Original Article

Associations of triglyceride glucose-related parameters with kidney stones: a cross-sectional study from NHANES 2007–2020

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Background: The triglyceride-glucose (TyG) index, combined with obesity-related indicators such as body mass index (BMI), waist circumference (WC), and waist-to-height ratio (WHtR), has been proven to be reliable for assessing insulin resistance (IR). The objective of this study is to investigate the relationships between TyG-related parameters and the prevalence of kidney stones among adults in the United States (US).

Methods: This cross-sectional study utilized data from the National Health and Nutrition Examination Survey (NHANES) spanning 2007–2020 to evaluate the associations of TyG-related parameters with kidney stones. Weighted logistic regression, restricted cubic spline (RCS) analysis, receiver operating characteristic (ROC) analysis, and subgroup analysis were employed to investigate these relationships.

Results: A total of 15,590 participants were included in the analysis. Significant differences were observed in the distributions of TyG-related parameters between those with and without kidney stones. In the fully adjusted model, participants in the highest quartile of TyG-related parameters had a higher risk of kidney stones compared to those in the lowest quartile [TyG-WC: odds ratio (OR): 2.08, 95% confidence interval (CI): 1.66–2.60; TyG-BMI: OR: 2.03, 95% CI: 1.61–2.57; TyG-WHtR: OR: 2.21, 95% CI: 1.72–2.84]. RCS analysis indicated that these associations were non-linear (P for nonlinearity <0.05). ROC analysis showed that TyG-WC had the highest diagnostic accuracy (area under curve: 0.6130). Subgroup analysis further revealed a stronger positive association between TyG-WC and TyG-WHtR and the prevalence of kidney stones in participants without hypertension (P for interaction <0.05).

Conclusions: Taken together, there are strong positive correlations between TyG-related parameters and the prevalence of kidney stones in US adults. Our findings suggest that managing IR and preventing obesity may help reduce the risk of kidney stone formation.

Keywords: Triglyceride glucose-body mass index (TyG-BMI); triglyceride glucose-waist to height ratio (TyG-WHtR); triglyceride glucose-waist circumference (TyG-WC); kidney stones; insulin resistance (IR)

Submitted Sep 23, 2024. Accepted for publication Feb 06, 2025. Published online Feb 25, 2025.
doi: 10.21037/tau-24-516
View this article at: https://dx.doi.org/10.21037/tau-24-516

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Introduction

Kidney stones are one of the most common urological disorders, affecting approximately 11% of the population in the United States (US) (1). Notably, the recurrence rate can reach up to 50% within five years (2). This high prevalence and recurrence rate have a significant impact on the health and quality of life of patients and is a major economic burden on society and healthcare systems (3). It is anticipated that the prevalence of kidney stones will continue to increase over the next few years, driven by changes in dietary and lifestyle habits (4). Several key risk factors for kidney stone formation have been identified, including obesity, inadequate fluid intake, low consumption of fruits and vegetables, and excessive intake of sugar-sweetened beverages (5,6). These factors are closely linked to modern dietary patterns and sedentary lifestyles, which have become more widespread in recent decades. Therefore, developing effective strategies for the prevention and management of kidney stones is crucial. Early identification of high-risk individuals, along with preventive measures such as lifestyle modifications and targeted interventions, will be key to reducing the burden of kidney stones on both individuals and healthcare systems.

Previous research has identified metabolic syndrome (MetS) and its components as independent risk factors for kidney stone formation, with insulin resistance (IR) playing a central role in this relationship (7-11). IR, a key pathological feature of MetS, occurs when the body's cells become less responsive to insulin. The hyperinsulinemic-euglycemic clamp test is widely regarded as the gold standard for assessing insulin sensitivity and action *in vivo* (12). However, the invasive nature, complexity and high cost of this procedure hamper its widespread applicability in clinical practice (12). Given the limitations of the hyperinsulinemic-euglycemic clamp test, several alternative methods have been developed, including the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR), Quantitative Insulin Sensitivity Check Index (QUICKI), and Triglyceride-Glucose Index (TyG Index) (12,13). Unlike HOMA-IR and QUICKI, the TyG index does not rely on insulin level measurements, making it a more practical option for clinical use. Furthermore, recent studies have demonstrated that combining obesity-related indicators such as body mass index (BMI), waist circumference (WC), and waist-to-height ratio (WHtR) with the TyG index represents a more efficacious approach for assessing the risk of several diseases, such as IR, cardiovascular disease (CVD), and MetS, in comparison to solely utilizing the TyG index (14-17). However, no studies have yet examined the associations of TyG-related parameters with kidney stones.

To address this knowledge gap, a population-based study was conducted to explore the relationships between TyG-related parameters and kidney stone risk, with the aim of identifying more practical clinical indicators for risk assessment. We present this article in accordance with the STROBE checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-24-516/rc) (18).

Highlight box

Key findings

- There are strong positive correlations between triglyceride-glucose (TyG) related parameters (TyG-waist circumference, TyG-waist to height ratio, and TyG-body mass index) and the prevalence of kidney stones among adults in the United States.

What is known and what is new?

- The TyG index is associated with kidney stones.
- This study is the first to comprehensively investigate the associations of TyG-related parameters and kidney stones.

What is the implication, and what should change now?

- TyG-related parameters are more effective than the TyG index alone in predicting the risk of kidney stones.

Methods

Study population

The study employed data from the National Health and Nutrition Examination Survey (NHANES), a comprehensive, ongoing survey conducted by the National Center for Health Statistics (NCHS) under the Centers for Disease Control and Prevention (CDC). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The NHANES research protocol was approved by the NCHS Institutional Review Board, and all individuals provided written informed consent prior to participation. NHANES employs a complex sampling method, including stratified sampling and multistage sampling, aiming to collect information from the non-institutionalized civilian population and provide representative samples of the general population which can reflect the health and nutritional status. The survey collects extensive data through a combination of structured interviews, physical examinations, and laboratory tests, conducted by trained personnel. Each survey cycle

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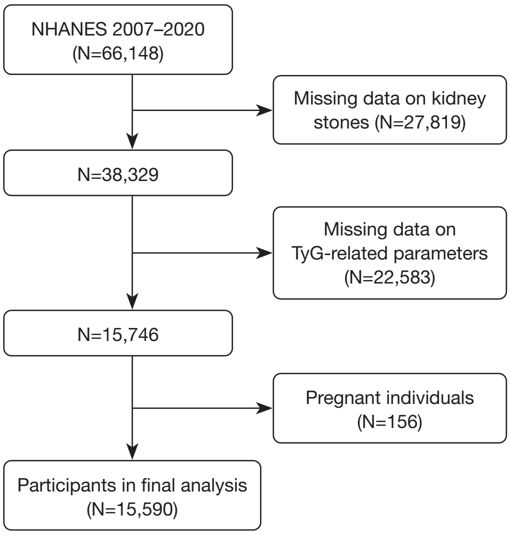

Figure 1 Flow chart of participant selection. NHANES, National Health and Nutrition Examination Survey; TyG, triglyceride glucose.

typically spans two years. NHANES database is publicly available and widely recognized for its utility in exploring the prevalence of diseases, identifying risk factors, and examining the relationships between diet, lifestyle, and health outcomes (19-22).

In our study, six successive survey cycles spanning from 2007 to 2020 were included, encompassing a total of 66,148 participants. The following criteria were employed to exclude participants: (I) individuals with incomplete kidney stones data; (II) individuals with lacking data on triglycerides, fasting blood glucose, or body measurements; and (III) individuals who were pregnant. Eventually, 15,590 participants were incorporated in the study (*Figure 1*).

Measurement of TyG-related parameters

The TyG-related parameters were computed in accordance with the following formulas:

(I) BMI = Weight (kg)/Height (m)^2
(II) WHtR = WC (cm)/Height (cm)
(III) TyG = ln[triglycerides (mg/dL) × fasting blood glucose (mg/dL)/2]
(IV) TyG-WC = TyG × WC
(V) TyG-WHtR = TyG × WHtR
(VI) TyG-BMI = TyG × BMI

All recruited participants were classified into four categories based on the TyG-related parameter quartiles. The first quartile was designated as the reference group.

Assessment of kidney stones

The history of kidney stone formation was assessed using the question, "Have you ever had kidney stones?". Those who responded "Yes" were deemed to have kidney stones. The reliability of self-reported stone history has been previously documented (6).

Covariates

Several variables that might potentially influence the results were identified as confounding factors. Specifically, demographic characteristics encompassed age, sex, race/ethnicity, family poverty-to-income ratio (PIR), and education level. Lifestyle factors included smoking status, alcohol consumption, physical activity, and dietary health. The health conditions included hypertension, diabetes, hyperlipidemia, CVD and chronic kidney disease (CKD). The supplementary materials provided comprehensive details regarding the covariates (Appendix 1).

Statistical analysis

Due to the coronavirus disease 2019 pandemic, the survey cycle for 2019–2020 was terminated in March 2020. In order to maintain the nationally representative nature of the data, data from NHANES 2017–2018 and 2019–March 2020 were combined to create a new data file (NHANES 2017–March 2020 Pre-pandemic), which represents a period of 3.2 years, rather than 2 years like the previous cycles (23). Thus, as recommended by NCHS, the final analysis weights were adjusted as follows: the survey weight of 2007–2016 and 2017–2020 were multiplied by 2/13.2 and 3.2/13.2, respectively.

All missing values in covariates were imputed by the random forest method, which performed by using the "*missForest*" package (24). Continuous data were summarized as weighted averages with standard errors (SE), whereas categorical data were presented as frequency distributions with weighted percentages. Intergroup comparisons of categorical variables and continuous variables between the two groups were conducted by Chi-squared and *t*-tests, respectively. The associations between TyG-related parameters and kidney stones were evaluated by four weighted logistic regression models. Since both WC and WHtR were strongly connected with BMI, the

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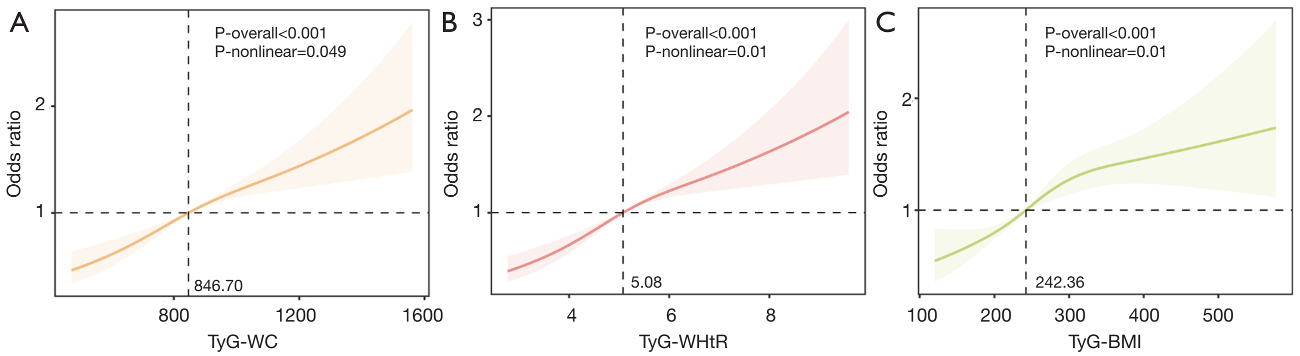

Figure 2 Associations between TyG-WC (A), TyG-WHtR (B), and TyG-BMI (C) with kidney stones were assessed by RCS analysis after adjusted for all covariates. TyG-WC, triglyceride glucose-waist circumference; TyG-WHtR, triglyceride glucose-waist to height ratio; TyG-BMI, triglyceride glucose-body mass index; RCS, restricted cubic spline.

multivariate logistic regression models did not control for BMI. The dose-response relationships between three TyG-related parameters and nephrolithiasis were estimated using restricted cubic spline (RCS) models. The effectiveness of TyG and its associated parameters in estimating the risk of kidney stones was compared by using receiver operating characteristic (ROC) curves.

To further assess the associations of TyG-related parameters with kidney stones, subgroup and interaction analyses were applied according to sex, age, hypertension, diabetes, hyperlipidemia, CVD and CKD. Furthermore, two sensitivity analyses were carried out to examine the reliability of our main findings. Initially, the complete data was used to repeated analysis. Subsequently, for further validation, participants were reclassified into two groups based on the median values of TyG-related factors.

The whole analyses were carried out with R version 4.2.0. The "*survey*" package was used to handle the NHANES complex survey design. All P values were two-sided, with P values of less than 0.05 indicating statistically significant differences.

Results

Baseline characteristics

This cross-sectional study comprised 15,590 participants, among whom 7,950 (50.89%) were female and 7,640 (49.11%) were male. The average age of these participants was 47.96 (SE: 0.27) years. Among these participants, 1,486 (9.92%) reported a history of kidney stones. Compared to participants without history of kidney stones, those with kidney stones had higher TyG-related parameters (Table S1). Individuals with kidney stones tended to be male, elderly, white, smokers, alcohol drinkers, as well as having an unhealthy diet. Furthermore, they were more likely to have comorbidities, including hypertension, diabetes, hyperlipidemia, CVD and CKD (Table S1). Tables S2-S4 summarize the participants' characteristics according to quartiles of TyG-related parameters.

Associations of TyG-related parameters with kidney stones

Table 1 illustrates that either the unadjusted or the adjusted models exhibited a positive correlation between kidney stone and TyG-related parameters (All P for trend <0.05). In the full adjusted model, participants in the fourth quartile of TyG-related parameters had higher risk of kidney stones in comparison to those in the first quartile [odds ratio (95% confidence interval): 2.08 (1.66–2.60) for TyG-WC; 2.21 (1.72–2.84) for TyG-WHtR; 2.03 (1.61–2.57) for TyG-BMI, respectively].

RCS analysis was further employed to visualize the associations of TyG-related parameters with kidney stones. As shown in *Figure 2A-2C*, nonlinear relationships were observed (All P-nonlinear <0.05).

The diagnostic efficacy of various TyG-related parameters for kidney stones was compared using ROC analysis. As illustrated in *Figure 3*, TyG-WC demonstrated the highest diagnostic effectiveness [area under curve (AUC): 0.6130], followed by TyG-WHtR, TyG-BMI and TyG (AUC: 0.6127, 0.5955, and 0.5714, respectively).

Subgroup analysis

The results of the subgroup analysis were summarized

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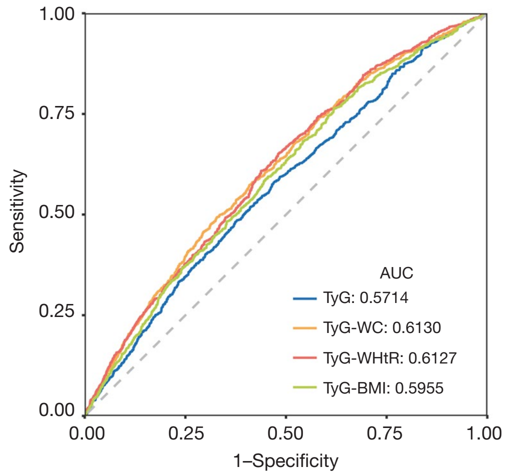

Figure 3 ROC curves of the TyG and its related parameters for predicting kidney stones. AUC, area under curve; ROC, receiver operating characteristic; TyG, triglyceride glucose; TyG-WC, triglyceride glucose-waist circumference; TyG-WHtR, triglyceride glucose-waist to height ratio; TyG-BMI, triglyceride glucose-body mass index.

and visualized in forest plots (*Figure 4*). TyG-related parameters were found to be related to a higher likelihood of developing kidney stones across subgroups based on sex, age, diabetes, and hyperlipidemia. However, there were significant interactions for relationships between TyG-WC, TyG-WHtR and kidney stones in the subgroup of hypertension (P for interaction <0.05), and these significant associations were only observed in non-hypertensive individuals.

Sensitive analysis

After excluding missing data on covariates, participants with higher TyG-related parameters had an increased risk of kidney stones (Table S5). Similarly, these positive relationships remained significant after regrouping (Table S6).

Discussion

In this cross-sectional study, we examined the relationships between TyG-related parameters and kidney stones among US adults. We found that TyG-related parameters (TyG-WC, TyG-WHtR, and TyG-BMI) were significantly positive associated with the prevalence of kidney stones. Notably, TyG-WC demonstrate the highest diagnostic value for kidney stones identification. These findings indicate the potential of TyG-related indicators as surrogate biomarkers for identifying high-risk populations, thereby facilitating the early detection and reduction of kidney stone burden.

While research directly linking TyG-related parameters to kidney stones is limited, the association of TyG index with kidney stones has been extensively studied. The TyG index is increasingly acknowledged as a validated indicator for the identification of IR due to its simplicity and high sensitivity and specificity (13). Two previous studies, which employed data from NHANES, have demonstrated a significant correlation between a higher TyG index and an elevated risk of kidney stones formation and recurrence, highlighting the potential of the TyG index as a reliable indicator for predicting kidney stones (25,26). Furthermore, HOMA-IR has been found to be related to kidney stone formation (11,27,28), further supporting the link between IR and kidney stones. In addition to IR-related indices, obesity and its associated indicators are found to be critical factors in kidney stones formation. A cross-sectional and longitudinal study employed participants from Taiwan Biobank found that five obesity-related indices (including BMI, WC, WHtR, abdominal volume index and body roundness index) were associated with both a higher prevalence of kidney stones and an increased risk of incident kidney stones (29). These results emphasize the critical role of adiposity in kidney stone formation. Recent research suggests that the novel index combining the TyG index and measurements of adiposity offers superior diagnostic value for various diseases compared to TyG alone, particularly in evaluating IR (14,15). A recent cross-sectional study using data from NHANES 2015–2018 revealed a significant association between TyG-BMI and a history of kidney stones (30). Our findings are consistent with this result. However, our study utilized a larger sample size, covering data from 2007–2020, which enhances the robustness of our analysis. Moreover, in addition to evaluating TyG-BMI, we also assessed the relationships between TyG-WC and TyG-WHtR with kidney stone risk. Notably, our results demonstrate that TyG-WC and TyG-WHtR exhibit superior diagnostic efficacy for kidney stones compared to TyG-BMI.

Interestingly, subgroup analysis showed that elevated TyG-WC and TyG-WHtR were linked to an increased risk of kidney stones in non-hypertensive individuals (P for interaction <0.05). One possible explanation is that individuals with hypertension may adopt healthier eating habits, such as the Dietary Approaches to Stop

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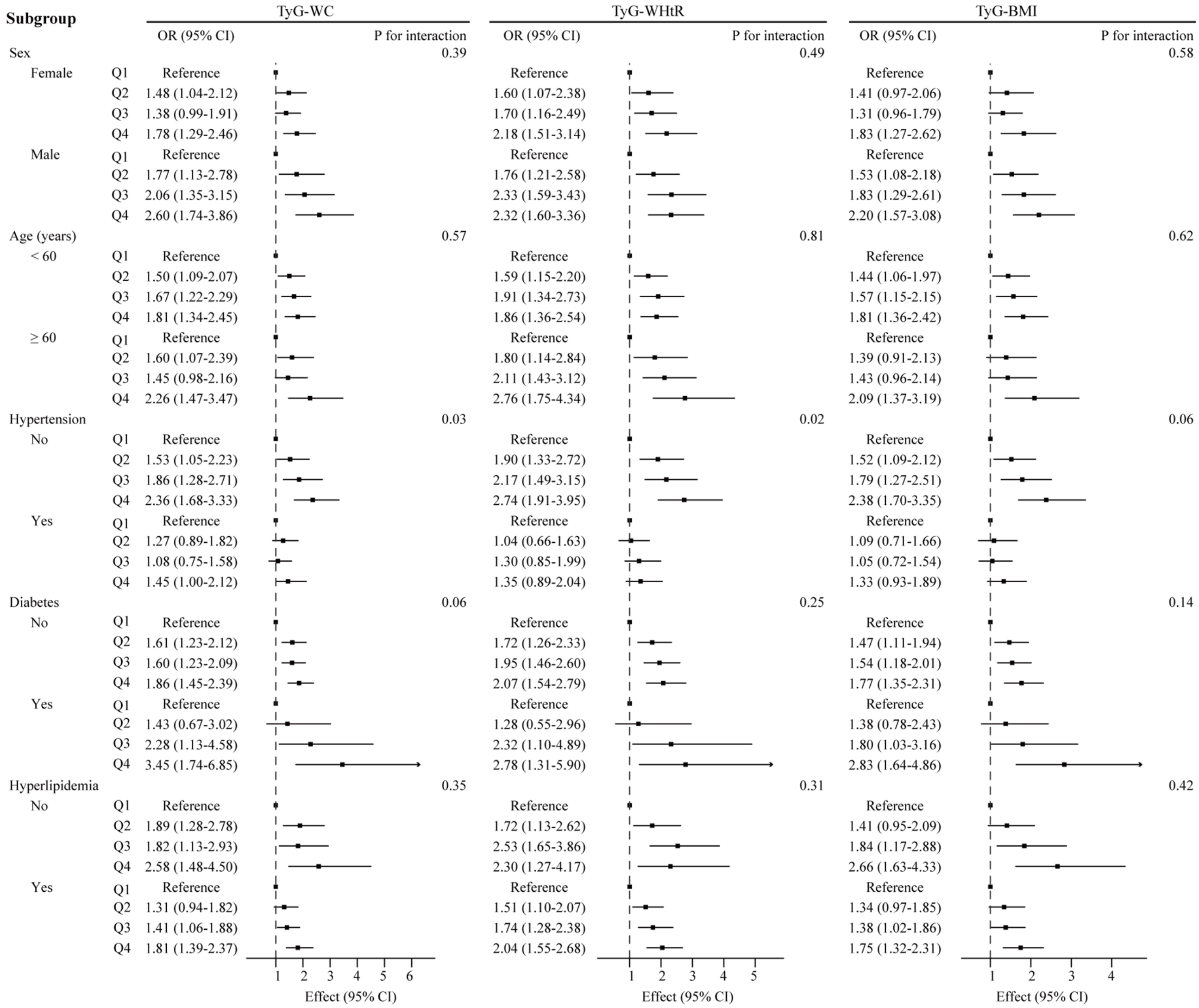

Figure 4 Subgroup analysis of the association between TyG-related parameters and kidney stones. TyG, triglyceride glucose; TyG-WC, triglyceride glucose-waist circumference; TyG-WHtR, triglyceride glucose-waist to height ratio; TyG-BMI, triglyceride glucose-body mass index; OR, odds ratio; CI, confidence interval.

Hypertension diet, which has been shown to improve IR and reduce kidney stone risk (16,31,32). Moreover, research from Iran suggests that IR may have a more pronounced effect on CVD risk in non-hypertensive individuals than in those with hypertension (33). These findings suggest that there is a need for regular monitoring of kidney stones and TyG-related obesity measures, particularly in individuals without underlying health conditions.

The biological mechanisms linking TyG-related parameters and kidney stones are plausible. IR may contribute to stone formation by altering urine composition, such as impairing ammonia excretion, which lowers urine pH and subsequently raises the possibility of uric acid stone formation (34,35). IR may also decrease urinary citrate levels, a critical inhibitor for calcium stone formation (36,37). Additionally, IR has been associated with higher urine calcium (38), which could contribute to the formation of calcium stone. Another potential mechanism by which IR may be linked to the formation of kidney stones is inflammation. Epidemiological evidence indicates that there is a distinct correlation between IR and inflammation (39). Furthermore, chronic inflammation induced by obesity,

Table 1 Association between TyG-related parameters with kidney stones

Subgroup	Case/N	Crude model		Model 1		Model 2		Model 3	
		OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value	OR (95% CI)	P value
TyG-WC index			<0.001†		<0.001†		<0.001†		<0.001†
Q1	211/3,898	Reference		Reference		Reference		Reference	
Q2	327/3,897	1.78 (1.41–2.26)	<0.001	1.55 (1.21–1.96)	<0.001	1.52 (1.19–1.94)	0.001	1.52 (1.18–1.95)	0.002
Q3	393/3,897	2.06 (1.65–2.55)	<0.001	1.70 (1.34–2.15)	<0.001	1.65 (1.31–2.09)	<0.001	1.58 (1.24–2.02)	<0.001
Q4	555/3,898	3.08 (2.55–3.71)	<0.001	2.51 (2.06–3.06)	<0.001	2.41 (1.97–2.94)	<0.001	2.08 (1.66–2.60)	<0.001
TyG-BMI index			<0.001†		<0.001†		<0.001†		<0.001†
Q1	234/3,898	Reference		Reference		Reference		Reference	
Q2	353/3,897	1.67 (1.30–2.14)	<0.001	1.45 (1.12–1.86)	0.005	1.42 (1.11–1.82)	0.006	1.41 (1.09–1.82)	0.01
Q3	401/3,897	1.86 (1.50–2.30)	<0.001	1.63 (1.31–2.04)	<0.001	1.59 (1.27–1.99)	<0.001	1.52 (1.19–1.94)	0.001
Q4	498/3,898	2.64 (2.16–3.22)	<0.001	2.44 (1.98–3.00)	<0.001	2.35 (1.91–2.89)	<0.001	2.03 (1.61–2.57)	<0.001
TyG-WHtR index			<0.001†		<0.001†		<0.001†		<0.001†
Q1	203/3,899	Reference		Reference		Reference		Reference	
Q2	334/3,895	1.94 (1.49–2.52)	<0.001	1.66 (1.27–2.17)	<0.001	1.62 (1.24–2.11)	<0.001	1.62 (1.22–2.14)	0.001
Q3	423/3,899	2.47 (1.95–3.13)	<0.001	2.07 (1.62–2.65)	<0.001	2.01 (1.58–2.56)	<0.001	1.95 (1.50–2.54)	<0.001
Q4	526/3,897	3.18 (2.58–3.91)	<0.001	2.66 (2.14–3.32)	<0.001	2.55 (2.05–3.18)	<0.001	2.21 (1.72–2.84)	<0.001

†, P value for trend. Model 1: Adjusted for age, sex and race/ethnicity. Model 2: adjusted for age, sex, race/ethnicity, family income-poverty ratio, educational level, smoking status, alcohol consumption, physical status, dietary health. Model 3: adjusted the chronic disease condition (hypertension, diabetes, hyperlipidemia, chronic kidney disease, and cardiovascular disease) based on the model 2. TyG, triglyceride glucose; OR, odds ratio; CI, confidence interval; WC, waist circumference; Q, quartile; BMI, body mass index; WHtR, waist to height ratio.

particularly visceral fat accumulation, can impair insulin sensitivity (40,41). Kidney stone development is also linked to inflammation. An *in vitro* study has demonstrated that inflammation is involved in the damage to renal tubular epithelial cells, which may further promote the adhesion of crystals (42). Inflammation is also thought to be involved in the formation of Randall's plaques, which are key sites for the attachment and growth of calcium oxalate stones (43,44).

The vascular hypothesis, first proposed by Stoller *et al.* in 2004, provides additional support for understanding the formation of Randall's plaques and subsequent calcium oxalate stones (45). This hypothesis suggests that the turbulent, relatively hypoxic, and hyperosmotic environment of the renal papillae can promote microvascular damage, and the repair of this damage leads to the deposition of Randall's plaques (46). Interestingly, this process is thought to share similarities with the formation of atherosclerotic plaques (47). MetS, a known risk factor for atherosclerosis, has been closely linked to IR, systemic inflammation, and oxidative stress (48). Given these connections, we speculate that IR may play a critical role in the development of kidney stones by impacting vascular health. IR exacerbates endothelial dysfunction and promotes the pro-inflammatory environment conducive to microvascular damage and plaque formation (39,49,50). This shared pathophysiological pathway may explain the observed overlap between MetS, CVD, and kidney stone risk. Future research should aim to elucidate the molecular and cellular pathways underlying these relationships, with the goal of identifying potential therapeutic targets for preventing kidney stone formation.

There are several strengths in this study. It provides valuable evidence of positive associations between TyG-related parameters and kidney stones, and the use of survey weights allows us to apply our findings to the entire population of the US. Additionally, sensitivity analyses confirm the robustness of our findings. Nonetheless, it is essential to acknowledge some limitations. First, the cross-sectional design of this study makes it impossible to demonstrate a causal association between kidney stones and TyG-related parameters. Second, self-reported

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questionnaires were used to assess the history of kidney stones in the present study, which may result in recall bias and omit asymptomatic cases. Moreover, self-reported stone history can be influenced by socioeconomic factors, such as access to healthcare, as well as age-related memory biases. Additionally, owing to the limitation of the NHANES database, information on the composition of kidney stones was lacked, thus, we were unable to explore the effect of IR on the specific type of stones. Third, since the research was conducted using data from the US population, its conclusions might not apply to other areas or ethnic groups. Lastly, despite adjusting for several confounding factors, there were still unmeasured and undetected confounders which might influence our findings. Thus, well-designed prospective cohort or randomized trial studies are required to elucidate the causal association between kidney stones and TyG-related parameters.

Conclusions

In summary, our findings suggested that TyG-related parameters were substantially related to the prevalence of kidney stones among US adults, with TyG-WC exhibiting the highest predictive capability for kidney stones. These results underscore the significance of IR in the development of kidney stones. Future well-designed cohort studies are required to verify these results in more diverse populations.

Acknowledgments

We thank all the NHANES participants and staff for their contributions.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://tau.amegroups.com/article/view/10.21037/tau-24-516/rc

Peer Review File: Available at https://tau.amegroups.com/article/view/10.21037/tau-24-516/prf

Funding: None.

Conflicts of Interest: Both authors have completed the ICMJE uniform disclosure form (available at https://tau.amegroups.com/article/view/10.21037/tau-24-516/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

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Cite this article as: Yu H, Wu J. Associations of triglyceride glucose-related parameters with kidney stones: a cross-sectional study from NHANES 2007–2020. Transl Androl Urol 2025;14(2):379-388. doi: 10.21037/tau-24-516

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