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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

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ABSTRACT

Aims. We evaluated the potential role of the triglyceride–glucose index (TyG index) as a predictor of diabetes in a White European cohort, and compared it to fasting plasma glucose (FPG) and triglycerides.

Methods. 4820 patients of the Vascular-Metabolic CUN cohort (VMCUN cohort) were examined and followed up for 8.84 years (±4.39). We performed a Cox proportional hazard ratio with repeated-measures analyses to assess the risk of developing type 2 diabetes across quartiles of FPG, triglycerides and the TyG index (ln[fasting triglycerides (mg/dl) × fasting plasma glucose (mg/dl)/2]), and plotted a receiver operating characteristics (ROC) curve for discrimination.

Results. There were 332 incident cases of type 2 diabetes involving 43,197.32 person-years of follow-up. We observed a progressively increased risk of diabetes in subjects with TyG index levels of 8.31 or more. Among those with normal fasting glucose at baseline, <100 mg/dl, subjects with the TyG index in the fourth quartile were 6.87 times more likely to develop diabetes (95% CI, 2.76–16.85; P for trend < 0.001), as compared with the bottom quartile. The areas under the ROC curves (95% CI) were 0.75 (0.70–0.81) for TyG index, 0.66 (0.60–0.72) for FPG and 0.71 (0.65–0.77) for TG, in subjects with normal fasting glucose ($p = 0.017$).

Conclusions. Our data suggest that the TyG index is useful for the early identification of individuals at risk of type 2 diabetes. The TyG index seems to be a better predictor than FPG or triglycerides of the potential development of type 2 diabetes in normoglycemic patients.

Introduction

The prevalence of type 2 diabetes is increasing worldwide, placing a tremendous burden on health economies and leading to a global epidemic due to its complications (Shaw et al., 2010). Insulin resistance (IR), the decreased insulin sensitivity of peripheral tissues, plays a major role in the pathogenesis of diabetes as well as metabolic syndrome, and it may appear 1–2 decades before the formal diagnosis of type 2 diabetes (Fernandez-Berges et al., 2011; Knowler et al., 2002). This theory is supported by the usefulness of IR as a marker of future diabetes or the prevention of type 2 diabetes by insulin-sensitizing agents (Knowler et al., 2002). Multivariate scores have been developed to identify healthy individuals at high risk of diabetes, based on a combination of risk factors (history of gestational diabetes, first degree relative with diabetes, metabolic syndrome), but their predictive value is often poor (Buijsse et al., 2011). Early biological circulating markers such as tumor necrosis factor-alpha, interleukin-6 or high-sensitivity C-reactive protein, may be used to accurately predict future diabetes

Abbreviations: AUC, area under the curve; BMI, body mass index; CUN, University of Navarra Clinic; FPG, fasting plasma glucose; HDL-C, HDL cholesterol; HR, hazard ratio; IFG, impaired fasting glucose; IR, insulin resistance; Lp(a), lipoprotein(a); LDL-C, LDL cholesterol; NFG, normal fasting glucose; ROC, receiver operating characteristics; TyG index, triglyceride–glucose index; TC, total cholesterol; TG, triglycerides; VMCUN cohort, Vascular-Metabolic CUN cohort.

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(Liu et al., 2007). However, they are inconvenient and costly for a daily practice, as well as inefficient for screening. Therefore, novel markers or risk factors are needed to identify individuals at high risk of developing diabetes in order to implement preventive models on populations.

Triglyceride–glucose index (TyG index), the product of fasting plasma glucose (FPG) and triglycerides (TG), has been suggested as a marker of IR (Du et al., 2014). Indeed, it has shown correlation with the HOMA-IR (Wan et al., 2015; Simental-Mendía et al., 2008), the insulin suppression test (Abbasi and Reaven, 2011) and the gold standard diagnosis method of IR, the hyperinsulinemic–euglycemic clamp (Vasques et al., 2011; Guerrero-Romero et al., 2010). This index has been tested in both an Iranian and a Korean population with promising results (Lee et al., 2014; Janghorbani et al., 2015), but it may not be applicable worldwide among all ethnic groups, and no study to date has examined type 2 diabetes incidence with the TyG index in a White European population.

We aimed, first, to settle whether the TyG index could be a helpful marker for predicting diabetes in a cohort of a non-diabetic White European population, and secondly, to compare the TyG index to FPG and to TG as predictors of type 2 diabetes.

Methods

Subjects

The Vascular-Metabolic CUN cohort (VMCUN cohort) is a population-based, epidemiological study designed to examine the incidence of cardiovascular and metabolic diseases including type 2 diabetes, hypertension, obesity, stroke or coronary heart disease in a large White European population. The cohort has been described previously elsewhere (Sánchez-Íñigo et al., 2016). Briefly, 6071 people fulfilled the inclusion criteria. We excluded patients with prevalent diabetes, erroneous and missing laboratory values and those subjects lost to follow-up. This left 4820 participants for the current analysis. The research was conducted according to the standards of the Declaration of Helsinki on medical research (Declaration of Helsinki., 1976), and was approved by the Ethics Committee of the Universidad de Navarra (30/2015).

Measurements

Data regarding on medical history, lifestyle behavior and blood analyses of the subjects were retrieved on the day of inclusion in the study and in each successive consultation in order to perform a repeated-measures analysis. The median of follow-up was 10 years (mean 8.84 ± 4.39 years), with a median number of 3 visits per patient (range 2 to 8 visits) and a median time gap of 2 years between each clinical visit.

The recorded information from each visit included the following data:

1. Personal lifestyle behavior including cigarette smoking (none, former smoker or current smoker), daily alcohol intake (yes/no) and lifestyle pattern (physically active/sedentary behavior).
2. Anthropometric measurements (weight, height and BMI) and BP, which were performed by a trained nurse according to standardized methods. Weight was quantified with subjects wearing light clothing and to the nearest 0.1 kg; height was measured without shoes to the nearest 0.1 cm. BMI was calculated as the body mass divided by the square of the body height and expressed in units of kg/m^2. The participants were categorized as normal weight, overweight, or obese by the commonly accepted BMI ranges. Prior to the BP measurement, the subjects were asked to remain seated for 5 min. The BP on the indistinctly right or left arm was measured twice with an aneroid sphygmomanometer (Riester® Minimus II 1312) and a stethoscope (Littman® Classic II S.E.) following the World Health Organization (WHO) criteria (Anon., 1993), and the average was recorded.
3. Clinical history and relevant information about cardiovascular disease (coronary heart disease, cerebrovascular disease, peripheral arterial disease), cancer and psychiatric diseases were recorded. Hypertension was defined according to the basis of the WHO—International Society of Hypertension Guidelines (Anon., 1993) as ≥140 (systolic BP)/90 (diastolic BP) mm Hg or when a subject reported having been prescribed antihypertensive medication.
4. Routine biochemical data including FPG, total cholesterol (TC), TG, HDL cholesterol (HDL-C), and LDL cholesterol (LDL-C) were also retrieved. Blood samples were drawn after an 8-h fast and analyzed in a central laboratory with a Hitachi 711 Chemistry Analyzer under strict quality control. FPG was measured through the hexokinase method. TC, HDL-C and TG were determined using enzymatic colorimetric tests and LDL-C was calculated using the Friedewald formula (Friedewald et al., 1972). We considered as missing the values of LDL-C in patients with TG levels greater than 400 mg/dl. The TyG index was calculated as the ln[fasting TG (mg/dl) × FPG (mg/dl)/2] (Simental-Mendía et al., 2008).

Definition of diabetes

The diagnosis of type 2 diabetes was defined as the primary end point of the study. We diagnosed diabetes according to the ADA criteria published in 1997 (Bloomgarden, 1997): symptoms of diabetes plus random plasma glucose concentration ≥ 200 mg/dl (11.1 mmol/l), or FPG ≥ 126 mg/dl (7.0 mmol/l), or 2-h postload glucose ≥ 200 mg/dl (11.1 mmol/l) during an OGTT. However, from February 2010 to the end of follow-up, we diagnosed those with diabetes onset according to the update ADA criteria published in 2010 (American Diabetes A, 2010), which include the previous plus the criteria of levels of HbA1c ≥ 6.5%. Each criterion, in the absence of unequivocal hyperglycemia, was achieved by repeated testing on a different day.

Statistical analysis

Continuous variables were expressed as the mean ± SD. Categorical variables were presented as percentages. The Student's t test, one-way ANOVA or χ^2 test was used to compare the characteristics of the TyG index quartiles. A general linear model was used to fit the median of the quartiles as a continuous variable to estimate the trend of variables across quartiles. We used the multiple imputation procedure in Stata (mi command) to impute the missing data of the variables cigarette smoking (16.6% missing values), daily alcohol intake (25.4% missing values) and lifestyle pattern (30.9% missing values). Twenty imputed datasets were created to reduce sampling variability from the imputation process. The variables included in the imputation procedure were: age, sex, BMI, cardiovascular disease, hypertension, TyG index, FPG, TG and the outcome, and type 2 diabetes. A run length of 100 iterations was used between each dataset. All variables included before imputation had normal distribution.

We conducted a Cox proportional-hazard analysis to estimate the hazard ratio (HR) and their 95% CI of type 2 diabetes in each quartile of TyG index, FPG and TG. The lowest quartile of risk was determined as the reference category and repeated-measures ANOVA was used to assess changes over time. We fitted three models: a crude (univariate) model and two Cox regression multivariate-adjusted models: (a) controlling for age (continuous) and sex (as an interaction factor); (b) additionally adjusted for baseline BMI (continuous), cigarette smoking (never, current and former smokers), daily alcohol intake (yes/no), lifestyle pattern (physically active/sedentary behavior), hypertension (yes/no), cardiovascular disease (yes/no), LDL-C (continuous) and HDL-C (continuous). We stratified analysis by sex and conducted a Cox regression multivariate-adjusted model including the covariates in model (c), except sex. Interaction terms between sex and the quartiles of FPG, TyG index and TG were used to test for differences in association.

The patients were then stratified by the glucose levels in two subgroups: normal fasting glucose (NFG) and impaired fasting glucose (IFG). We conducted a Cox regression multivariate-adjusted model (b) in the 3291 patients with NFG and in the 1529 participants with IFG, considering the ADA criteria of FPG ≥ 100 mg/dl. The area under the curve (AUC) of the receiver operating characteristics (ROC) plot and the 95% CI were calculated to compare the predictive power of the TyG index, FPG and TG in both subgroups. Finally, we performed a sensitivity analysis to assess the robustness of the results by rerunning all the models under different assumptions.

All statistical analyses were performed with STATA version 12 (Stata Corp., College Station, TX, USA). All p-values are two-tailed and statistical significance was set at the conventional cut-off of $p < 0.05$.

Results

A total of 6071 people were initially included at baseline, from whom 649 subjects without follow-up, 211 with erroneous or missing