**TITLE: Triglyceride glucose index predicting cardiovascular mortality in Chinese initiating peritoneal dialysis: a cohort study**

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**ABSTRACT**

**Background**

Insulin resistance is increased among people with end stage kidney diseases (ESRD). The Triglyceride glucose (TyG) index is a marker of insulin resistance and is also associated with the prognosis of cardiovascular disease among patients initiating peritoneal dialysis. We aimed to examine associations between TyG index and cardiovascular deaths in patients initiating peritoneal dialysis.

**Methods and results**

3,054 patients initiating peritoneal dialysis between 2007 and 2014 were included in a prospective cohort derived from Henan Peritoneal Dialysis Registry, TyG index alongside other baseline characteristics were measured when ESRD patients initiated peritoneal dialysis. Logistic regression adjusting for age, gender and major cardiovascular risk factors estimated the association between TyG index with subsequent cardiovascular mortality within 2 years since the initiation of peritoneal dialysis.

**Results**

TyG index was positively associated with cardiovascular mortality: adjusted incidence rates ratio (95% CI) comparing the highest vs lowest TyG index quartile was 2.32 (2.12 to 2.55) in all, 2.22 (2.01 to 2.46) in those with body mass index (BMI) <25kg/m2 and 2.82 (2.24 to 3.54) in those with BMI≥25kg/m2, respectively. Linear dose-response relationships were revealed in all and by BMI.

**Conclusions**

TyG index might be a prognostic factor in predicting cardiovascular mortality among patients initiating peritoneal dialysis.

**INTRODUCTION**

Chronic kidney disease (CKD) has become a worldwide heath problem (1). In particular, end-stage renal disease (ESRD) triggers premature mortality and is a substantial health economic burden (1). It has been estimated that more than 10.8% of Chinese adults (around 130 million) have CKD with dialysis needed at some point in their lives (2). The Chinese medical insurance scheme has now increased its coverage, making dialysis, especially peritoneal dialysis (PD), more affordable among Chinese patients with ESRD (3).

Cardiovascular disease (CVD) is the main cause of death in peritoneal dialysis (PD) patients (4), a situation that can be explained by a combination of traditional and non-traditional risk factors for CVD in these patients (5, 6). Glucose and insulin homeostasis are altered in chronic kidney disease (CKD) patients even in the early stages of CKD, leading to insulin resistance (IR) by various pathways (7). Several factors have been implicated in the pathogenesis of IR, including anemia, dyslipidemia, uremia, malnutrition, excess of parathyroid hormone, vitamin D deficiency, metabolic acidosis, and increase in plasma free fatty acids and proinflammatory cytokines (8). IR and dyslipidaemia are observed and increase with the progression of CKD, playing an important role in the pathogenesis of hypertension and atherosclerosis (9). Particularly in PD patients, exposure to glucose from dialysis fluid accentuates the foregoing metabolic abnormalities. IR and altered glucose metabolism are frequently observed in CKD, and perhaps alter PD patient survival (10).

IR is a pivotal component in the pathophysiology of Type 2 diabetes mellitus and has often existed 10-20 years prior to the diagnosis (10-12). However, measurement of IR is costly and complex (13). Therefore, a simple, reliable and reproducible index to measure IR is needed.

Many recent studies have shown that the triglyceride glucose (TyG) index is associated with IR (14-17), as assessed by hyperinsulinemic (euglycemic) clamp testing and HOMA IR. The clamp is a complex method and not used in clinical practice. Similarly, HOMA IR cannot be used routinely due to cost of insulin assays (if not on insulin therapy), and lack proof validity among patients treated with insulin therapy. Thus, the TyG index has been proposed as a reliable and simple surrogate marker of IR in clinical practice (14-17).

Consistent with these data, there is growing evidence to suggest that the TyG index is associated with cardiovascular disease (18-20). However, to best of our knowledge few studies have examined the relationship between the TyG index and deaths mainly due to CVD in incident PD patients. Therefore, in the present study, we investigated the relationship between the TyG index and cardiovascular mortality among patients initialiating peritoneal dialysis.

**METHODS**

**Data source and study population**

Data from the Henan Peritoneal Dialysis Registry (HPDR) were used. A province in Central China, the population of Henan is over 100 million. The First Affiliated Hospital of Zhengzhou University Department of Nephrology manages the HPDR providing an independent audit and analysis of renal care in the province.

Over the study period, electronic information was routinely and prospectively collected from all nephrological units across Henan. Data reached the HPDR are subjected to an algorithm which identifies suspicious records (for example, body mass index over 65 kg/m2), which are then further verified and corrected where necessary by contacting the nephrological unit (overall response rate 97.5%).

The present study was designed as a cohort study, which incorporated all incident PD patients aged more than 18 years who initiated PD between 2007–2014 and who had at least two years’ follow-up. Patients who died, underwent transplant or whose kidney function recovered within 90 days after initiation of PD were dropped off (n = 16) to avoid a reverse causal association between exposures and outcome.

Ethics approval was granted by the Clinical Research Ethics Committee of the First Affiliated Hospital of Zhengzhou University. Written informed consent was obtained from all participants before inclusion.

**Outcome definition**

We defined our primary outcome as recorded death, on the HPDR, with clinically diagnosed cardiovascular disease (including coronary heart disease, heart failure, myocardial infarction, arrhythmia or stroke) as the cause of death. (6, 21)

**Exposure definition**

TyG index was calculated as the ln[fasting triglyceride (mg/dl) × fasting glucose (mg/dl)/2]. (14) Patients were classified into four groups by quartiles of TyG index: Group 1 (TyG index <8.10), Group 2 (TyG index in 8.10-8.39); Group 3 (TyG index in 8.39-8.69), and Group 4 (TyG index ≥ 8.69).

**Co-variables and missing information**

All available information, including demographic characteristics, self-reported comorbidities, and clinical measurements at the time of patients initializing the PD were evaluated.(6) For co-variables, our cohort had missing information on body mass index (13.51%), phosphorus (20.92%), albumin (19.92%), total protein (22.57%), total cholesterol (24.25%), low density lipoprotein (24.58%), fasting glucose (15.92%), sodium (8.02%), systolic blood pressure (4.82%), and diastolic blood pressure (4.82%). We used multiple imputation to replace missing values by using a chained equation approach based on all candidate predictors. We created 30 imputed datasets for missing variables that were then combined across all datasets by using Rubin’s rule to obtain final estimates.

**Statistical analysis**

In descriptive analyses, differences in participant characteristics by TyG index categories were assessed by logistic regression model for categorical variables, and generalized linear model for continuous variables.

Logistic regression was used to estimate crude and adjusted incidence rates ratios of cardiovascular mortality by TyG index categories with adjustment of covariables (including clinical measurements, comorbidities and treatments) presented in Table-1. The dose-response relationships between TyG index and risks of cardiovascular mortality were estimated using a linear model, a natural cubic spline model with three equally spaced knots determined from the levels of TyG index measures, and a quadratic spline model. The natural cubic spline model was chosen as the best fit model for the relationship curve by its minimum Akaike information criterion (AIC) compared with the linear model or quadratic spline model. The linear test was used in the natural cubic spline model to test the linearity of the relationship. The break-point test(11) was carried out to target the potential thresholds (P5 to P95 of TyG index measures) by incorporating the piecewise term into the cubic spline model. The threshold with a significant break in the regression coefficients and achieving the minimum AIC was chosen as the final threshold.(22) The 95% CI of the threshold was obtained from 1000 bootstrap samples.

As the most important confounder, the role of the body mass index in the association between TyG index and risks of cardiovascular mortality was examined by categorical analysis.

All analyses were performed using STATA (STATA/MP 15.0 StataCorp, College Station, TX, USA). All *P* values were calculated using two-tailed tests and a *P* value < 0.05 was taken to indicate statistical significance.

**RESULTS**

**Table 1** shows patient characteristics among patients with initiated PD by TyG index levels. Compared with those with a low level of TyG index (TyG index < 8.10), patients with high levels of TyG index were more likely to be female, have existing cardiovascular disease and/or type 2 diabetes, taking an antidiabetes agent and be less likely to be taking antihypertensive treatment. Patients with high levels of TyG index were also more likely to have higher levels of haemoglobin, packed cell volume, reticulocytes, phosphate, albumin, total iron binding capacity, transferrin, total protein, pre-albumin, total cholesterol, low density lipoprotein, fasting glucose, C-reaction protein, systolic blood pressure and body mass index, and a lower level of FeTIBC, estimated glomerular filtration rate, sodium, high density lipoprotein and diastolic blood pressure.

**Table 2** shows the cardiovascular mortality rates by TyG index groups. Patients with higher levels of TyG index were more likely to have higher cardiovascular mortality rates, as 8.49% (of 766 patients), 12.63% (of 760 patients), 16.97% of (766 patients), and 19.16% (of 762 patients) for TyG index < 8.10, 8.10-8.38, 8.39-8.68 and ≥8.69, respectively.

The cardiovascular mortality rates by TyG index groups were the same pattern in patients with a body mass index <25 kg/m2 and patients with body mass index ≥ 25 kg/m2. Among patients with body mass index <25 kg/m2, cardiovascular mortality rate was 8.85% (of 610 patients), 13.76% (of 596 patients), 17.91% (of 603 patients), and 19.37% (of 542 patients) for TyG index < 8.10, 8.10-8.38, 8.39-8.68 and ≥8.69, respectively. Among patients with body mass index ≥25 kg/m2, cardiovascular mortality rate was 7.05% (of 156 patients), 8.54% (of 164 patients), 14.20% (of 162 patients), and 18.10% (of 221 patients) for TyG index < 8.10, 8.10-8.38, 8.39-8.68 and ≥8.69, respectively.

**Table 2** also shows that the risks of cardiovascular mortality increased significantly with increasing TyG index compared with those with the lowest TyG index group (TyG index < 8.10):adjusted incidence rates ratio (IRR) for cardiovascular mortality 1.62 (95% CI: 1.47 to 1.78), 1.96 (1.79 to 2.15) and 2.32 (2.12 to 2.55) for TyG index in 8.10-8.38, 8.39-8.68, and ≥8.69, respectively. The adjusted IRRs were the same pattern in patients with body mass index <25 kg/m2 and patients with body mass index ≥ 25 kg/m2. Among patients with body mass index <25 kg/m2, the adjusted IRR was 1.48 (1.34 to 1.65), 1.74 (1.57 to 1.93) and 2.22 (2.01 to 2.46) for TyG index in 8.10-8.38, 8.39-8.68, and ≥8.69, respectively. Among patients with body mass index ≥ 25 kg/m2, the adjusted IRR was 1.18 (0.92 to 1.51), 2.40 (1.90 to 3.03) and 2.82 (2.24 to 3.54) for TyG index in 8.10-8.38, 8.39-8.68, and ≥8.69, respectively.

A linear relationship between TyG index and cardiovascular mortality was found (P-values for linear test > 0.05). Relationship curves were derived from the natural cubic spline models with adjustment of covariates in **Figure** **1**. Similar linear relationships were revealed in the sensitivity analyses modelling the associations in patients with body mass index < 25kg/m2 (P-values for linear test >0.05) as shown as the middle panel of **Figure 1 and** in patients with body mass index ≥ 25kg/m2 (P-values for linear test> 0.05) as shown as the right panel of **Figure 1**.

**DISCUSSION**

In this large prospective cohort of patients initiating PD in a province of China, we provide evidence that TyG index may be a prognostic factor for subsequent risk of cardiovascular mortality, the most common reason for death among patients with ESRD. To our knowledge, this is the first study to identify TyG index measured in the initiation of PD as an independent risk factor of cardiovascular mortality. Increased levels of TyG index were associated with a greater risk of cardiovascular mortality, even after adjusting for potential confounders such as eGFR, comorbidities, blood pressure, and other lipid measurements. The TyG index, a marker indicating the severity of IR, among patients in the highest quartile showed a 2.32-fold increased risk of cardiovascular mortality compared with patients in the lowest quartile.

Although TyG index is a good surrogate of IR, prior studies have been most focused on its relationship to the risk of development of type 2 diabetes (8, 23-25). To date, these have reported significant associations between the TyG index level and risk of incident diabetes in both general and metabolically high-risk populations (23-25). Some other studies also reported significant associations between TyG index and arterial stiffness (26), subclinical atherosclerosis (27), coronary artery calcification (CAC) (28), and cardiac autonomic neuropathy (29), which all suggest that the TyG index is a surrogate for IR, which in turn contributed to the development and prognosis of cardiovascular diseases. Notably, in our study, we identified the TyG index, a commonly used proxy of IR (23), as a novel prognostic factor for cardiovascular mortality for patients initializing PD. Although the TyG index has not previously been examined in the relationship with the risk of cardiovascular mortality among PD patients, our findings are consistent with others showing an increased level of measures of glucose and cardiovascular risk factors (e.g., elevated fasting glucose, C-reaction protein) among patients with higher levels of the TyG index. Taken together, these findings suggest that higher level of TyG index, which could result from impaired insulin and metabolism status, could be related to the prognosis of cardiovascular diseases in patients with ESRD.

In prior studies, IR measured by HOMA-IR was documented to be associated with parameters of metabolic disorders such as body mass index, impaired fasting glucose, and triglyceride, et al among patients with prevalent PD. In addition, increased HOMA-IR was significantly associated with new-onset cardiovascular events. For example, in a Chinese PD case cohort study, patients with a HOMA-IR between 2.85-19.5 compared with those with HOMA-IR between 0.83-2.71 had a 17-fold increased risk of new-onset cardiovascular events (30). In a Korean PD case cohort, there was an 18% increased risk of new-onset major cardiovascular events in PD patients with an average HOMA-IR of 4.7 compared with PD patients with an average HOMA-IR of 2.6 (31). Consistent with previous findings, among patients initiating PD we observed more severe IR measured by the TyG index was significantly associated with higher risk of cardiovascular mortality after adjusting for potential confounders. In particular, compared with incident PD patients who had a TyG index < 8.10, incident PD patients who had TyG index >8.69 had an almost threefold greater risk of cardiovascular mortality.

Although the mechanism underlying the relationship between the TyG index and CAC has not been clarified, it may be linked to IR. Some studies have suggested that IR leads to chronic inflammation, altered coagulation and atherosclerosis (32, 33). Furthermore, an independent association between IR and CAC has been reported (34, 35). Both the HOMA-IR and the TyG index are well known representative markers of IR, and they are closely related to each other. However, our findings showed that the TyG index was better associated with the presence of coronary artery atherosclerosis than was HOMA-IR, and this result may be explained by the fact that the two indices reflect different aspects of IR. While the TyG index reflects IR mainly in the muscle (36, 37), HOMA-IR indicates IR mainly in the liver (38, 39), which may have caused the difference. Peripheral IR may be a very useful surrogate of coronary artery atherosclerosis (40). Moreover, it has been suggested that IR, inflammation and malnutrition complex interact closely on the progress of atherosclerosis among dialysis patients (41).

As an observational study, it is difficult to prove a causal association between TyG index and cardiovascular mortality among incident PD patients. However, prior studies among dialysis patients have suggested that the progression of IR and associated subsequent cardiovascular events could be altered by intervening with eg strict dietary management, intense antihypertensive treatments, anti-diabetes treatments, and lipid lowering treatments (42, 43). As a useful prognostic factor, TyG index as the surrogate of IR might be used to routinely screen high cardiovascular risk patients for tailored interventions and treatments in the PD clinic.

There are several strengths to our study. First, our study uses a prospective case cohort design incorporating incident PD patients with a relatively large sample size. The HPRD is the only PD registry data in Henan including all patients receiving PD care in Henan who will be followed up for their lifetime; therefore selection bias and respondent bias were relatively small in this study. Second, the HPRD is located in Henan, the province with the largest population size in China, suggesting our study is likely to be a representative sample. Third, because other metabolic risk factors may influence IR and the onset of cardiovascular events, an additional strength of this study was that most metabolic risk factors were measured and accounted for in our primary analyses. There are some limitations in our study. First, there was some distinctive differences between the patients in our study and other non-Chinese ESRD patients, typical European ESRD patients, for example, young age, lower BMI, lower prevalence of comorbidities and lower percentage of treatment, which suggests potential adjustments might be needed when examining the association between TyG index and cardiovascular mortality in external non-Chinese ESRD populations, especially European ESRD populations. Second, some traditional risk factors, like smoking and prior health information were not accessible in our study. Third, the relatively high missing percentage of some variables, for example, phosphate and albumin might have some impact on extrapolation of our findings especially in the external population.

**CONCLUSIONS**

In summary, findings from this cohort study suggest that incident PD patients with IR, namely with higher TyG index levels, are more prone to suffer from cardiovascular events. This study also adds an important piece of evidence that TyG index might be a good prognostic factor in predicting cardiovascular deaths among patients initiating PD.

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**DISCLOSURE STATEMENT**

The authors declare that they have no competing interests.

References

1. Ojo A: Addressing the global burden of chronic kidney disease through clinical and translational research. Trans Am Clin Climatol Assoc 2014;125:229-43; discussion 243-6.

2. Li PK, Chow KM, Van de Luijtgaarden MW, Johnson DW, Jager KJ, Mehrotra R, Naicker S, Pecoits-Filho R, Yu XQ, Lameire N: Changes in the worldwide epidemiology of peritoneal dialysis. Nat Rev Nephrol 2017;13:90-103.

3. Zhang X, Chen Y, Cai Y, Tian X, Xiao J, Zhao Z, Yu D: Characteristics of Patients Initializing Peritoneal Dialysis Treatment From 2007 to 2014: Analysis From Henan Peritoneal Dialysis Registry data. Iran J Kidney Dis 2018;12:178-184.

4. Vanholder R, Annemans L, Brown E, Gansevoort R, Gout-Zwart JJ, Lameire N, Morton RL, Oberbauer R, Postma MJ, Tonelli M, Biesen WV, Zoccali C, European Kidney Health Alliance: Reducing the costs of chronic kidney disease while delivering quality health care: a call to action. Nat Rev Nephrol 2017;13:393-409.

5. Krediet RT, Balafa O: Cardiovascular risk in the peritoneal dialysis patient. Nat Rev Nephrol 2010;6:451-460.

6. Yu D, Cai Y, Chen Y, Chen T, Qin R, Zhao Z, Simmons D: Development and validation of risk prediction models for cardiovascular mortality in Chinese people initialising peritoneal dialysis: a cohort study. Sci Rep 2018;8:1966-018-20160-3.

7. Rabbani N, Thornalley PJ: Advanced glycation end products in the pathogenesis of chronic kidney disease. Kidney Int 2018;93:803-813.

8. Fortes PC, de Moraes TP, Mendes JG, Stinghen AE, Ribeiro SC, Pecoits-Filho R: Insulin resistance and glucose homeostasis in peritoneal dialysis. Perit Dial Int 2009;29 Suppl 2:S145-8.

9. Lo WK: Metabolic syndrome and obesity in peritoneal dialysis. Kidney Res Clin Pract 2016;35:10-14.

10. de Moraes TP, Pecoits-Filho R: Metabolic impact of peritoneal dialysis. Contrib Nephrol 2009;163:117-123.

11. Lee SH, Kwon HS, Park YM, Ha HS, Jeong SH, Yang HK, Lee JH, Yim HW, Kang MI, Lee WC, Son HY, Yoon KH: Predicting the development of diabetes using the product of triglycerides and glucose: the Chungju Metabolic Disease Cohort (CMC) study. PLoS One 2014;9:e90430.

12. Warram JH, Martin BC, Krolewski AS, Soeldner JS, Kahn CR: Slow glucose removal rate and hyperinsulinemia precede the development of type II diabetes in the offspring of diabetic parents. Ann Intern Med 1990;113:909-915.

13. Zhang M, Wang B, Liu Y, Sun X, Luo X, Wang C, Li L, Zhang L, Ren Y, Zhao Y, Zhou J, Han C, Zhao J, Hu D: Cumulative increased risk of incident type 2 diabetes mellitus with increasing triglyceride glucose index in normal-weight people: The Rural Chinese Cohort Study. Cardiovasc Diabetol 2017;16:30-017-0514-x.

14. Guerrero-Romero F, Simental-Mendia LE, Gonzalez-Ortiz M, Martinez-Abundis E, Ramos-Zavala MG, Hernandez-Gonzalez SO, Jacques-Camarena O, Rodriguez-Moran M: The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. J Clin Endocrinol Metab 2010;95:3347-3351.

15. Vasques AC, Novaes FS, de Oliveira Mda S, Souza JR, Yamanaka A, Pareja JC, Tambascia MA, Saad MJ, Geloneze B: TyG index performs better than HOMA in a Brazilian population: a hyperglycemic clamp validated study. Diabetes Res Clin Pract 2011;93:e98-e100.

16. Mohd Nor NS, Lee S, Bacha F, Tfayli H, Arslanian S: Triglyceride glucose index as a surrogate measure of insulin sensitivity in obese adolescents with normoglycemia, prediabetes, and type 2 diabetes mellitus: comparison with the hyperinsulinemic-euglycemic clamp. Pediatr Diabetes 2016;17:458-465.

17. Song do K, Lee H, Sung YA, Oh JY: Triglycerides to High-Density Lipoprotein Cholesterol Ratio Can Predict Impaired Glucose Tolerance in Young Women with Polycystic Ovary Syndrome. Yonsei Med J 2016;57:1404-1411.

18. Lee EY, Yang HK, Lee J, Kang B, Yang Y, Lee SH, Ko SH, Ahn YB, Cha BY, Yoon KH, Cho JH: Triglyceride glucose index, a marker of insulin resistance, is associated with coronary artery stenosis in asymptomatic subjects with type 2 diabetes. Lipids Health Dis 2016;15:155-016-0324-2.

19. Sanchez-Inigo L, Navarro-Gonzalez D, Fernandez-Montero A, Pastrana-Delgado J, Martinez JA: The TyG index may predict the development of cardiovascular events. Eur J Clin Invest 2016;46:189-197.

20. Vega GL, Barlow CE, Grundy SM, Leonard D, DeFina LF: Triglyceride-to-high-density-lipoprotein-cholesterol ratio is an index of heart disease mortality and of incidence of type 2 diabetes mellitus in men. J Investig Med 2014;62:345-349.

21. Zhang X, Yu D, Cai Y, Shang J, Qin R, Xiao J, Tian X, Zhao Z, Simmons D: Dose-Response Between Cardiovascular Risk Factors and Cardiovascular Mortality Among Incident Peritoneal Dialysis Patients. Kidney Blood Press Res 2018;43:628-638.

22. Yu D, Simmons D: Association between blood pressure and risk of cardiovascular hospital admissions among people with type 2 diabetes. Heart 2014;100:1444-1449.

23. Low S, Khoo KCJ, Irwan B, Sum CF, Subramaniam T, Lim SC, Wong TKM: The role of triglyceride glucose index in development of Type 2 diabetes mellitus. Diabetes Res Clin Pract 2018;143:43-49.

24. Lee DY, Lee ES, Kim JH, Park SE, Park CY, Oh KW, Park SW, Rhee EJ, Lee WY: Predictive Value of Triglyceride Glucose Index for the Risk of Incident Diabetes: A 4-Year Retrospective Longitudinal Study. PLoS One 2016;11:e0163465.

25. Navarro-Gonzalez D, Sanchez-Inigo L, Pastrana-Delgado J, Fernandez-Montero A, Martinez JA: Triglyceride-glucose index (TyG index) in comparison with fasting plasma glucose improved diabetes prediction in patients with normal fasting glucose: The Vascular-Metabolic CUN cohort. Prev Med 2016;86:99-105.

26. Lee SB, Ahn CW, Lee BK, Kang S, Nam JS, You JH, Kim MJ, Kim MK, Park JS: Association between triglyceride glucose index and arterial stiffness in Korean adults. Cardiovasc Diabetol 2018;17:41-018-0692-1.

27. Lambrinoudaki I, Kazani MV, Armeni E, Georgiopoulos G, Tampakis K, Rizos D, Augoulea A, Kaparos G, Alexandrou A, Stamatelopoulos K: The TyG Index as a Marker of Subclinical Atherosclerosis and Arterial Stiffness in Lean and Overweight Postmenopausal Women. Heart Lung Circ 2018;27:716-724.

28. Kim MK, Ahn CW, Kang S, Nam JS, Kim KR, Park JS: Relationship between the triglyceride glucose index and coronary artery calcification in Korean adults. Cardiovasc Diabetol 2017;16:108-017-0589-4.

29. Akbar M, Bhandari U, Habib A, Ahmad R: Potential Association of Triglyceride Glucose Index with Cardiac Autonomic Neuropathy in Type 2 Diabetes Mellitus Patients. J Korean Med Sci 2017;32:1131-1138.

30. Li Y, Zhang L, Gu Y, Hao C, Zhu T: Insulin resistance as a predictor of cardiovascular disease in patients on peritoneal dialysis. Perit Dial Int 2013;33:411-418.

31. Yoon CY, Lee MJ, Kee YK, Lee E, Joo YS, Han IM, Han SG, Oh HJ, Park JT, Han SH, Kang SW, Yoo TH: Insulin resistance is associated with new-onset cardiovascular events in nondiabetic patients undergoing peritoneal dialysis. Kidney Res Clin Pract 2014;33:192-198.

32. Kahn AM, Allen JC, Seidel CL, Zhang S: Insulin inhibits migration of vascular smooth muscle cells with inducible nitric oxide synthase. Hypertension 2000;35:303-306.

33. Defronzo RA: Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 2009;58:773-795.

34. Meigs JB, Larson MG, D'Agostino RB, Levy D, Clouse ME, Nathan DM, Wilson PW, O'Donnell CJ: Coronary artery calcification in type 2 diabetes and insulin resistance: the framingham offspring study. Diabetes Care 2002;25:1313-1319.

35. Yamazoe M, Hisamatsu T, Miura K, Kadowaki S, Zaid M, Kadota A, Torii S, Miyazawa I, Fujiyoshi A, Arima H, Sekikawa A, Maegawa H, Horie M, Ueshima H, SESSA Research Group: Relationship of Insulin Resistance to Prevalence and Progression of Coronary Artery Calcification Beyond Metabolic Syndrome Components: Shiga Epidemiological Study of Subclinical Atherosclerosis. Arterioscler Thromb Vasc Biol 2016;36:1703-1708.

36. Han T, Cheng Y, Tian S, Wang L, Liang X, Duan W, Na L, Sun C: Changes in triglycerides and high-density lipoprotein cholesterol may precede peripheral insulin resistance, with 2-h insulin partially mediating this unidirectional relationship: a prospective cohort study. Cardiovasc Diabetol 2016;15:154-016-0469-3.

37. Kelley DE, Goodpaster BH: Skeletal muscle triglyceride. An aspect of regional adiposity and insulin resistance. Diabetes Care 2001;24:933-941.

38. Tripathy D, Almgren P, Tuomi T, Groop L: Contribution of insulin-stimulated glucose uptake and basal hepatic insulin sensitivity to surrogate measures of insulin sensitivity. Diabetes Care 2004;27:2204-2210.

39. Bonora E, Targher G, Alberiche M, Bonadonna RC, Saggiani F, Zenere MB, Monauni T, Muggeo M: Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. Diabetes Care 2000;23:57-63.

40. Irace C, Carallo C, Scavelli FB, De Franceschi MS, Esposito T, Tripolino C, Gnasso A: Markers of insulin resistance and carotid atherosclerosis. A comparison of the homeostasis model assessment and triglyceride glucose index. Int J Clin Pract 2013;67:665-672.

41. Pecoits-Filho R, Lindholm B, Stenvinkel P: The malnutrition, inflammation, and atherosclerosis (MIA) syndrome -- the heart of the matter. Nephrol Dial Transplant 2002;17 Suppl 11:28-31.

42. Cioni A, Sordini C, Cavallini I, Bigazzi R, Campese VM: Angiotensin receptor blocker telmisartan improves insulin sensitivity in peritoneal dialysis patients. Perit Dial Int 2010;30:66-71.

43. Wong TY, Szeto CC, Chow KM, Leung CB, Lam CW, Li PK: Rosiglitazone reduces insulin requirement and C-reactive protein levels in type 2 diabetic patients receiving peritoneal dialysis. Am J Kidney Dis 2005;46:713-719.

**FIGURE LEGENDS**

**Figure-1**. Dose-response association between TyG and adjusted incidence rates ratio of cardiovascular mortality in all and by body mass index

*BMI indicates body mass index. In the left panel, covariables presented in table-1 were adjusted. In the middle and the right panels, covariables presented in table-1 except for body mass index were adjusted.*

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**Table-1**. Baseline characteristics and their comparisons according to TyG index quartiles.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  |  |  |  |  |  |
|  | Quartile 1  (<8.10) | Quartile 2  (8.10-8.39) | Quartile 3  (8.39-8.69) | Quartile 4  (≥8.69) | P |
| N | 766 | 760 | 766 | 762 | - |
| Age, years | 46 (35 to 56) | 47 (37 to 56) | 48 (39 to 61) | 48 (39 to 60) | 0.2356 |
| Male gender, n (%) | 502 (65.5) | 419 (55.1) | 432 (56.4) | 437 (57.3) | <0.001 |
| Haemoglobin, g/L | 88.7 (74.0 to 103.0) | 93.0 (80.0 to 102.0) | 95.0 (81.0 to 107.0) | 94.0 (81.0 to 108.0) | <0.001 |
| Packed cell volume | 19.0 (1.7 to 28.0) | 0.3 (0.2 to 25.1) | 14.5 (0.3 to 28.5) | 20.5 (0.3 to 30.1) | <0.001 |
| Reticulocytes, % | 34.0 (2.8 to 58.0) | 58.0 (31.6 to 85.0) | 49.5 (21.0 to 83.5) | 55.0 (24.1 to 79.0) | <0.001 |
| Phosphate, mg/dl | 1.7 (1.4 to 2.1) | 1.8 (1.4 to 2.1) | 1.7 (1.4 to 2.0) | 1.7 (1.4 to 2.1) | <0.001 |
| Albumin, g/L | 33.2 (29.5 to 36.5) | 32.5 (30.1 to 36.8) | 34.0 (30.2 to 37.0) | 34.2 (30.9 to 38.7) | <0.001 |
| Total iron binding capacity , μmol/L | 42.2 (33.5 to 52.0) | 52.0 (40.9 to 52.0) | 52.0 (41.4 to 53.0) | 47.1 (34.4 to 52.1) | <0.001 |
| FeTIBC, mmol/L | 26.0 (21.1 to 40.1) | 23.1 (22.6 to 37.3) | 23.1 (20.0 to 36.0) | 23.1 (20.3 to 31.3) | <0.001 |
| Estimated Glomerular Filtration rate, mL/min/1.73 m2 | 1.6 (0.4 to 3.7) | 1.5 (0.6 to 3.1) | 1.4 (0.5 to 3.8) | 1.5 (0.5 to 3.0) | <0.001 |
| Transferrin, mg/dl | 181.1 (75.1 to 36.5) | 164.2 (106.0 to 258.0) | 167.0 (100.4 to 308.3) | 238.0 (154.0 to 405.4) | <0.001 |
| Total protein, g/L | 54.8 (50.4 to 60.1) | 57.6 (52.2 to 60.4) | 58.0 (53.6 to 62.3) | 59.0 (54.5 to 64.4) | <0.001 |
| Pre-albumin, mg/L | 304.2 (221.0 to 350.0) | 345.0 (246.0 to 409.0) | 313.0 (250.0 to 406.0) | 342.0 (257.0 to 395.0) | <0.001 |
| Total Cholesterol, mmol/L | 3.9 (3.3 to 4.6) | 4.3 (3.6 to 5.0) | 4.5 (3.7 to 5.1) | 4.9 (4.1 to 5.1) | <0.001 |
| Triglyceride, mmol/L | 0.8 (0.6 to 0.9) | 1.0 (0.9 to 1.1) | 1.1 (0.6 to 1.5) | 1.8 (1.5 to 2.1) | <0.001 |
| Low density lipoprotein, mmol/L | 2.3 (1.3 to 2.8) | 2.6 (2.0 to 3.1) | 2.6 (2.0 to 3.2) | 2.8 (2.1 to 3.4) | <0.001 |
| High density lipoprotein, mmol/L | 1.2 (1.0 to 1.4) | 1.1 (1.0 to 1.3) | 1.2 (1.0 to 1.3) | 1.1 (0.9 to 1.3) | <0.001 |
| Fasting glucose, mmol/L | 4.2 (3.9 to 4.6) | 4.6 (4.3 to 5.1) | 4.9 (4.4 to 5.3) | 5.0 (4.5 to 5.6) | <0.001 |
| Sodium, mEq/L | 141.0 (138.0 to 143.2) | 141.0 (138.0 to 144.0) | 140.3 (138.0 to 143.0) | 140.0 (137.2 to 142.5) | <0.001 |
| C-reactive protein, mg/dl | 2.0 (1.0 to 6.1) | 1.2 (0.6 to 2.8) | 2.3 (1.0 to 5.8) | 3.0 (1.3 to 5.2) | <0.001 |
| Body mass index, kg/m2 | 22.2 (20.6 to 24.1) | 22.5 (20.8 to 24.6) | 22.7 (20.8 to 25.1) | 23.3 (21.1 to 25.2) | <0.001 |
| Systolic blood pressure, mmHg | 140.0 (132.0 to 154.0) | 142.0 (135.0 to 155.0) | 145.0 (135.0 to 156.0) | 145.0 (135.0 to 155.0) | <0.001 |
| Diastolic blood pressure, mmHg | 89.0 (80.0 to 98.0) | 86.0 (80.0 to 92.0) | 85.0 (80.0 to 93.0) | 85.0 (80.0 to 92.0) | <0.001 |
| Cardiovascular diseases, n (%) | 310 (40.5) | 327 (43.0) | 336 (43.9) | 411 (53.9) | <0.001 |
| Type 2 Diabetes, n (%) | 99 (12.9) | 108 (14.2) | 113 (14.8) | 129 (16.9) | <0.001 |
| Taking antihypertensive treatment, n (%) | 333 (43.5) | 320 (42.1) | 315 (41.1) | 289 (37.9) | <0.001 |
| Taking antidiabetes agent, n (%) | 96 (12.5) | 105 (13.8) | 108 (14.1) | 120 (15.7) | <0.001 |

**Table-2**. Incidence and incidence rates ratio of cardiovascular mortality according to TyG Index quartiles in all and by body mass index status

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | Outcome | Denominator | Incidence Rates (95% CI) | Incidence rates ratio 1 (95%CI)‡ | Incidence rates ratio 2 (95%CI)§ | Incidence rates ratio 3 (95%CI)¶ |
|  | All | | | | | |
| Quartile 1 (<8.10) | 65 | 766 | 8.49 (6.55 to 10.82) | Reference | Reference | Reference |
| Quartile 2 (8.10-8.38) | 96 | 760 | 12.63 (10.23 to 15.43) | 1.49 (1.43 to 1.56) | 1.63 (1.48 to 1.79) | 1.62 (1.47 to 1.78) |
| Quartile 3 (8.39-8.68) | 130 | 766 | 16.97 (14.18 to 20.15) | 2.00 (1.86 to 2.16) | 1.95 (1.78 to 2.14) | 1.96 (1.79 to 2.15) |
| Quartile 4 (≥8.69) | 146 | 762 | 19.16 (16.18 to 22.53) | 2.26 (2.08 to 2.47) | 2.34 (2.13 to 2.56) | 2.32 (2.12 to 2.55) |
|  | Body mass index < 25 kg/m2 | | | | | |
| Quartile 1 (<8.10) | 54 | 610 | 8.85 (6.65 to 11.55) | Reference | Reference | Reference |
| Quartile 2 (8.10-8.38) | 82 | 596 | 13.76 (10.94 to 17.08) | 1.55 (1.48 to 1.65) | 1.48 (1.33 to 1.64) | 1.48 (1.34 to 1.65) |
| Quartile 3 (8.39-8.68) | 108 | 603 | 17.91 (14.69 to 21.62) | 2.02 (1.87 to 2.21) | 1.72 (1.55 to 1.91) | 1.74 (1.57 to 1.93) |
| Quartile 4 (≥8.69) | 105 | 542 | 19.37 (15.84 to 23.45) | 2.19 (2.03 to 2.38) | 2.23 (2.01 to 2.46) | 2.22 (2.01 to 2.46) |
|  | Body mass index ≥ 25 kg/m2 | | | | | |
| Quartile 1 (<8.10) | 11 | 156 | 7.05 (3.52 to 12.62) | Reference | Reference | Reference |
| Quartile 2 (8.10-8.38) | 14 | 164 | 8.54 (4.67 to 14.32) | 1.21 (1.13 to 1.33) | 1.19 (0.93 to 1.52) | 1.18 (0.92 to 1.51) |
| Quartile 3 (8.39-8.68) | 23 | 162 | 14.20 (9.00 to 21.30) | 2.01 (1.69 to 2.56) | 2.44 (1.93 to 3.07) | 2.40 (1.90 to 3.03) |
| Quartile 4 (≥8.69) | 40 | 221 | 18.10 (12.93 to 24.65) | 2.57 (1.95 to 3.67) | 2.81 (2.23 to 3.53) | 2.82 (2.24 to 3.54) |

‡ indicates unadjusted incidence rates ratio. § indicates adjusted incidence rates ratio in the model with adjustment of age and gender. ¶ indicates adjusted incidence rates ratio in the model with adjustment of baseline characteristics presented in the Table-1.