Contents lists available at ScienceDirect

Diabetes Research and Clinical Practice

journal homepage: www.elsevier.com/locate/diabres

Coronary disease risk and fasting glucose levels in a non-diabetic population

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ARTICLE INFO

Article history:
Received 26 August 2010
Received in revised form
1 November 2010
Accepted 29 November 2010
Published on line 3 January 2011

Keywords:
Cigarette smoking
Coronary heart disease
C-reactive protein
Plasma glucose
Plasma insulin
Pro-inflammatory state

ABSTRACT

We addressed whether or not the risk of coronary heart disease (CHD) in non-diabetic persons is linear at the lower end of fasting glucose levels. Middle-aged Turkish adults (n = 2893) free from diabetes and CHD at baseline were studied prospectively over a 7.6-year follow-up. Participants with fasting glucose measurements were analyzed in 3 groups separated by 90 mg/dl and 110 mg/dl limits. Outcomes were analyzed by Cox regression.

Cox regression for CHD incidence (n = 374) showed an increased age-adjusted risk in the <90 mg/dl fasting glucose group (n = 788) [HR 1.32 (1.03; 1.68)], compared with the 90–110 mg/dl group after adjustment for sex, age and the glucose groups. Further adjustment for waist circumference, C-reactive protein and conventional risk factors attenuated the HR to 1.27 (p = 0.077). The risk profile in the low-glucose group could not be accounted for by age, smoking status, systolic blood pressure or fasting insulin levels but tended to show higher levels of circulating C-reactive protein.

The increased CHD risk observed in individuals with lower compared with higher normal glucose concentrations is likely to be related to an associated pro-inflammatory state.

1. Introduction

It remains unclear as to whether fasting glucose levels in non-diabetic people exhibit a linear risk of coronary heart disease (CHD) [1–3]. A U-shaped relationship between fasting glucose and mortality was documented in a large prospective cohort such that, after adjusting for positive variables, subjects with glucose levels from <80 to 109 mg/dl had a 2- to 3-fold higher risk of CVD mortality and increased risk of all-cause mortality compared with subjects with glucose levels of 80–109 mg/dl [4]. Similar results were reported in at least 4 other studies on different ethnicities [5–8], in males or both sexes combined, using cut-offs ranging from <86 to <74 mg/dl.

Few studies have examined the relationship between smoking and fasting glucose levels. It has been suggested that such an excess risk might be linked to cigarette smoking [4], yet no study has documented such a relationship. Among non-diabetic middle-aged Italian men, smokers were found to have lower fasting glucose levels and had fewer instances of hyperglycemia to be less frequent than never-smokers [9]. Smoking was not found to be related to glucose intolerance among middle-aged Japanese men [10]. In the D.E.S.I.R study men who reduced smoking by 10 cigarettes per day over 3 years had an associated significant increase in fasting glucose and insulin levels [11].

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0168-8227/$ – see front matter
doi:10.1016/j.diabres.2010.11.035

The Turkish Adult Risk Factor (TARF) study reported associations between smoking and a lower risk of developing abdominal obesity in both males and females and significant protection against the development of type-2 diabetes in females, when age-adjusted [12–14]. We did not previously directly examine whether or not a J-shaped relationship exists between the lower end of fasting glucose and CHD risk and this hypothesis is explored in the current study.

2. Population and methods

2.1. Population sample

The TARF is a longitudinal population-based cohort study on cardiac disease and its risk factors in adults in Turkey, carried out biennially in 59 communities in all geographical regions [15]. It involves a random sample of the Turkish adult population, representatively stratified for sex, age, geographical regions and for rural–urban distribution [15]. Combined measurements of waist circumference and high-density lipoprotein (HDL)-cholesterol were first made at the follow-up visit in 1997/98 and formed the baseline. Participants, 28 years of age or older at baseline, were examined periodically up to the survey 2008/09. Individuals with prevalent diabetes ($n = 269$), CHD ($n = 153$), glucose concentration <50 mg/dl ($n = 3$), missing glucose values ($n = 155$) and no follow-up ($n = 269$) were excluded and the remaining 2893 participants (free from diabetes and CHD) comprised the cohort of the current study (Fig. 1). The survey conformed to the principles embodied in the Declaration of Helsinki and was approved by the Istanbul University Ethics Committee. Individuals of the cohort gave written consent for participation. Data were obtained by history of the past years via a questionnaire, physical examination of the cardiovascular system, sampling of blood and recording of a resting 12-lead electrocardiogram.

2.2. Measurements of risk variables

Blood pressure (BP) was measured while seated, using the right arm, with a sphygmomanometer (Erka, Bad Tölz, Germany). The mean of two recordings taken at least 3 min apart was recorded. Waist circumference was measured with a tape (Roche LI95 63B 00), the subject standing and wearing only underwear, at the level midway between the lower rib margin and the iliac crest. Self-reported cigarette smoking was categorized into never-smokers (never having smoked), former smokers (having stopped for at least 3 months prior to the study) and smokers (regularly one or more cigarettes daily).

Plasma concentrations of total and HDL cholesterol, fasting triglycerides and glucose were determined at baseline examination by the enzymatic dry chemistry method using a Reflotron apparatus. Low-density lipoprotein (LDL)-cholesterol values were calculated according to the Friedewald formula. In the final four examinations, the previously measured parameters, as well as insulin and C-reactive protein (CRP) values were assayed in a single central laboratory. Blood samples were shipped to Istanbul to be stored at $-75\ ^{\circ}C$, until analyzed. Concentrations of insulin were determined by electrochemiluminescence immunoassay (ECLIA) on Roche Elecsys 2010 (Roche Diagnostics, Mannheim, Germany). Serum concentrations of CRP were measured by the Behring nephelometry (Behring Diagnostics, Marburg, Germany). External quality control was performed with a reference laboratory in a random selection of 5–6% of participants. Data on baseline triglycerides, CRP and insulin were available in 74%, 83%, and 56% of participants, respectively.

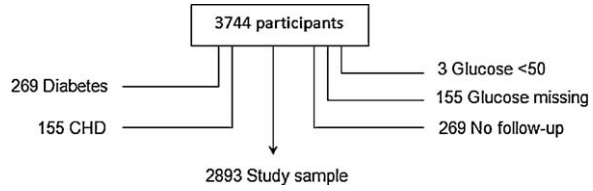

Fig. 1 – Diagrammatic representation of the selection of the baseline study sample from the cohort. CHD denotes coronary heart disease.

2.3. Definitions and outcomes

Individuals with type-2 diabetes were diagnosed using the criteria of the American Diabetes Association [16], that is, when plasma fasting glucose $\geq$126 mg/dl (or 2 h postprandial glucose $\geq$200 mg/dl) and/or the current use of diabetes medication. Impaired glucose tolerance (IGT) was defined as a post-prandial (1–3 h after breakfast) glucose concentration of 140–199.9 mg/dl. Impaired fasting glucose (IFG) was identified as a fasting level of 110–125.9 mg/dl (according to the World Health Organization definition [17]). Individuals with abdominal obesity were identified using waist circumference cut-points of $\geq$95 cm in men [12] and $\geq$88 cm in women [13], as assessed in the Turkish Adult Risk Factor study.

Diagnosis of non-fatal CHD was based on the presence of angina pectoris, of a history of myocardial infarction with or without accompanying Minnesota codes of the ECG [18], or on a history of myocardial revascularization. Typical angina and, in women, age $>$45 years were prerequisite for a diagnosis when angina was isolated. ECG changes of ''ischemic type'' of greater than minor degree (Codes 1.1-2, 4.1-2, 5.1-2, 7.1) were considered as myocardial infarction sequelae or myocardial ischemia, respectively. Cause of death was assigned in accordance with the information on the mode of death obtained from first-degree relatives and/or local health personnel, considering also pre-existing clinical and laboratory findings elicited during biennial examinations.

2.4. Data analysis

Results are shown as mean $\pm$ standard deviation (SD), as percentages, and as adjusted mean $\pm$ standard error (SE). Due to skewed distribution, values derived from log-transformed (geometric) means were used for serum CRP and insulin. Two-sided *t*-tests and Pearson's chi-square tests were used to analyze the differences between means and proportions of two groups. ANOVA was used to detect differences between means of multiple groups, followed by pairwise comparisons with Tukey HSD tests; pairwise comparisons with Bonferroni