Triglyceride-glucose index is prospectively associated with chronic kidney disease progression in Type 2 diabetes – mediation by pigment epithelium-derived factor

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Abstract

**Background:** Triglyceride-glucose (TyG) index is a surrogate marker of insulin resistance. Its role in chronic kidney disease (CKD) progression in Type 2 Diabetes Mellitus (T2DM) is unclear. We investigated the association between TyG index and CKD progression, and possible mediation of the association by pigment epithelium-derived factor (PEDF).

**Methods:** This was a prospective study on 1571 patients with T2DM. CKD progression was defined as worsening across KDIGO estimated glomerular filtration rate (eGFR) categories with ≥25% reduction from baseline. PEDF was quantitated using enzyme-linked immunosorbent assay method. Cox proportional hazards regression model was used to assess the relationship between TyG index and CKD progression.

**Results:** Over a follow-up period of up to 8.6 years (median 4.6 years, IQR 3.0–3.6), 42.7% of subjects had CKD progression. Every unit increase in TyG was associated with hazards of 1.44 (95%CI 1.29–1.61; p < 0.001) in unadjusted analysis and 1.21 (1.06–1.37; p = 0.004) in fully adjusted model. Compared to tertile 1, tertiles 2 and 3 TyG index were positively associated with CKD progression with corresponding hazard ratios HRs 1.24 (1.01–1.52; p = 0.037) and 1.37 (1.11–1.68; p = 0.003) in fully adjusted models. PEDF accounted for 36.0% of relationship between TyG index and CKD progression.

**Conclusions:** Higher TyG index independently predicted CKD progression in T2DM. PEDF mediated the association between TyG index and CKD progression.

**Keywords**

Type 2 diabetes, triglyceride-glucose index, chronic kidney disease, pigment epithelium-derived factor

Introduction

One of the key complications of Type 2 diabetes mellitus (T2DM) is chronic kidney disease (CKD) which affects 25–40% of patients with T2DM.¹ There is a higher susceptibility to diabetes-related kidney disease in Asians compared to other ethnicities.² Hence there is a strong impetus to understand the natural history of CKD in patients with T2DM in order to identify potential intervention points to prevent or delay its progression.

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The 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease (CKD) defined decline of estimated glomerular filtration rate (eGFR) as decrease in eGFR categories coupled with ≥25% reduction of eGFR from baseline.\textsuperscript{3} This provides a timely opportunity for us to study CKD progression before it reaches end-stage renal disease. Hypertension, hyperlipidemia, prolonged duration of diabetes and suboptimal glycemic control are known to contribute to diabetes-related CKD but more understanding of the underlying pathophysiology besides these conventional risk factors is needed.\textsuperscript{4}

Triglyceride-glucose (TyG) index, an logarithmized product of triglyceride (TG) and glucose in fasting state, has gained accumulating interest as a simple surrogate measure of insulin resistance.\textsuperscript{5} It correlates well with euglycemic-hyperinsulinemic clamp, and has similar validity as the homeostatic model assessment insulin resistance (HOMA-IR) index.\textsuperscript{5,6} Studies have found association of TyG index with various clinical outcomes such as development of DM\textsuperscript{7} and hypertension,\textsuperscript{8} non-alcoholic fatty liver disease\textsuperscript{9} and arteriosclerotic cardiovascular disease.\textsuperscript{10} Given that insulin resistance confers higher risk of CKD progression,\textsuperscript{11} it is plausible that TyG, which reflects insulin resistance, may be implicated in the pathogenesis and progression of CKD in T2DM. In recent years, a few studies have reported an association between TyG index and CKD in community-dwelling populations\textsuperscript{11,12} and individuals with T2DM.\textsuperscript{13–16} Data on the relationship between TyG index and CKD progression in T2DM, however, remains scarce as most of these studies were cross-sectional.\textsuperscript{13–15}

It was postulated that insulin resistance triggers oxidative stress, inflammation and metabolic acidosis which themselves contribute to pathogenesis of CKD.\textsuperscript{11} Pro-inflammatory cytokines such as tumor necrosis factor (TNF-\textalpha) and interleukin (IL)-6 also promote endothelial dysfunction that is related to the development of CKD.\textsuperscript{11} Of note, pigment epithelium-derived factor (PEDF) is a novel biomarker which may play a role in renal decline.\textsuperscript{17} PEDF, a member of the serpin family, is a glycoprotein with anti-oxidant, anti-inflammatory and anti-angiogenic properties.\textsuperscript{18} PEDF in kidney may confer reno-protection by decreasing fibrosis, inflammation, vascular hyper-permeability and podocyte renal cell apoptosis resulting from advanced glycation end-product.\textsuperscript{18–20} On the other hand, plasma level of PEDF may increase due to compensation for reduced levels of kidney-specific PEDF.\textsuperscript{21} To date, there is no study on the role of PEDF as a potential mediator of the association between TyG index and CKD progression in T2DM.

We aimed to study the association between TyG index and CKD progression, and possible mediation of the association by PEDF.

### Methods

#### Population

We recruited patients with T2DM on follow-up at the Diabetes Centre in a public hospital and primary care polyclinics in northern part of Singapore under the Singapore Study of Macro-angiopathy and Micro-vascular Reactivity in Type 2 Diabetes (SMART2D). This was an ongoing prospective cohort study which recruited patients during March 2011 to March 2014. The patients visited the Diabetes Centre and primary care polyclinics for their routine follow-up for diabetes management every 3–4 months. Their renal function, reflected by estimated glomerular filtration rate (eGFR), was tracked during these follow-ups from their enrolment in the study till March 2020. Patients were excluded if they had active cancer, active inflammation, took oral steroids with dosage >7.5 mg/day, and/or took non-steroidal anti-inflammatory drugs on the day of assessment. Written informed consent was given by all the participants. For the purpose of this analysis, patients were excluded if they had estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73 m\textsuperscript{2} at commencement of study, < 2 readings of eGFR and < 1-year follow-up duration. There were 1571 subjects, out of 2252 participants, who were included for the analysis.

#### Data collection

Data on demographics, medical history and medications was captured using a standardised questionnaire administered to the patients. Blood pressure was measured with a standard automated sphygmomanometer (HEM-C7011-C1, OMRON Corp., Kyoto, Japan) for the patients at a seated position after a rest period of at least 10 min.

Blood and urine sample collected at study entry were sent to the hospital laboratory. The following assays (COBAS-Roche, Mannheim, Germany) were used to quantitate biological specimens: enzymatic colorimetric test for serum creatinine, TG and low-density lipoprotein cholesterol (LDL-C); Tinaquant Haemoglobin A1c Gen.3 for Haemoglobin A1c (HbA1c) and immunoturbidimetric assay for urinary albumin; Hexokinase method was used to measure fasting plasma glucose (FPG). Enzyme-linked immunosorbent assay method was used to measure PEDF (BioVendor, Heidelberg, Germany) and insulin (Mercodia, Sweden). We calculated homeostatic model assessment of insulin resistance (HOMA2-IR) using an online programme HOMA Calculator v2.2.\textsuperscript{22} eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation.\textsuperscript{23} TyG index was calculated as \textit{Ln} \textit{[fasting TG level (mg/dl) x FPG (mg/dl/2)].}\textsuperscript{24,25}
**Outcome.** We defined CKD progression as ≥25% decrease in eGFR together with worsening across eGFR categories (stage 1, ≥90 mL/min/1.73 m²; stage 2, 60–89 mL/min/1.73 m²; stage 3a, 45–59 mL/min/1.73 m²; stage 3b, 30–44 mL/min/1.73 m²; and stage 4, 15–29 mL/min/1.73 m²), with reference to the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease. Patients who had CKD progression were the “progressor group” and those without CKD progression were the “non-progressor group”.

**Statistical analysis.** Data on baseline characteristics were expressed as means ± standard deviation (SD) or median with interquartile range (IQR). Chi-Square test for categorical variables and Student t-test or Wilcoxon rank-sum test for continuous variables were used to compare baseline characteristics between outcomes. We examined the association between per unit of TyG index and risk of CKD progression with multivariable cox proportional hazards model. Model 1 was adjusted for age, gender and ethnicity. Model 2 was additionally adjusted for DM duration, body mass index (BMI), systolic blood pressure (SBP), LDL, eGFR categories, urinary albumin-to-creatinine ratio (uACR) categories, use of hypolipidemic agent, use of insulin and use of renin-angiotensin system (RAS) antagonist. These covariates were selected for the model as they were associated with CKD progression in univariate analysis (p < 0.05) or were known risk factors of CKD progression. We repeated the analysis with TyG expressed in tertiles. The assumption of proportion hazard was not violated based on the global test which uses scale Schoenfeld residuals.

To examine the role of PEDF as a possible mediator on the relationship between TyG index and CKD progression, binary mediation analysis was conducted using the Baron and Kenny framework. This required us to examine the following criteria: pathway a, TyG index as an independent variable was associated with PEDF which acted as a mediator; pathway b, PEDF was associated with CKD progression which acted as a dependent variable; pathway c, TyG index was associated with CKD progression; pathway c’, there was attenuation in the association between TyG index and CKD progression with the addition of PEDF in the model. The total effect of TyG index on CKD progression was total effect c which was calculated as sum of indirect effect c’ and indirect effect a*b. The proportion of mediation was calculated as indirect effect a*b/total effect c. We used STATA version 14.0 (STATA Corporation, College Station, Texas) to perform statistical analysis. Results with p < 0.05 were considered statistically significant.

**Results**

**Baseline characteristics of patients with and without CKD progression**

Table 1 shows the baseline characteristics of the patients. The mean age was 57.3 ± 11.0 years. There was a slight preponderance of males (51.4%). The distribution across the ethnicities was 51.7% Chinese, 19.6% Malay and 24.6% Indian. More than half of the study population had ≥10 years DM duration. The mean TyG index was 9.1 ± 0.7. TyG is correlated with HOMA2-IR (rho 0.31; p < 0.001) and PEDF (rho 0.26; p < 0.001) (not shown in table). Table 1 also showed the baseline characteristics stratified by TyG index in tertiles. Age decreased while BMI, FPG, LDL, TG and uACR increased with tertile augmentation (p < 0.001).

There were 670 patients (42.7%) who had CKD progression over a follow-up of up to 8.6 years (median 4.6 years (IQR 3.0–6.6)). As shown in Table 2, the progressor group tended to be older and had higher BMI, SBP, HbA1c, TG, TyG index and uACR (p < 0.05). They were also more likely to have lower eGFR (p < 0.001) and longer DM duration of ≥10 years (p < 0.001).

**Association between TyG index and CKD progression**

In Table 3, every unit increase in TyG index was associated with hazards of 1.44 (95% Confidence Interval (CI) 1.29–1.61; p < 0.001) of CKD progression. The positive association remained in Model 1 which was adjusted for age, gender and ethnicity and in Model 2 which was additionally adjusted for clinical covariates and medications. The corresponding hazards ratios (HRs) for Model 1 and Model 2 were 1.51 (95%CI 1.34–1.69; p < 0.001) and 1.21 (95%CI 1.06–1.37; p = 0.004).

Figure 1 showed the Kaplan-meier survival curves of CKD progression by TyG index in tertiles. In Figure 1, tertile 3 TyG index had poorer event-free survival compared to tertiles 1 and 2 TyG index (log-rank test statistics: 35.91; p < 0.001). The patients with tertiles 2 and 3 TyG index had higher hazards of CKD progression with HRs 1.32 (95% CI 1.09–1.60) and 1.76 (95% CI 1.46–2.13; p < 0.001) respectively. The association persisted in Model 1 with corresponding HRs 1.28 (95% CI 1.06–1.56; p = 0.012) and 1.83 (95% CI 1.51–2.22; p < 0.001). In the fully adjusted Model 2, the association between tertiles 2 and 3 with CKD progression persisted. The corresponding fully adjusted HRs were 1.24 (95% CI 1.01–1.52; p = 0.037) and 1.37 (1.11–1.68; p = 0.003). (Results not shown in Table)
Mediation of the association between TyG index and CKD progression

In the mediation analysis shown in Figure 2, each 1-unit increase in TyG index was positively associated with plasma PEDF (coefficient for pathway a = 1.58; \( p < 0.001 \)); PEDF was positively associated with CKD progression (coefficient for pathway b = 0.05; \( p = 0.001 \)); TyG index was positively associated with CKD progression (coefficient for pathway c = 0.21; \( p = 0.049 \)); and the association between TyG index and CKD progression was attenuated and lost statistical significance when PEDF was added to the model (coefficient for pathway c' = 0.15; \( p = 0.182 \)). PEDF mediated 36.0% of the association between TyG index and CKD progression (\( p = 0.002 \)).

Discussion

In the current study, we observed that higher TyG index independently predicted CKD progression. PEDF played a
role in mediating the association between TyG index and CKD progression.

A few studies have previously demonstrated a link between TyG index and CKD or diabetic nephropathy. For example, the cross-sectional study by Liu L and Colleagues (2021) observed that higher TyG index was shown to be associated with diabetic nephropathy with odds ratio (OR) of 1.91 (95% CI 1.29–2.85) in patients with T2D.13 On the other hand, another cross-sectional study by Ou Y and Colleagues (2021) observed that TyG index was not associated with advanced kidney disease (eGFR <30 mL/min/1.73 m²).15 Of note, most of the earlier studies13–15 were cross-sectional in design and hence could not establish the causality of the relationship between TyG index

| Table 2. Baseline characteristics stratified by CKD progression. |
|---------------------------------------------------------------|
|                | No                   | Yes                  | p-value |
| Number         | 901                  | 670                  |         |
| Age (years)    | 55.5 ± 11.5          | 59.7 ± 9.7           | <0.001  |
| Male (%)       | 473 (52.5)           | 334 (49.9)           | 0.299   |
| Ethnicity (%)  | —                    | —                    | <0.001  |
| Chinese (%)    | 493 (54.7)           | 319 (47.6)           |         |
| Malay (%)      | 115 (12.8)           | 193 (28.8)           |         |
| Indian (%)     | 258 (28.6)           | 129 (19.3)           |         |
| Other (%)      | 35 (3.9)             | 29 (4.3)             |         |
| DM duration (%)| —                    | —                    | <0.001  |
| <10 years (%)  | 480 (53.3)           | 231 (34.5)           |         |
| I0–19 years (%)| 268 (29.7)           | 238 (35.6)           |         |
| ≥20 years (%)  | 153 (17.0)           | 200 (29.9)           |         |
| BMI (kg/m²)    | 27.4 ± 5.2           | 28.2 ± 5.2           | 0.003   |
| SBP (mmHg)     | 135.2 ± 15.8         | 144.4 ± 18.5         | <0.001  |
| HbA1c (%)      | 7.7 ± 1.3            | 8.1 ± 1.4            | <0.001  |
| HbA1c (mmol/mol)| 60.7 ± 14.2          | 65.0 ± 15.3          | <0.001  |
| FPG (mmol/l)   | 8.3 ± 2.7            | 8.4 ± 2.9            | 0.193   |
| LDL (mmol/l)   | 2.7 ± 0.8            | 2.7 ± 0.8            | 0.892   |
| TG (mmol/l)    | 1.4 (1.0–1.9)        | 1.6 (1.1–2.1)        | <0.001  |
| TyG            | 9.1 ± 0.6            | 9.2 ± 0.7            | <0.001  |
| TyG categories (%) | —         | —                    | <0.001  |
| Tertile 1      | 340 (37.7)           | 184 (27.5)           |         |
| Tertile 2      | 301 (33.4)           | 223 (33.3)           |         |
| Tertile 3      | 260 (28.9)           | 263 (39.3)           |         |
| HOMA2-IR       | 1.1 (0.7–1.8)        | 1.2 (0.7–2.2)        | 0.009   |
| PEDF (µg/mL)   | 15.2 ± 4.8           | 17.8 ± 5.6           | <0.001  |
| eGFR (ml/min/1.73 m²) | 97.4 (83.2–107.8) | 81.1 (58.2–98.4) | <0.001  |
| eGFR category (%) | —                 | —                    | <0.001  |
| G1, ≥90 ml/min/1.73 m² | 582 (64.6) | 272 (40.6) |         |
| G2, 60–89 ml/min/1.73 m² | 227 (25.2) | 213 (31.8) |         |
| G3a, 45–59 ml/min/1.73 m² | 41 (4.6)  | 84 (12.5)  |         |
| G3b, 30–44 ml/min/1.73 m² | 38 (4.2)  | 62 (9.3)   |         |
| G4, 15–29 ml/min/1.73 m² | 13 (1.4)  | 39 (5.8)   |         |
| uACR (mg/g)    | 14.7 (5.5–38.5)      | 66.2 (17.7–342)      | <0.001  |
| uACR category (%) | —                 | —                    | <0.001  |
| Normoalbuminuria | 617 (68.6)   | 231 (34.7)          |         |
| Microalbuminuria | 251 (27.9)   | 256 (38.4)          |         |
| Macroalbuminuria | 32 (3.6)     | 179 (26.9)          |         |
| Use of hypolipidemic treatment (%) | 730 (81.3) | 574 (85.9) | 0.015   |
| Use of insulin (%) | 219 (24.4) | 269 (40.5) | <0.001  |
| Use of RAS antagonist (%) | 484 (53.9) | 495 (74.1) | <0.001  |

DM, diabetes mellitus; BMI, body mass index; SBP, systolic blood pressure; HbA1c, Haemoglobin A1c; FPG, fasting plasma glucose; LDL, low-density lipoprotein cholesterol; TG, triglycerides; TyG, triglyceride-glucose index; HOMA2-IR, homeostatic model assessment insulin resistance; PEDF, pigment epithelium-derived factor; eGFR, estimated glomerular filtration rate; uACR, urinary albumin-to-creatinine ratio; RAS, renin angiotensin system
and CKD progression in T2DM. In a longitudinal study on the general population by Okamura T and Colleagues (2019), TyG index was shown to predict incident CKD with hazards ratio (HR) 1.32 (95% CI 1.02–1.70) in men and 1.50 (95% CI 1.05–2.13) in women. However, it is uncertain if the findings could be extended to patients with T2DM. Although the longitudinal study by Lv L and Colleagues (2021) in patients with T2DM revealed that patients with the high tertile of baseline TyG index experienced higher hazards of developing diabetic kidney disease (DKD) than those in the lower tertile (HR 1.727; 95% CI 1.042–2.863; \( p = 0.034 \)), the follow-up duration was up to 2 years and it is uncertain if the findings can be extended to the general T2DM population which also includes those with pre-existing DKD. Our results have added to the limited pool of evidence on the relationship

### Table 3. Association between TyG and chronic kidney disease progression.

|                     | Hazards ratio (95% confidence Interval) | \( p \)-value |
|---------------------|----------------------------------------|--------------|
| TyG                 | 1.44 (1.29–1.61) \( p < 0.001 \)        |              |
| Age (per year)      | 1.03 (1.03–1.04) \( p < 0.001 \)        | 1.01 (1.00–1.02) \( p = 0.007 \) |
| Male                | 1.02 (0.87–1.19) \( p = 0.810 \)         | 0.91 (0.77–1.07) \( p = 0.255 \) |
| Ethnicity           |                                        |              |
| Chinese             | 1.00                                   | 1.00         |
| Malay               | 2.03 (1.69–2.44) \( p < 0.001 \)        | 1.98 (1.63–2.41) \( p < 0.001 \) |
| Indian              | 0.86 (0.70–1.06) \( p = 0.163 \)         | 0.90 (0.73–1.11) \( p = 0.306 \) |
| Other               | 1.33 (0.91–1.95) \( p = 0.140 \)         | 1.34 (0.91–1.99) \( p = 0.140 \) |
| DM duration         |                                        |              |
| <10 years           | 1.00                                   |              |
| 10–19 years         | 1.18 (0.97–1.43) \( p = 0.099 \)         |              |
| \( \geq 20 \) years | 1.20 (0.95–1.50) \( p = 0.124 \)         |              |
| BMI (per kg/m²)     | 1.00                                   | 0.677        |
| SBP (per mmHg)      | 1.01 (1.01–1.02) \( p = 0.001 \)         |              |
| LDL (per mmol/l)    | 0.95 (0.85–1.05) \( p = 0.297 \)         |              |
| eGFR category       |                                        |              |
| G1, \( > 90 \) mL/min/1.73 m² | 1.00                         |              |
| G2, 60–89 mL/min/1.73 m² | 1.50 (1.24–1.83) \( p < 0.001 \) |              |
| G3a, 45–59 mL/min/1.73 m² | 1.58 (1.20–2.09) \( p = 0.001 \) |              |
| G3b, 30–44 mL/min/1.73 m² | 1.46 (1.08–1.98) \( p = 0.014 \) |              |
| G4, 15–29 mL/min/1.73 m² | 1.38 (0.95–2.00) \( p = 0.095 \) |              |
| uACR category (%)   |                                        |              |
| Normoalbuminuria    | 1.00                                   |              |
| Microalbuminuria    | 1.51 (1.25–1.83) \( p < 0.001 \)         |              |
| Macroalbuminuria    | 4.55 (3.58–5.78) \( p < 0.001 \)         |              |
| Use of hypolipidemic treatment | 0.93 (0.74–1.17) \( p = 0.540 \) |              |
| Use of insulin      | 1.34 (1.13–1.60) \( p = 0.001 \)         |              |
| Use of RAS antagonist | 1.22 (1.01–1.48) \( p = 0.039 \)       |              |

DM, diabetes mellitus; BMI, body mass index; SBP, systolic blood pressure; LDL, low-density lipoprotein cholesterol; TyG, triglyceride-glucose index; eGFR, estimated glomerular filtration rate; uACR, urinary albumin-to-creatinine ratio; RAS, renin angiotensin system

Model 1: Adjusted for age, gender and ethnicity
Model 2: Adjusted for age, gender, ethnicity, DM duration, BMI, SBP, LDL, eGFR categories, uACR categories, use of hypolipidemic agent, use of insulin and use of RAS antagonist

**Figure 1.** Kaplan-meier survival curve for CKD progression by TyG in tertiles.
between TyG index and CKD progression in T2DM patients with and without CKD in a longitudinal analysis with a fairly long follow-up duration of up to 8.6 years.

Our study has uncovered a previously unobserved finding of PEDF mediating the positive association between TyG index and CKD progression. Rats with streptozotocin-induced diabetes had lower concentrations of PEDF in the kidneys than rats with no diabetes. It is plausible that insulin resistance may have downregulated the level of PEDF in the kidney with compensatory increase in the concentration of plasma PEDF. Given that several cell types (e.g. adipocytes, hepatocytes and myocytes) produce PEDF, it is possible that these cells in distress may increase inflammation which itself elevates the concentration of plasma PEDF. Further investigation is needed to confirm the role of PEDF in TyG index-related risk of CKD progression.

Other factors may play a role in mediating the association between TyG index and CKD progression. For instance, insulin resistance, of which TyG index is a surrogate marker, blocks insulin-signaling pathway and increases production of monocyte chemoattractant protein 1 (MCP1), thereby increasing inflammation in the adipose tissue. Inflammation in the adipose tissue stimulates the action of macrophages, leading to enhanced production of proinflammatory cytokines including tumor necrosis factor (TNF)-α and interleukin (IL)-6. TNF-α and IL-6 reportedly contribute to endothelial dysfunction which in turn is associated with CKD. Further studies should investigate the action of TyG index on inflammatory markers (e.g. TNF-α and IL-6) and marker of endothelial dysfunction (e.g. Laser Doppler flowmetry).

TyG index is a potential risk marker of renal decline in T2DM. It may be utilized to bring about clinical benefits to patients with T2DM, such as in risk stratification and active clinical management targeting this marker to prevent or delay renal decline. Future large-scale longitudinal studies are needed to confirm the role of TyG index, in particular its mechanism of action, in CKD progression. This may pave the way for future therapeutic interventions which target TyG index in CKD progression in T2DM.

There are a few clinical implications in our findings. Healthcare providers should have a heightened awareness of the role of TyG index in predicting CKD progression. As TG and FPG are routine laboratory measurements, healthcare providers can incorporate the calculation of TyG index in clinical management of T2DM. They can risk-stratify patients using TyG index and actively control this clinical parameter in an effort to prevent or slow down CKD progression.

\[ \text{Indirect effect} = a \times b \]
\[ \text{Direct effect} = c' \]
\[ \text{Total effect} = c = a \times b + c' \]
\[ \text{Proportion of mediation} = \frac{\text{indirect effect}}{\text{total effect}} = 36.0\% \]

PEDF, pigmented epithelium derived factor; TyG, triglyceride glucose index; CKD, chronic kidney disease

Adjusted for age, gender, ethnicity, DM duration, BMI, SBP, LDL, eGFR categories, uACR categories, use of hypolipidemic agent, use of insulin and use of RAS antagonist

**Figure 2.** Mediation of PEDF between baseline TyG index and CKD progression.
Our study has a prospective design which enables us to follow-up the participants for their eGFR longitudinally in a group of participants with fairly well-preserved eGFR at baseline. This highlights that the role of TyG index in CKD progression is fairly upstream compared to other biomarkers such as haptoglobin which worked as a fairly downstream predictor of renal decline. The follow-up period is fairly long, the study size is relatively large and the analysis included an extensive array of covariates for adjustment. We also conducted mediation analysis to elucidate the pathophysiological mechanism accounting for the relationship between TyG index and CKD progression.

There are, however, limitations in our study. First, this study was conducted on patients with T2DM who were on follow-up at the Diabetes Centre in a public hospital or polyclinics; the findings cannot be generalised to the entire diabetes population. Second, we did not collect data on socio-economic status and lifestyle such as diet and physical activity at baseline which may account for possible residual confounding.

Conclusions
In conclusion, higher TyG index independently predicted CKD progression in T2D. PEDF mediated the association between TyG index and CKD progression. TyG index is a simple and inexpensive marker for predicting CKD progression in T2D.

Authors contribution
S.L. was the main writer. She carried out the conceptualisation and design of the study, participated in data collection and performed statistical analysis. S.P.L.T., A.M., K.A. and K.J. were involved in data collection, manuscript review and editing process. Y.S. was involved in data extraction, data preparation, manuscript review and editing process. W.E.T. and Z.L. reviewed and edited the manuscript. T.S. and C.F.S participated in the conceptualisation of the study, reviewed and edited the manuscript. SCL acquired the funding, supervised and edited the manuscript.

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Ethical approval
Ethical approval for this study was granted by the National Healthcare Group National Healthcare Group Domain Specific Review Board in Singapore (DSRB Ref: 2014/00,667).

Informed Consent
All participants gave informed written consent.

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