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Silent coronary artery disease and incidence of cardiovascular and mortality events at different levels of glucose regulation; results of greater than a decade follow-up ☆

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ABSTRACT

Background: To determine the impact of silent coronary artery disease (CAD), in different levels of glucose regulation at baseline, i.e., those with normal fasting glucose/normal glucose tolerance (NFG/NGT), pre-diabetic and newly diagnosed diabetes mellitus (NDM), on cardiovascular disease (CVD) and total mortality in Iranian populations.

Methods: The study population included 1809 individuals, aged ≥50 years, free of CVD at baseline with a median follow-up of 12.1 years. To explore the risk of CVD and mortality associated with the presence of silent CAD (as defined by Minnesota coding criteria for baseline electrocardiogram (ECG) in the absence of a history of CVD) in each of the glucose regulation categories, multivariate adjusted hazard ratios (HRs) were calculated for the presence of silent CAD, compared to the corresponding non-silent CAD counterpart, as reference.

Results: During follow-up 382 CVD (321 coronary heart disease) and 208 deaths (91 CVD mortality) occurred. Among the female population, the presence of silent CAD, independent of traditional risk factors, significantly increased the risk of CVD for population with NFG/NGT [2.40 (1.33–4.35)] and pre-diabetes [HR: 2.04 (1.14–3.63)]; however, in the male population the risk was significant for CVD [3.04 (1.53–6.05)] and mortality events [2.60 (1.22–5.56)] in the NDM population and marginally significant for mortality events in NFG/NGT.

Conclusion: Different strategies should be considered for silent CAD in males and females with different levels of glucose regulation. It might be justified that screening ECG for prevention of CVD events should be considered mainly among non-diabetic women and men with NDM.

1. Introduction

Silent myocardial ischemia, first described by Stern [1], is defined as an ischemic episode documented by any objective method of diagnosis without having related symptoms [2]. Despite the increasing attention given to ischemic heart disease during recent decades, coronary heart disease (CHD) remains the first cause of mortality in many countries. One of the proposed reasons might arise from the fact that about 70–80% of ischemic episodes detected by Holter monitoring remain silent [3,4] and only some of these episodes present with angina or ischemic associated symptoms.

On the other hand studies report higher incidences of cardiovascular complications among diabetic and pre-diabetic patients [5,6]. Asymptomatic diabetic persons experience higher rate of cardiovascular complications associated with silent coronary artery disease (CAD) and have a poorer prognosis compared to non-diabetic individuals [7]. It was also recently shown that in newly diagnosed diabetic mellitus (NDM) patients, evidence of silent myocardial infarction (MI) increased the risk of fatal MI and all-cause mortality [8]. Furthermore, the status of silent ischemia and its prognosis among pre-diabetic individuals have been poorly evaluated (i.e., those with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) or both) [9]. To the best of our knowledge, only one study has so far assessed cardiovascular morbidities of patients with IFG, but they did not use oral glucose tolerance test (OGTT) to exclude cases of NDM [10].

The public health burden of diabetes mellitus (DM) is growing globally, especially in the Middle Eastern region [11,12]. It was determined that about one third of Tehranian adults, aged ≥20 years were affected by some degrees of hyperglycemia, including impaired glucose tolerance or DM [13]. Furthermore, it was shown that the impact of DM

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and pre-diabetes status on cardiovascular disease (CVD) among females was stronger than in their male counterparts [14,15].

This study was conducted in a large community based cohort of the Tehran Lipid and Glucose Study (TLGS), to determine the impact of silent CAD in different glucose tolerance statuses i.e., those with normal fasting glucose/normal glucose tolerance (NFG/NGT), prediabetic and NDM patients, on CVD/CHD events and total mortality in Iranians, which could facilitate designing of appropriate health strategies.

2. Methods

2.1. Study population

In brief, TLGS is a prospective population-based cohort study carried out on 15,005 people, aged ≥3 years, living in district 13 of Tehran, to ascertain the risk factors for non-communicable diseases and to develop population-based measures to develop healthy lifestyles to prevent the growing trends in non-communicable disease risk factors. Age and sex distributions of the population in the district were representative of the overall population of Tehran at the time of the baseline examination [16]. From the overall general population those aged ≥50 years at the baseline TLGS examination (February 1999–August 2001) entered the study (n = 3394). Participants who were treated by antidiabetic medications (n = 460), with history of CVD (n = 443) and those with missing data on fasting plasma glucose (FPG) or 2 hour post load glucose (2 h-PLG) or electrocardiogram (ECG) data (n = 501) were excluded, leaving 1990 participants of which 1809 (female = 957) participants were followed up until 20th March 2012, a median of 12.1 years (Fig. 1).

All participants provided written, informed consent. The protocol of the present study was designed in accordance with the principles of the Helsinki declaration, and was approved by the Research Council of Research Institute of Endocrine Sciences of Shahid Beheshti University.

2.2. Clinical, anthropometric, and laboratory measurements

The details of data gathering have been described elsewhere [16]. Using pretested questionnaires which included demographic data, age, past medical history of CVD, drug consumption and smoking behavior, subjects were interviewed privately, face-to-face by trained interviewers. Weight, height, waist circumference (WC), and blood pressure were measured according to the standard methods [16]. Body mass index (BMI) was calculated as weight (kg) divided by square of height (m^2). A 12-lead resting ECG was recorded by two trained technicians according to a standard recording protocol developed by the School of Public Health, University of Minnesota [17] using a PC-ECG 1200 machine. Two trained physicians coded the ECGs independently according to the Minnesota codes using a measuring loupe specially manufactured by the University of Minnesota [18]. For assurance of quality, a third trained physician recoded 10% of ECGs and all the data were doubly entered and rechecked.

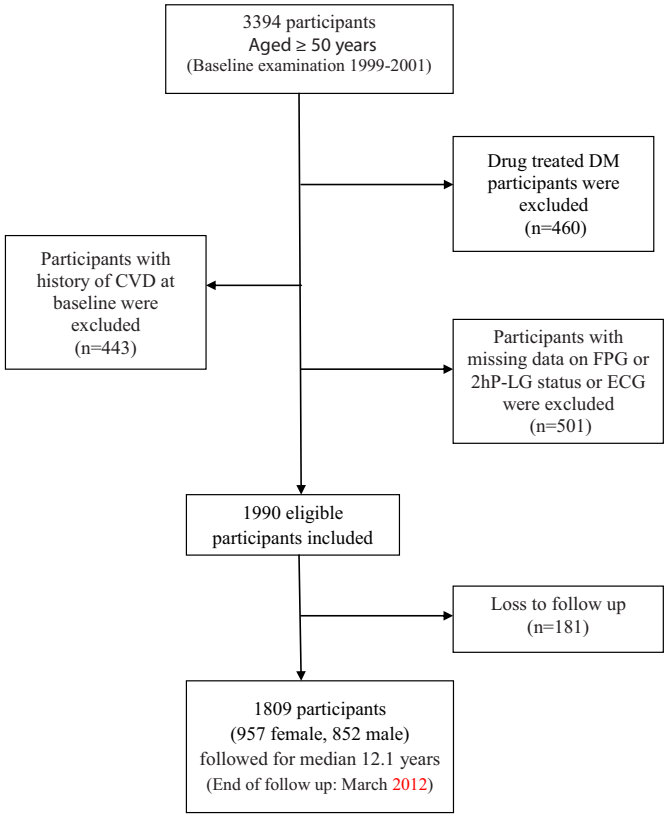

Fig. 1. Flow chart of study population. DM, diabetes mellitus; CVD, cardiovascular disease; FPG, fasting plasma glucose; 2 h-PLG, 2 hour post load glucose; ECG, electrocardiogram.

A blood sample was taken after 12–14 h overnight fasting at the TLGS research laboratory. Details for measurements of FPG, 2 h-PLG and total cholesterol (TC) have been reported elsewhere [16].

2.3. Definition of terms

DM was defined as either FPG ≥7 mmol/l or if their 2 h-PLG test was ≥11.1 mmol/l, according to American Diabetes Association (ADA) criteria [19] or current use of antidiabetic drugs [20], NDM as FPG ≥7 mmol/l or, 2 h-PLG ≥11.1 mmol/l [11]; IFG as FPG of 5.6–6.9 mmol/l and IGT as 2 h-PLG of 7.8–11.0 mmol/l [9]. In the current study we defined pre-diabetes as having IFG and/or IGT. Smoking status was categorized as current smokers (regular or occasionally) versus non-smokers (past smoker or never smoker). Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg or the current use of antihypertensive medication based on JNC 7 [21]. Hypercholesterolemia was defined as total cholesterol ≥6.2 mmol/l or current use of lipid lowering drugs.

ECG determined CHD was defined according to the Minnesota code [22] and Whitehall criteria [23], in which subjects were categorized into three groups: Probable CHD, included major Q or QS wave (Minnesota codes 1.1, 1.2) or complete left bundle branch block (Minnesota code 7.1.1); possible CHD, included small Q or QS wave (Minnesota code 1.3); ST depression (Minnesota codes 4.1–4.3), or T-wave items (Minnesota codes 5.1–5.3) and no CHD (ECGs that had none of these criteria). We combined probable and possible groups as a single group of silent CAD. A minor ischemic ECG change was also defined as T-wave items (Minnesota codes 5.3–5.4) and minor ST depression changes (Minnesota codes 4.3–4.4).

2.4. Definition of outcome

Details of the collection of cardiovascular outcome data have been published elsewhere [24]. To go over the main points briefly, each participant was followed up by a trained nurse annually by phone calls for any medical event and then a trained physician collected complementary data regarding that event during a home visit and by acquisition of data from medical files. An outcome committee consisting of an internist, an endocrinologist, a cardiologist, an epidemiologist and other experts, when needed, evaluated the collected data to assign a specific outcome for every event. In this study, our desired events were incidence of CHD which included cases of definite MI diagnosed by ECG and biomarkers, probable MI (positive ECG findings plus cardiac symptoms or signs and biomarkers showing negative or equivocal results), unstable angina pectoris (new cardiac symptoms or changing symptom patterns and positive ECG findings with normal biomarkers) and angiographic proven CHD. CVD was specified as a composite measure of any CHD events, stroke, or cerebrovascular events.

2.5. Statistics

Continuous variables were reported as mean ± standard deviation (SD), values and frequencies (%) were used for categorical variables of baseline characteristics. Analyses of different baseline characteristics between categories of glucose regulation were done using Chi square tests for binary variables and ANOVA for continuous variables.

The multivariate adjusted hazard ratio (HR) for CVD/CHD incidents and total mortality was determined by Cox proportional hazard model in different glycemic statuses considering NFG/NGT as reference, similarly we calculated the HR for the different outcomes regarding baseline CAD status, considering those without silent CAD as reference. To explore the risk of CVD/CHD incidents and mortality associated with adding silent CAD to each of the glucose regulation categories, we calculated HRs in age as well as multivariate adjusted models in each glycemic status category in the presence of silent CAD, compared to the corresponding nonsilent CAD counterpart, as the reference using Cox analysis. Finally, to examine the multivariate and sex adjusted risk of different events for the population with minor ischemic change at baseline in different glucose regulation categories, we excluded those with major Q or QS wave (Minnesota codes 1.1, 1.2) or complete left bundle branch block (Minnesota code 7.1.1) from our data file and HR was calculated using the Cox model. Potential confounding factors in the multivariate analyses were age, BMI, hypertension, hypercholesterolemia, and smoking. The period between entrance to study and the end points, which were the CVD/CHD event, and total mortality was considered as the follow-up duration. The censoring time of an individual was the time from entry into the study to loss to follow-up or leaving the residence area or occurrence of CVD/CHD event or death, whichever occurred first.

Interactions between sex and different glucose regulation statuses were examined in the multivariate model. Since we found significant interaction between sex and NFG/NGT status (p = 0.016 and 0.012 regarding CVD and CHD, respectively) and also sex and prediabetes status (p = 0.005 and p = 0.003 regarding CVD and CHD outcomes, respectively), all analyses were sex-stratified. The proportional hazard assumption in the Cox model was assessed with the Schoenfeld residual test and all proportionality assumptions were