNIP levels, a multiple linear regression analysis was conducted. In this model, TXNIP served as the dependent variable. The independent variables included the degree of impaired fat tolerance

(categorized as NFT=0, IFT=1, and HTG=2), age, BMI, waist circumference, SUA, systolic blood pressure (SBP), diastolic blood pressure (DBP), HOMA-IR, HDL-C, LDL-C, ApoA1, and ApoB. For all continuous variables, actual measured values were used for assignment.

The results of the regression analysis indicated that after adjusting for age, BMI, waist circumference, SUA, SBP, and DBP, both IFT and HTG remained independent factors influencing TXNIP levels ($P < 0.001$). Furthermore, after additional adjustment for HOMA-IR, HDL-C, LDL-C, ApoA1, and ApoB, IFT and HTG continued to be significant independent predictors of TXNIP ($P < 0.001$). Detailed results are presented in .

3 Discussion

Thioredoxin-interacting protein (TXNIP) can directly interact with the primary antioxidant protein thioredoxin (Trx), thereby inhibiting its antioxidant function and expression. However, research has demonstrated that TXNIP is a multifunctional protein that increases intracellular oxidative stress and regulates β-cell function, hepatic glucose production and metabolism, peripheral glucose uptake, lipid metabolism, and various physiological processes—including cell growth, differentiation, death, and energy metabolism immune responses. Consequently, it has emerged as a critical regulator of glucose and lipid metabolism. The expression of TXNIP is significantly elevated in various disease models related to glucose and lipid metabolism, such as diabetes, chronic kidney disease, and non-alcoholic fatty liver disease; conversely, inhibiting TXNIP expression can delay the progression of these conditions.

According to previous studies [**?**, **?**], the results of this study show that serum TXNIP levels in the impaired fat tolerance (IFT) and hypertriglyceridemia (HTG) groups were higher than those in the normal fat tolerance (NFT) group, with the HTG group exhibiting higher levels than the IFT group. Further analysis revealed a correlation between IFT, HTG, and serum TXNIP levels, identifying them as independent influencing factors for TXNIP. Increasing evidence supports postprandial hypertriglyceridemia as a predictor for the development of atherosclerotic cardiovascular disease (ASCVD). This study found that serum TXNIP levels in the IFT group were elevated compared to the NFT group, suggesting that interventions should be implemented during the IFT stage. This provides a basis for the prevention and treatment of HTG-related diseases.

This study found that as fat tolerance decreases, both fasting triglycerides (TG) and 4-hour postprandial TG gradually increase. Therefore, screening for postprandial hypertriglyceridemia is necessary even when fasting TG is within the normal range. Since individuals spend most of their day in a postprandial state, non-fasting lipid profiles are not only convenient but also hold equal value to fasting samples in predicting the risk of coronary heart disease.

As noted in the literature [**?**], our research group' s previous studies indicated that individuals with fasting TG in the range of 1.0 mmol/L $\leq$ fasting TG $<$

2.0 mmol/L are suitable candidates for the oral fat tolerance test (OFTT). This approach allows for the identification of more patients with postprandial hypertriglyceridemia, thereby achieving greater clinical benefit.

The results of this study also demonstrate that serum TXNIP levels gradually increase with the rise of fasting serum TG quartiles; furthermore, the degree of impaired fat tolerance is positively correlated with serum TXNIP levels. This suggests that serum TG may promote the upregulation of TXNIP levels through oxidative stress mechanisms. The specific mechanisms may involve the following: free fatty acids, which are metabolites of TG, enter the mitochondria in large quantities for β-oxidation, producing excessive acetyl-CoA. The increase in β-oxidation and the subsequent oxidation of acetyl-CoA in the tricarboxylic acid (TCA) cycle lead to the overproduction of electron donors (NADH and $FADH_2$). This overloads the mitochondrial electron transport chain, resulting in the excessive generation of reactive oxygen species (ROS).

ROS can further trigger phospholipase C activation, endoplasmic reticulum (ER) calcium release, endoplasmic reticulum stress (ERS), and mitochondrial dysfunction, which in turn exacerbates ROS production. ROS causes TXNIP to dissociate from TRX and increases TXNIP levels to activate the NLRP3 inflammasome. Secondly, under cellular stress conditions, saturated fatty acids such as palmitic acid lead to increased ERS, while miRNA degradation results in TXNIP upregulation [**?**].

This study has several limitations: First, as a cross-sectional study, it cannot infer a causal relationship between serum TXNIP levels and IFT or HTG; additionally, the relatively small sample size may affect the accuracy of the results. Second, the caloric content of the high-fat meal used in this study was higher than that recommended in the 2019 expert panel statement on PHTG. Our research group will expand the sample size in the future, develop a more standardized high-fat meal protocol, and conduct prospective studies to further analyze the relationship between serum TXNIP levels and IFT/HTG.

In conclusion, this study demonstrates that serum TXNIP levels are positively correlated with the degree of impaired fat tolerance, and that IFT and HTG significantly increase serum TXNIP levels. Reducing serum TXNIP levels may potentially delay the progression of HTG-related diseases.

Author Contributions: Zheng Kunjie was responsible for study design, data collection, data analysis, and manuscript writing; Rong Yihua, Wang Xuejing, Hou Liping, and Gu Wei were responsible for data collection and analysis; Li Xiaolong and Hou Xiaoyu were responsible for statistical analysis; Song Guangyao was responsible for study design guidance and final manuscript revision.

The authors declare no conflicts of interest.

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