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Relationship between Early-onset stroke and Triglyceride-glucose index among young Chinese adults

Abstract

Background: The triglyceride–glucose index (TyG-index), an alternative indicator of peripheral insulin resistance (IR), is associated with cardiovascular disease (CVD) in the general population. The aim of this research was to determine the correlation between early-onset stroke and the TyG-index among young Chinese adults.

Methods: Participants (age ≤40 years) who attended their first physical examination in Kailuan General Hospital or its 11 subsidiary hospitals between 2006 and 2012 were enrolled. A Cox proportional hazard models was employed to assess the correlation between early-onset stroke incident and the TyG-index . Restricted cubic spline analysis was further conducted to examine nonlinear associations. TyG-index was calculated as Ln [Triglyceride (TG, mg/dl) × Fasting Blood Glucose (FBG, mg/dl)/2].

Results: Overall, 35999 subjects met the inclusion criteria. Their mean age was 30.82±5.66 years, and 77.1% of subjects were males. During a median observation period of 11 years, 281 stroke events occurred (62 hemorrhagic strokes and 219 ischemic strokes). Compared to the Q1 group, subjects in groups Q2-Q4 had significantly higher risks of early-onset stroke ($P<0.05$) after adjustment for relevant confounders in the Cox proportional hazards model. The restricted cubic splines revealed that the risk of stroke progressively increased with a high TyG-index ≥ 8.41.

Conclusions: The TyG-index may be a major risk factor for early-onset stroke among young Chinese adults. TyG-index ≥8.41 can be used as an indicator for screening high-risk stroke groups.

Keywords: *Triglyceride-glucose index; early-onset stroke; young Chinese adults*

Background

Stroke is the most common cerebrovascular emergency in the general population and the leading cause of mortality and disability worldwide [1, 2]. The total number of disability-adjusted life years due to stroke has steadily increased since 1990, reaching 143 million deaths in 2019 (the number of deaths increased by 43.0% compared to 1990) [1]. Moreover, the incidence of stroke among the younger population has also been steadily increasing; globally, the incidence rate of stroke in young people aged 15-39 has increased from 26.14/100,000-27.82/100,000 between 2012 and 2019 [3, 4]. In addition, the proportion of 20-64 years old subjects among all persons with stroke has risen from 25% in 1990 to 31% in 2010 [3, 4]. Hypertension, diabetes, being overweight, obesity, and a poor lifestyle have been identified as the major risk factors related to stroke [5]. However, the conventional risk factors do not entirely explain the increased stroke risk among young adults.

Insulin resistance (IR) has been confirmed as a dominant risk factor for diabetes, hypertension, and coronary heart disease [6-10]. In addition, epidemiological studies [11], animal studies [12], and clinical trials [13, 14] have all confirmed the association between IR and stroke. Hyperinsulinemic-euglycemic clamp (HEC) is regarded as the well-recognized gold standard for monitoring IR [15]. However, considering the economic benefits and clinical feasibility, clinical standardization has not yet been achieved. On the other hand, characteristics such as cost-effectiveness, simplicity, and efficiency make the TyG-index a reliable surrogate for IR for preclinical and clinical applications [16, 17]. Furthermore, several studies confirmed the correlation between the TyG-index and IR [18]. Previous studies within the general population have proposed that TyG-index is a major risk factor in predicting cardio-cerebrovascular disease [19-21]. However, as no previous study investigated the correlation between early-onset stroke and TyG-index among young Chinese adults, the aim of this research was to overcome this gap and address this issue.

Methods

Study subjects

The Kailuan Study is a multistage population-based cohort study whose aim is to investigate and intervene on the risk factors of cardiovascular and cerebrovascular diseases. Briefly, the cohort was initiated in July 2006, and examination rounds with registered employees and retirees were performed on average every 2 years at the Kailuan General Hospital and its 11 subsidiary hospitals. Currently, this project has completed seven follow-ups. FBG and TG were measured at baseline and at each follow-up period. Since 2006, subjects were followed up annually to evaluate the occurrence of cardiovascular disease (CVD) incidents, including stroke. The individuals who attended the physical health examination for the first time in 2006-2012 and were ≤ 40 years old were selected as the research subjects.

Participants with an obvious history of myocardial infarction (MI) or stroke were excluded. Also, those with missing data from FBG and TG data at baseline were excluded. The protocol for this study was in accordance with Kailuan General Hospital Ethics Committee. All the subjects signed written informed consent before every survey circle (**Figure 1**).

Data collection

Baseline information on demographic characteristics (age and sex), physical examination (body weight and height, blood pressure), lifestyle characteristics (smoking habits, drinking habits, physical activity, salt intake, and educational level), history of the disease (stroke and MI), and medical history (the use of medication at baseline and during follow-up, such as antihypertensive agents, lipid-lowering agents, and hypoglycemic agents) were collected by experienced physicians in every circle. Hypertension was based on either receiving medications for hypertension, a self-reported history of diagnosed hypertension, or blood pressure ≥140/90 mmHg [22]. Diabetes status was based on either receiving hypoglycemic drugs, a self-reported history of diagnosed diabetes, or FBG ≥7.0 mmol/L[23]. The remaining detailed design and basic description were obtained from published literature [24].

An equivalent of 5 mL peripheral venous blood sample was extracted from 7:00–9:00 am on the day of health examination after overnight (>8 h) fasting. FBG was assessed using the hexokinase method with the upper limit of linearity of 33.3 mmol/L (coefficient of variation was <2%). Serum TG was assessed using the enzymatic colorimetric method. The laboratory tests, such as high sensitivity C-reactive protein (hs-CRP), high-density lipoprotein cholesterol (HDL-C), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C), were analyzed by the auto-analyzer (Hitachi, Tokyo, Japan). The corresponding kits were purchased from Zhongsheng North Control Biotechnology Co., Ltd. The professional quality controller regularly monitored these parameters.

TyG-index calculation

TyG-index was calculated as ln [TG (mg/dl)×FBG (mg/dl)/2] [16]. The subjects were classified into four categories based on the quartile of TyG index: Q1 (6.38≤TyG<8.01), Q2 (8.01≤TyG<8.41), Q3 (8.41≤TyG<8.86), and Q4 (8.86≤TyG<14.20).

Outcomes and follow-up

The starting point of follow-up was the date of completion of the physical health examination for the first time in 2006-2012; the endpoint of follow-up was either the first occurrence of stroke, the time of death, or the deadline of follow-up (December 31, 2020). Stroke was typically categorized as ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage, with the latter two being grouped into a hemorrhagic stroke. When combined with neuroimaging, stroke is generally defined in clinical practice as a syndrome of rapid onset characterized by focal cerebral dysfunction [25]. If two or more events occurred, the first one was considered the primary endpoint. The data of all events were obtained through the Medicare system in Kailuan General Hospital. The endpoints and adverse events were recorded by trained medical personnel, and a physician confirmed all diagnoses.

Statistical analysis

SAS 9.4 (SAS Institute Inc., Cary, NC) was performed for all analyses. The baseline data were displayed as the mean ± standard deviation (X±S), numbers (percentage), or medians (P25, P75), where appropriate. Different groups were compared using the ANOVA test, the Kruskal-Wallis test, and the Chi-square test. The cumulative incidence of time to the event was graphically represented using the Kaplan-Meier curves, and the difference of each group was compared by log-rank test. The hazard ratios (HRs) and 95% CIs for stroke and subtypes were determined by a cox proportional hazards analysis according to the TyG-index. Competing risk regression analyses were conducted for the competing risk of death by considering the sub-distribution hazard with non-stroke deaths as the competing risk [26]. Additionally, restricted cubic spline models were fitted to explore the shape of the correlation between the risk of early-onset stroke and baseline TyG-index. Several sensitivity analyses were adopted to guarantee the robustness of the optimization results by excluding the participants who used antihypertensive, antiglycemic, and lipid-lowering drugs, respectively. The researchers stratified the analyses of baseline TyG-index and the incident early-onset stroke according to the following factors: alcohol drinking (never or ever/current), smoking (never or ever/current), physical activity (never or ever/current); hypertension (no or yes), diabetes (no or yes), obesity [BMI <28 or 28 kg/m2]. A two-tailed *p*-value was set at 0.05.

Results

Characteristics of the Study Population

Among 35999 participants, 77.10% were men and their mean age was 30.82±5.66 years. The median (IQR) of the baseline TyG-index was 8.41 (8.48±0.68). The clinical parameters of the study subjects, according to quartiles of the TyG-index, are listed in **Table 1**. Subjects in the elevated TyG-index group were more inclined to be current alcohol drinkers and smokers, with a higher level of hs-CRP, FBG, TG, and LDL-C. They also had higher proportions of diabetes and hypertension. A statistically significant between-group difference was recorded ($P<0.05$).

Characteristics of stroke and subtypes

The length of the follow-up period was 11.50±2.61 years. During this period, 281 (0.78%) participants suffered a stroke, 219 of whom had an ischemic stroke, and the remaining had hemorrhage stroke. The first stroke incidence occurred at a mean±SD age of 43.83±6.25 years. The incidence rate of stroke events was 0.27, 0.57, 0.64, and 1.22/1000 person-years for the Q1-Q4 groups, respectively (**Table 2**). Concurrently, the incidence rate of ischaemic stroke was 0.19, 0.45, 0.47, and 1.02/1000 person-years for Q1-Q4 groups, respectively (**Table 2**). Thus, there was a tendency of increased risk of stroke and its subtypes among groups. The cumulative incidence of stroke and its subtypes for each of the TyG-index quartiles was calculated using the log-rank test ($P<0.05$). However, no apparent difference was detected in the hemorrhage stroke between-groups ($P>0.05$, **Figure 2**).

Association of early-onset stroke and TyG-index

Taking account of multiple potential confounders, data were adjusted for sex, age, salt intake, physical activity, education level, alcohol abuse, smoking status, hs-CRP, HDL-C, LDL-C, systolic blood pressure (SBP), diastolic blood pressure (DBP), BMI, history of antidiabetic drugs, lipid-lowering drugs, antihypertensive drugs, and hypertension. The primary result of Cox regression analysis showed that compared to the TyG-index level in Q1, the adjusted HRs (95% CI) for stroke in the Q2- Q4 were 1.57 (1.00–2.47), 1.35 (0.86–2.12), and 1.78 (1.15–2.74), respectively. With increasing TyG-index quartiles, multivariable-adjusted HRs (95% CI) for ischemic stroke within Q2-Q4 groups were 1.78 (1.03–3.07), 1.36 (0.79–2.36), and 1.98 (1.17–3.35), respectively. However, there was a non-significant association between hemorrhage stroke and baseline TyG-index (**Table 2**). Essentially similar results were revealed according to the competing risk analyses (**Table 3**).

After adjusting for confounding factors, results from restricted cubic splines revealed a linear association of stroke and ischemic stroke with the TyG-index (*P* linearity=0.02, 0.01; *P* non-linearity=0.49, 0.44). Moreover, while TyG-index was ≥8.41, the risk of stroke started to increase with the rising TyG-index (**Figure 3**).

Compared to previous studies [19, 20, 27], Cox proportional hazards regression model and competing risks analyses did not detect any significant change in the relationship between ischemic stroke and TyG-index after further adjusting TG and FBG, respectively (**Table S1-S2**).

Subgroup analysis

In addition, stratified analyses were performed to identify the potentially confounding factors. No significant interactions were detected between potential risk factors, such as drinking, smoking, physical exercise, obesity, hypertension, and diabetes, and the TyG-index for the risk of early-onset stroke. Using the lowest quartile group (Q1) as reference, significant positive associations were observed for non-drinkers, nonsmokers, physical activity, non-hypertension, and non-diabetes groups; the HRs (95% CI) were 2.57 (1.32–5.01), 2.07 (1.12–3.81), 2.09 (1.27–3.43), 2.03 (1.18–3.49), and 1.84 (1.19–2.85), respectively. However, no statistically significant differences were found in drinking, smoking, no physical activity, hypertension, and diabetes groups (**Table S3**).

Sensitivity analyses

The subjects on antihypertensive medications, anti-glycemic medications, and lipid-lowering medications at baseline and the duration of follow-up were excluded, and the analysis using a Cox regression-based model was repeated. The results were concordant with the primary findings. Consequently, no significant change was found in the relationship of outcomes and the TyG-index, indicating the robustness of this finding (**Table S4**).

Discussion

TyG-index (as the surrogate marker of IR) might be considered a significant risk factor for early-onset stroke among young adults, particularly ischemic stroke. Moreover, the association of early-onset stroke with the TyG-index had a linear dose-response relationship independent of other conventional risk factors. In addition, the association was more significant in participants without traditional risk factors, such as drinking, smoking, no physical exercise, obesity, hypertension, and diabetes, than in those with traditional risk factors.

During the 11-year follow-up period, the future risk of early-onset stroke was found to be positively related to baseline TyG-index. Compared to the Q1 group, the TyG-index in the Q4 group had a 78% more risk for incident early-onset stroke. Notably, after adjusting the results for the competing risk analysis and the impact of taking antihypertensive, antiglycemic, and lipid-lowering medications, the relationship of early-onset stroke and the TyG-index remained consistent with the primary outcome. While no previous study has discussed the correlation between early-onset stroke and TyG-index among young individuals, a collaborative meta-analysis of 8 prospective studies found that ischemic stroke was more likely to occur in people with high TyG-indexes. As compared with subjects in the bottom quartiles of the TyG-index, these findings suggested that subjects in the upper quartiles had a 1.26-fold increased risk of stroke [19]. In their study, Wang *et al*. [21] also demonstrated that the positive correlation between the occurrence of stroke and TyG-index among the 18-98-year-old general population was positively associated with the presence of stroke. Compared to subjects in the lowest quartile (3.61≤TyG<8.18), the risk of stroke in the highest quartile group (9.05≤TyG<12.5) was increased by 32%. Although the risk values varied, the positive correlation tendency was consistent with this finding.

After stratification by traditional risk factors, no interaction was detected between the relative risk of early-onset stroke and the TyG-index. The hierarchical analyses showed an association between early-onset stroke and high TyG-index in the non-drinking, non-smoking, non-hypertension, non-diabetes, and physical exercise in the low-risk population. Conversely, no association was observed in the high-risk population with traditional risk factors. These results strongly suggested that TyG-index was correlated with a high risk of early-onset stroke among a low-risk youth population. Yang *et al*. [28] demonstrated that this positive association was pronounced in the population with non-traditional risk factors, which was further supported by the present findings. Given the age of the population, the youth-adult without traditional risk factors had a lower 10-year atherosclerotic disease (ASCVD) risk, while the young population was lower [29]. Interestingly, the current results showed that the TyG-index was a dominant factor for stroke in the low-risk young population, independently. Thus, the current findings further our understanding of the risk factors for early-onset stroke in young adults. Moreover, TyG-index could also serve as a potential and new indicator for screening high-risk young individuals. Typically, when the TyG-index was >8.41, a strong correlation was established between the TyG-index and early-onset stroke, requiring a timely clinical intervention.

Previous studies demonstrated that using anti-hypertension [30], lipid-lowering [31], and hypoglycemic medications [32] could modify the effect on the risk of stroke. In order to exclude the effect of hypoglycemic, anti-hypertension, and lipid-lowering drugs as confounding factors, we undertook several sensitivity analyses; however, the results revealed no effect of any of the above-listed confounders. Nonetheless, the risk of stroke could not be decreased by eliminating the associated risk factors. These findings suggested that the TyG-index acts as a robust risk factor among young adults, irrespective of the other risk factors.

Although we found a strong correlation between the risk of early-onset stroke and IR assessed by the TyG index, there is still no clear understanding of the underlying mechanism. Previous studies have proposed several potential causal pathways. First, since hyperinsulinemia accompanies IR, it may result in sympathetic activation, as well as increased tubular sodium reabsorption and endothelin secretion, all of which favor a rise in blood pressure [33, 34]. The potential underlying mechanisms may also involve excessive inflammation and oxidative stress, subsequently causing vascular endothelial function [9, 35, 36]. Second, IR may cause lipoprotein abnormalities, including hypertriglyceridemia, a decrease in HDL, and a change in LDL particle size, thus further aggravating IR. Plaques are regarded as a high-risk factor during the process of the occurrence of stroke. Lipoprotein abnormalities and endothelial dysfunction may accelerate the transformation of macrophages into foam cells, which are the key components of the pathogenesis of stroke. Additionally, IR is linked to diminished fibrinolysis and substantial platelet aggregation, which obstruct cerebral arteries and result in hemodynamic abnormalities and the creation of thrombi.[37].

Consistent with previous studies [21], TyG-index has been corroborated as a key risk factor for stroke independently. This study has expanded the existing knowledge on TyG-index and stroke. According to current understanding, this is the first prospective study in China that examined the association between early-onset stroke and TyG-index. Furthermore, this is also the first study that established the optimal threshold of the TyG-index for early-onset stroke. Our results underscore the importance of keeping the TyG-index below the threshold among young adults. The findings of this study have major public health and clinical implications. The current study confirmed that TyG-index is correlated with the relative risk of early-onset stroke among young Chinese adults, irrespective of the burden of traditional risk factors. Our findings provide a new basis for preventing early-onset stroke in the young population. Furthermore, the cutoff of the TyG-index for identifying stroke was not determined. The results implied that when TyG-index is ≥8.41, the risk of stroke increases with a high TyG-index. Thus, we recommend a threshold point of 8.14 for the TyG-index to identify young adults at future risk of stroke. Supposedly, early intervention is critical, and treatment should be administered when the TyG-index is >8.14. Lifestyle interventions, such as physical exercise and weight loss, remain the foundation of primary stroke prevention and have a significant desirable effect on TyG-index. Moreover, lipid-lowering drugs, including niacin and fibrates, should be administered to strengthen the lipid-lowering therapy that reverses poor outcomes.

The present study has several strengths. This research was based on a large community-based cohort design used to evaluate the correlation between early-onset stroke and TyG-index among young Chinese adults through extensive prospective data with up to 11 years of follow-up. Additionally, information about all participants, including whether a clinical stroke occurred, and the exact time of events that took place, were carefully recorded to ensure tracked accuracy and quality data. The present study also has some limitations. First, limited by human, material, and financial resources and other factors, and due to the absence of fasting insulin measurement and non-evaluation of HOMA-IR in the Kailuan Study [38], it was impossible to compare the differences between HOMA-IR and TyG-index on early-onset stroke. Second, participants included the typical Chinese population from northern China, most of whom were adult men from community-dwelling in a middle city in northern China. Although the subjects of this study comprised a young occupational population in northern China, the reported results still have a significant reference value because the incidence density of this study was not in contradiction with the previous reports (0.53/1000 person-year and 0.76/1000 person-year, respectively)[39, 40]. No lacunar stroke subjects were included in this cohort, which could underestimate the influences of the TyG-index on adverse outcomes. Finally, further studies are needed to explore the effect of the dynamic TyG-index on progressive stroke by using other methods, such as trajectory analysis.

Conclusion

Overall, the present study supports the evident association between early-onset stroke and TyG-index among young Chinese adults, especially ischemic stroke. Furthermore, we provided reference ranges in the risk threshold of the TyG-index (TyG=8.41). Thus, TyG-index may serve as a practical tool for early-onset stroke risk assessment in clinical applications. The TyG-index > 8.41 may be applied as a screening index to identify the high-risk population. Furthermore, timely emphasis on the primary prevention of TyG-index provides an opportunity for preventing or delaying early-onset stroke.

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