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Original article

Fasting hyperinsulinaemia and 2-h glycaemia predict coronary heart disease in patients with type 2 diabetes

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Abstract

Aim. – Patients with diabetes are at greater risk of cardiovascular events. Insulin resistance (IR) and hyperinsulinaemia are both related to an increased cardiovascular risk, but whether IR predicts coronary heart disease (CHD) independently of other risk factors in patients with type 2 diabetes (T2D) is a topic of considerable controversy. The aim of the present study was to evaluate the prospective relationship of fasting insulin, HOMA-IR, fasting plasma glucose (FPG) and 2-h post-load glucose (2hPG) load with CHD incidence among such patients.

Methods. – A total of 2607 patients with T2D were enrolled in a community-dwelling cohort and followed for an average of 7.2 years. Conventional CHD risk factors, FPG, 2hPG, fasting insulin levels and HOMA-IR index were measured at baseline. Cox regression hazard ratios (HRs) were used to assess CHD risk.

Results. – A total of 299 'hard' CHD events were registered (in 114 women and 185 men). Increasing levels of fasting insulinaemia were positively associated with CHD incidence. This correlation persisted after controlling for gender, body mass index, blood pressure, lipid profile, medication use and HbA_{1c} [HR for each increase in quartile (fully adjusted model): 1.18 (95% CI: 1.06–1.32); $P < 0.01$]. 2hPG showed a non-linear association with incident CHD [HR of highest *vs* lowest quartile: 1.64 (95% CI: 1.03–2.61)]. Fasting glycaemia was not associated with CHD risk, whereas HOMA-IR had a direct and independent correlation with CHD risk [HR for each one-quartile increase: 1.19 (95% CI: 1.07–1.34); $P < 0.01$].

Conclusion. – Fasting insulin levels are positively associated with incidence of CHD in T2D. Furthermore, 2hPG appears to be a significant predictor of incident CHD independently of other risk factors, including HbA_{1c}. These findings suggest that strategies targeting the reduction of insulinaemia and post-load glycaemia may be useful for preventing cardiovascular complications.

Keywords: Coronary heart disease; Hyperinsulinaemia; Insulin resistance; 2-h plasma glucose; Type 2 diabetes mellitus

1. Introduction

Coronary heart disease (CHD) is the leading cause of death among patients with type 2 diabetes (T2D) [1]. Numerous studies have reported up to a fourfold higher risk of coronary events in individuals who have the disorder [2–4]. However, the origins of the association are still not proven and remain at the level of hypothesis [5,6].

Conventional risk factors for CHD, including older age, hypertension, hypercholesterolaemia, diabetes, a positive family history and cigarette-smoking [7], can account for a certain

Abbreviations: ADA, American Diabetes Association; CVD, cardiovascular disease; DBP, diastolic blood pressure; EMRC, Endocrinology and Metabolism Research Center; FPG, fasting plasma glucose; HOMA-β, homoeostasis model assessment of beta-cell function; IR, insulin resistance; IS, insulin sensitivity; MAP, mitogen-activated protein; 2hPG, 2-h post-load glucose; SBP, systolic blood pressure; TUMS, Tehran University of Medical Sciences; TG, triglyceride.

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number of CHD events. However, the role of postprandial glucose excursions in the development of CHD in T2D is still unclear, a subject of debate and not well demonstrated [8].

The majority of epidemiological studies, which have revealed an association between post-load glucose peaks and CHD, have been performed with the general population, so that data are sparse for patients with T2D [9–13]. Thus, the relative contributions of postprandial plasma glucose, insulin resistance (IR) and insulin sensitivity (IS) in the development of CHD in people with T2D have not been fully examined.

IR is a characteristic feature of T2D and already present in the prediabetic stage [14]. There is also evidence to suggest that IR is associated with CHD in people without diabetes [15–20]. Hyperinsulinaemia can contribute to atherosclerosis through the direct effect of insulin on arterial smooth muscle proliferation [21,22]. The indirect effects of insulin on lipid metabolism and blood pressure [20] further contribute to an increased incidence of CHD. However, data for the relationship between hyperinsulinaemia and CHD risk in patients with T2D are lacking. Specifically, whether IR predicts cardiovascular disease (CVD) independently of conventional risk factors in those diagnosed with T2D has not been studied.

The aim of the present study was to determine the association of 2-h post-load glucose (2hPG), IR and IS with CHD incidence in T2D patients by assessing their individual and concurrent effect sizes to predict CHD, independent of the conventional risk factors of CHD, in an Iranian cohort of T2D patients not receiving insulin treatment.

2. Methods

2.1. Study population

The present study is part of an ongoing prospective open cohort of community-dwelling subjects in Tehran, Iran. The primary aim of the survey is to identify the determinants of cardiometabolic risk factors and their outcomes in a representative sample of people living in Tehran (the capital city of Iran). An organized sample selection for research purposes began in January 2005. Participants were recruited from four-health surveillance centres respectively located in the west, centre, south and east of the city. Individuals were invited to visit the health centres every 3 months. In cases of a missed visit, trained research assistants investigated the health status and attendance of the participant using their recorded information. December 2013 was the end point of the present study's follow-up period. Previously published studies from our centre have described in detail the sampling procedure, extrapolation of data to the general population and specified characteristics of the survey population during the follow-up [23,24].

The original cohort survey involved two sub-cohorts of people with and without T2D. On entry, each participant underwent baseline examinations. For the present study, the diabetic sub-cohort was selected for analysis. This consisted of two groups of patients: the first group comprised patients with newly diagnosed T2D who had been either diagnosed at our centres or referred to one of the four health centres immediately after diagnosis; the second group included patients with T2D who had been monitored by our health centres prior to 2005. All participants were receiving treatment with either lifestyle modifications or oral hypoglycaemic agents (metformin and/or glibenclamide and/or pioglitazone), or both. Pancreatitis-related diabetes, type 1 diabetes and patients needing insulin therapy for glycaemic control were excluded from the present analysis.

Of the 5893 participants recruited into the original cohort, 2607 patients were included in the diabetic sub-cohort and eligible for the present study. Missing values accounted for <3% of the database and were replaced using the model-based expectation maximization algorithm technique. Effect sizes were compared with the results of complete-case analysis and multiple imputation, and were confirmed as statistically similar. Overall, 7.6% of individuals were lost to follow-up. Ultimately, 2607 patients with T2D were followed for an average of 7.2 years, accounting for 18,837 person-years of follow-up. Informed written consent was obtained prior to enrolment. The review board of the Endocrinology and Metabolism Research Centre (EMRC) at Tehran University of Medical Sciences (TUMS) approved the study protocol. All procedures were performed in accordance with the Declaration of Helsinki.

2.2. Data collection and laboratory investigations

Individual data, including gender, age and medication use, were obtained by careful history-taking. For each participant, height and weight were measured while wearing light clothing and no shoes. Waist circumference was measured in standing position and at normal end-expiration at a level midway between the iliac crest and lowermost rib. Values rounded to the nearest 0.1 cm were recorded. After at least 10 min of rest in a supine position, systolic and diastolic blood pressures (SBP and DBP, respectively) were measured using a standard mercury sphygmomanometer. After 12 h of overnight fasting, venous blood samples were drawn for the biochemical assessments. A standard 75-g oral glucose tolerance test (OGTT) was performed, and fasting plasma glucose (FPG) and 2hPG determined using the glucose oxidase method. High-performance liquid chromatography (HPLC; DS5 Pink Reagent kit; Drew Scientific, Miami Lakes, FL, USA) was used to determine haemoglobin A_{1c} (HbA_{1c}) levels. Radioimmunoassay using an antibody with no cross-reactions with C-peptide and proinsulin (Immunotech, Prague, Czech Republic) was used to determine plasma insulin. C-peptide was also determined by a radioimmunoassay method (Immunotech). Serum total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) were assessed by direct enzymatic methods (Parsazmun, Karaj, Iran). Serum creatinine was measured by the Jaffe method (Parsazmun).

2.3. Outcome measures and definitions

The main outcome of the present study was the first 'hard' CHD event, defined as myocardial infarction, angina pectoris, coronary insufficiency or death attributable to CHD. The participant first reported any CHD events, all of which were