Association Between Triglyceride-Glucose Index (TyG Index) and Type 2 Diabetes Mellitus: A Systematic Review

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ABSTRACT

Background: Insulin Resistance has a major role in the pathogenesis of diabetes mellitus where there is a decrease in sensitivity in peripheral tissues. The emergence of insulin resistance, 1-2 decades precedes before the diagnosis of type 2 diabetes mellitus is established. This theory is supported by the usefulness of insulin resistance as a marker of future diabetes or the prevention of type 2 diabetes by insulin-sensitizing agents. Recently, there is evidence that has been suggested to measure insulin resistance as surrogate marker by calculated the triglyceride and glucose which is so called as "Fasting triglyceride-glucose index" or can be shorten as "TyG index". This study reported a systematic review of association between TyG index and type 2 diabetes mellitus from various literatures to make a conclusion as a basis for further research.
Methods: A literature search in EBSCOhost, ProQuest, MEDLINE, and NCBI database was performed to retrieve and review studies reporting the association between TyG index and type 2 diabetes.
Results: All studies showed that higher TyG index were associated with higher type 2 diabetes (HR 4.36, 10.38, 9.54 for each).
Conclusion: This systematic review provides further evidence about higher TyG index is related to higher risk of development type 2 diabetes. It represents that TyG index can predicting the risk of incident T2DM.

Key words: TyG index, Triglyceride Glucose Index, T2DM, Type 2 Diabetes Mellitus

INTRODUCTION

Diabetes is the leading cause of death and morbidity worldwide [1-3]. The number of deaths caused by diabetes mellitus in 1990 to 2014 almost doubled [4]. According to the International Diabetes Federation, in 2015 75% of diabetics came from low and middle income countries [5]. Insulin Resistance (IR) has a major role in the pathogenesis of diabetes mellitus where there is a decrease in sensitivity in peripheral tissues. The emergence of IR 1-2 decades precedes before the diagnosis of type 2 diabetes mellitus is established [6,7]. Therefore, IR is useful as a marker of diabetes mellitus type 2 that is likely to occur.

There are several direct and indirect steps can be used to measuring insulin such as the euglycemic clamp test which is a standard measurement and other markers which include the HOMAIR, Matsuda Index and QUICKI

[8]. However, in reality at primary health care insulin measurement is difficult to be done because it is limited by the availability of tools, the costs and the stability of insulin which is still doubtful [9]. Therefore, a marker that is simple, accurate, affordable and available in primary health care is still needed to physician estimated the insulin resistance that can be developed into type 2 diabetes melitus (T2DM) [10].

Recently, there is evidence that has been suggested to measure insulin resistance as surrogate marker by calculated the triglyceride and glucose which is so called as "Fasting triglyceride-glucose index" or can be shorten as "TyG index" [10]. In the other hand, another evidence showed that Triglyceride-glucose index (TyG index) has association with HOMA-IR, the insulin supression test and hyperinsulinemic-euglycemic clamp [11-14].

The study about association between Triglyceride-glucose index and type 2 diabetes mellitus has been reported on amount of literatures but the systematically reviewed has not been reported. In this study, we conducted a systematic review about association between Triglyceride-glucose index and T2DM from various literatures to make a conclusion as a basis for further research.

METHODS

We used comprehensive and current database to the literature of association between TyG index and T2DM. This systematic review followed recommendations from the Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA). Articles included in this review were identified throught literature searches of EBSCOhost, ProQuest, MEDLINE, and NCBI for the years 2008 to 2018. Literature search was performed from July 4 to 5 2019. The search terms used were (Triglyceride-glucose[All Fields] AND ("abstracting and indexing"[MeSH Terms] OR ("abstracting"[All Fields] AND "indexing"[All Fields]) OR "abstracting and indexing"[All Fields] OR "index"[All Fields])) AND ("diabetes mellitus, type 2"[MeSH Terms] OR "type 2 diabetes mellitus"[All Fields]). The literatures inclusion that used in this review must be conducted on human, in english and on adult subjects. Therefore, studies published before 2008, editorials, grey literature, interventin studies and poor-quality studies were excluded in this review. The evidence database for the literature was assembled using established systematic review methods.

All relevant studies were assessed for risk of bias using the Newcastle Ottawa Scale (NOS) in order to be included in the review. Studies with NOS score above 7 were considered as high- quality; a score of 6 to 7 was considered as moderate; and a score less than 6 was considered as poor-quality [15].

Retrieved articles were reviewed independently by two investigators (IAL and NKP) in order to gain potentially relevant articles. All disagreements on inclusion/exclusion were discussed and resolved by consensus.

The term "hazard ratio" (HR) refers to the probability when an individual who is being observed in a clinical trial at time t, experiences an event at that time. It represents the instantaneous rate of occurence for an individual who has survived until the time "t''. As for interpret the measurement association, a value of hazard ratio 1 means lack of association, a value of hazard ratio bigger than 1 is interpreted as increased risk, and a value of hazard ratio below 1 is interpreted as a smaller risk [16].

In total, we screened 83 literatures from both sources. We obtained full text for 83 titles, of which we retained 9 for data extraction. After retrieving the full manuscript, literatures were excluded due to the measurement association and the included variabel. All of studies that were included as criteria used cohort as method.

The searching and data extracting was following the PRISMA flow diagram (Figure 1). Three studies were conducted in China, Korea and Europe (Table 1). The median follow-up ranged from 48.5 months to 10 years.

RESULTS

TyG index cut-off point

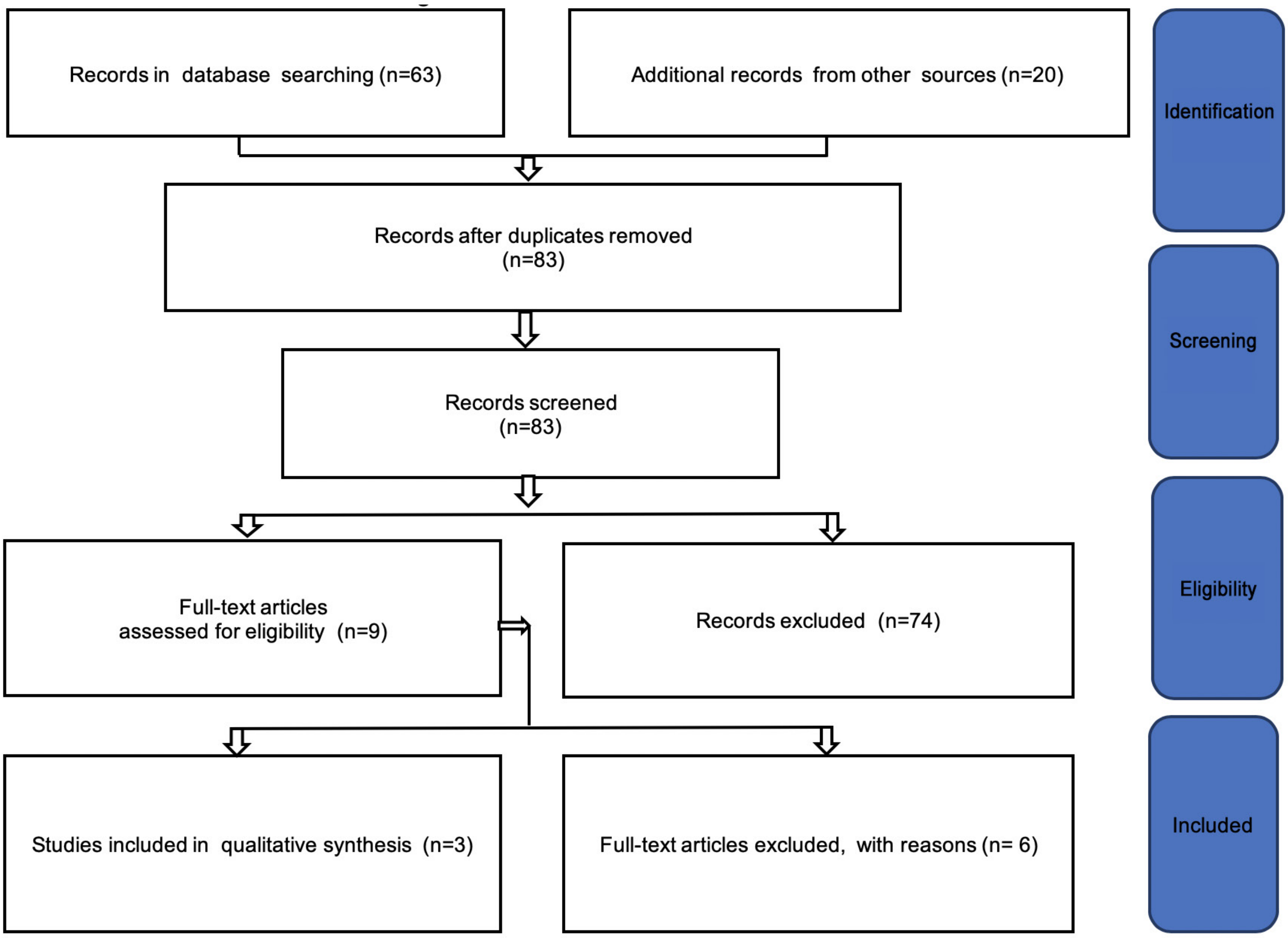
All of three studies assessed the risk of developing T2DM through the four quartiles of the TyG index, hazard ratio (HR) and the 95% confidence interval (CI) using the cox proportional hazard model. Those studies used first quartile as reference group. Lee et al and Zhang et al predicted risk of T2DM through follow-up using receiver operating character (ROC) curve to. Lee et al conducted a Kaplan-Meier survival analysis for assesed the progression to diabetes after 4 years according to the TyG index quartiles.

Zhang, et al explained the risk of incident diabetes increased at quartile 4 of TyG index which is 8.82 or more. For men, the area under ROC curve (AUC) for TyG index was 0.602 (0.583–0.622). Women performed larger AUC for TyG index than men 0.733 (0.717–0.748). It reported the best TyG index cut-off value for diagnosis T2DM for men was 8.64 with sensitivity 0.522 and specificity 0.642 and for women was 8.76 with sensitivity 0.650 and specificity 0.702 [17].

Research by Lee et.al, explained that during follow up period the proportion of subjects with incidence of diabetes increased in the TyG index quartile with quartile four reported had a significantly high risk of progression to diabetes. Quartile 4 had value of TyG index 8.97 or more. The cut-off point had optimal value at 8.8 and the AUC value was 0.751 with 95% CI 0.704–0.799 [18].

The study of Gonzales et al reported that the risk of diabetes increased progressively at value of TyG index was 8.31 or more. This study demonstrated subjects that had fourth quartile of TyG index (TyG index value between

FIGURE 1. PRISMA 2009 Flow Diagram of search and data extraction



8.67 and 10.15) with adjusted age and sex more likely to develop T2DM. This study reported the risk of type 2 diabetes development increased above TyG 8.43 for men and 8.19 for women [19].

Hazard ratios of incident diabetes

Zhang et al. Reported that an increased risk of incident T2DM occurred in quartiles 2, 3 and 4 compared to quartile 1 on the TyG index adjusted for gender, age and family history of diabetes.The HR for each quartiles were 1.19 (95% CI 0.43-3.30), 3.50 (1.50-8.16), 4.36 (1.89-10.05) with $P_{trend} < 0.001$ In summary, this study concluded that the risk of T2DM incident is increasing followed with increasing of TyG index among Chinese population, so that the index might be an important indicator to identify people with high risk of T2DM [17].

Lee et al., found that there were 101 cases of incident diabetes after follow up. The proportions of subjects with the incidence of diabetes during follow-up time span increased across TyG index quartiles 2 to 4 with the significantly higher risk of diabetes attached to quartile 4. The HR adjusted for age and sex of quartile 4 versus quartile 1 was 10.38 (95% CI, 3.68-29.28) [18].

Gonzalez et al., found 332 cases of incident type 2 diabetes involved with 10 years median of follow up. This study reported the value of HR that adjusted to age and sex for type 2 diabetes mellitus for fourth quartile reach out 9.54 with 95% CL: 6.13-14.05 and P for trend <0.001. the HRs for quartiles 2 and 3 1.44 (95% CI, 0.84-2.46), 4.21 (95% CI, 2.64-6.72) respectively [19].

Study quality

The critical review and bias risk analyses were conducted by using the Newcastle Ottawa Scale (Table 2). All of the included studies were identified as good quality as they reached a score of more than 7. All studies were included to this review considered as highquality based on each scores gained are 9.

TABLE 1. Characteristics of studies included in systematic review of associations between TyG index with Type 2 Diabetes Mellitus

Author	Publication year	Population	Design	TyG index cut-off point	Measure of associations	Outcome assesment
Zhang et al15	2017	5,706 (3,195 women and 2,511 men); normoweight; rural Chinese people; family history of diabetes; waist circumference; age ≥18 years old	Cohort	ROC curve analysis: AUC for women 0.733 (0.717-0.748) AUC for men: 0.602 (0.583-0.622) Cut-off points: 8.64 for men 8.76 for women	HR	The prevalence of high TyG index (quartile 4) was measured on 14.95% of women and 10.00% of men Risk of incident T2DM increased on quartile 2, 3 and 4 versus quartile 1 of TyG index (1.19 [95% CI 0.43-3.30], 3.50 [1.50-8.16], 4.36 [1.89-10.05]
Lee et al16	2016	2,900 (882 women and 2,078 men); Korean population; age ≥20 years old	Cohort	ROC curve analysis: AUC 0.751 (95% CI 0.704-0.799) Cut-off points: 8.8	HR	Risk of incident T2DM significantly increased on quartile 4 versus quartile 1 of TyG index 10.38 (95% CI 3.68-29.28)
Gonzalez et al17	2016	4,820 (1,889 women and 2,931 men); European population;	Cohort	ROC curve analysis: AUC 0.75 (95% CI 0.70-0.81) Cut-off points: Quartile 3 versus quartile 1 (8.43 for men and 8.19 for women)	HR	During 322 incident cases of diabetes 5.2% for women and 7.9% for men. Risk of incident T2DM significantly increased with quartile 4 vs 1 of TyG index 9.54 (95% CI 6.13-14.05)

TABLE 2. Quality of nonrandomised studies in meta-analyses of The Newcastle-Ottawa Scale

	Selection	Comparability	Outcome	Total
Zhang et al	****	**	***	9
Lee et al	****	**	***	9
Gonzalez et al	****	**	***	9

DISCUSSION

TyG index, a measurement of the fasting triglycerides and fasting glucose, currently can be used as a surrogate marker because it has been reported had significant results for insulin resistance assessment in Mexican, Chinese, Brazilian and Korean populations [12-14]. It has also proposed as a marker for classify metabolic health status [18].

The association between the TyG index and glycemic control has been explained by several mechanisms. Increased of free fatty acids caused by increased of triglycerides level which can have an impact on increasing free fatty acid flux from adipose to nonadipose tissue thus affecting glycemic control [20]. Several studies reported that higher triglyceride levels in muscles and liver can affect glucose metabolism in each target organ [21-24]. Insulin resistance has an important role to the patophysiology of type 2 diabetes, therefore examination of insulin resistance can be used as a marker of diabetes mellitus progression. Insulin resistance can be checked using hyperinsulinemic-euglycemic clamp, HOMA-IR and the other insulin sensitivity tests. In primary health care, the laboratory facilities are limited, so that TyG index can be used as a surrogate to predict the development of diabetes by using fasting triglyceride level and fasting glucose level. Besides, TyG index has been proven as a better tool to predicting the progression of diabetes mellitus compared to TG/HDL-C ratio and HOMA-IR [25,26].

The sensitivity and specificity of the TyG index were high for identifying insulin resistance in Mexico population [27]. A study in China that conducted at nine provinces (Liaoning, Heilongjiang, Jiangsu, Shandon, Henan, Hubei, Hunan, Guangxi, and Guizhou) reported TyG index was effective for predicting insulin resistance [21]. In Brazilian population, the study reported TyG index showed a better performance to identified insulin resistance compared to HOMA2-IR in clinical practice [14]. From the previous studies showed that TyG index can be used to estimate the incidence on T2DM.

This study has collected the data from previous study about the association between TyG index and incidence of T2DM to provide the evidence of its association. From 3 different populations, they showed the same cut off point with different cut off values based on gender. The association between higher TyG index and risk of development T2DM is significant, it's showed by the increasing of quartiles followed by the increasing incidence of diabetes.

CONCLUSION

This systematic review provides further evidence about higher TyG index is related to higher risk of development T2DM. Increasing of TyG index followed by increasing risk of development T2DM. It represents that TyG index can predicting the risk of incident T2DM.

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