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 insulinemia were positively associated with CHD incidence. This correlation persisted after controlling for gender, body mass index, blood pressure, lipid profile, medication use and HbA1c [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 HbA1c. These findings suggest that strategies targeting the reduction of insulinemia and post-load glycaemia may be useful for preventing cardiovascular complications.

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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
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 lowest 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 nocturnal 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; D55 Pink Reagent kit; Drew Scientific, Miami Lakes, FL, USA) was used to determine haemoglobin A1c (HbA1c) 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 (Parsazmун, Karaj, Iran). Serum creatinine was measured by the Jaffe method (Parsazmун).

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
then adjudicated by our centre’s physicians according to the International Classification of Diseases (ICD10–ICD12 blocks in CHD studies). The date of the CHD event was considered the participant’s endpoint in CHD cases. For individuals without CHD and for censored cases, the date of the last surveillance visit was considered the endpoint, with cumulative data updated every year (up to the end of 2013 in the present study).

Diagnosis of T2D was made according to American Diabetes Association (ADA) guidelines [25]. Newly diagnosed T2D was defined as an FPG ≥ 126 mg/dL (7.0 mmol/L) or a 2-h plasma glucose during OGGT ≥ 200 mg/dL (11.1 mmol/L), or a random plasma glucose level ≥ 200 mg/dL in a patient with classical symptoms of T2D (such as polyuria, polydipsia and unexplained weight loss). Participants who reported smoking within the preceding year were considered current smokers. Body mass index (BMI) was determined as weight divided by height squared (kg/m²). Homoeostasis model assessment for insulin resistance (HOMA-IR) was calculated as FPG (mg/dL) multiplied by fasting insulin (mU/L) divided by 405 [26]. The HOMA index for beta-cell function (HOMA-β) was calculated as 360 × fasting insulin divided by FPG–63 [27].

2.4. Statistical analysis

Baseline characteristics of the study population were expressed as means (SD) for different quartiles of HbA1c. One-way analysis of variance (ANOVA) was used for comparisons and P values for trend were extracted. Cox regression was used for analyses of CHD-free survival. Attained, defined as the subject’s age at the time of censorship, was used as the time scale. Five separate models were constructed using FPG, 2hPG and fasting insulin, and all three concurrently. Hazard ratios (HRs) for CHD were extracted for every one-quartile increase for each measure. Adjustments were performed for possible confounders, including gender, LDL-C, BMI, SBP, DBP, family history of CHD, smoking, medication use and HbA1c, with confounders selected according to Wilson et al. [28]. Also, two similar Cox models were designed using HOMA-IR (as a measure of insulin resistance) and HOMA-β (as a measure of beta-cell function), respectively, with similar adjustments performed to assess the independent association of an increase in each measure with incidence of CHD. IBM SPSS software version 18 (Armonk, NY, USA) and STATA software (version 11.2; StataCorp LP, College Station, TX, USA) were used for all analyses. A P value < 0.05 (two-sided) was set as the significance threshold.

3. Results

A total of 2607 patients with T2D participated in the present study. Their main characteristics are listed in Table 1. Patients were divided into quartiles of HbA1c, reflecting the status of their glycaemic control. Age, gender and BMI distribution were similar across the four groups, whereas waist circumference, SBP and DBP values were significantly different: the higher the HbA1c value, the greater the observed waist circumference (P < 0.05), SBP (P < 0.001) and DBP (P < 0.01).

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**Table 1.** Characteristics of the study population by HbA1c quartiles.

Table 1 also summarizes the risk factors for CHD by quartiles of HbA1c. Concentrations of FPG, 2hPG, total cholesterol, non-HDL cholesterol and TG, and the HOMA-IR, time since T2D diagnosis and a positive family history of T2D were also all significantly higher in the groups with higher HbA1c values (P < 0.05). Individuals in the highest quartile of HbA1c (≥ 8.8%) had significantly lower serum levels of C-peptide and fasting insulin, and HOMA-β scores, compared with participants with HbA1c levels < 8.8% (P < 0.05).

Overall, 299 hard CHD events were registered among our participants. The incidence of CHD events for each HbA1c quartile is shown in Table 1. Crude CHD incidence for the total population was 15.87 per 1000 person-years. Cumulative incidence of CHD was plotted for quartiles of 2hPG in all participants (Fig. 1). As shown in Fig. 1, those in the highest quartile of 2hPG had the greatest risk of CHD. There was no significant interaction between HbA1c (< vs ≥ 8.8%) and quartiles of 2hPG, suggesting the additive value of post-load glycaemia in those with good glycaemic control at baseline.

Table 2 shows the HRs for hard CHD events during the (average) 7.2 years of follow-up across quartiles of FPG, 2hPG and fasting insulin. After adjusting for CVD risk factors, both 2hPG and fasting insulin were significantly associated with incident CHD: HRs of the highest vs lowest quartile were 1.78 (95% CI: 1.24–2.58) for 2hPG and 1.66 (95% CI: 1.15–2.40) for fasting insulin. While additional adjustments for HbA1c did not alter the association between fasting insulin and incident CHD [HR = 1.18 per quartile increase (95% CI: 1.05–1.31)], the relationship between 2hPG and incident CHD was attenuated and became non-significant [HR = 1.09 per quartile increase (95% CI: 0.96–1.23)].

Table 3 presents the results of the Cox proportional hazards regression analyses when FPG, 2hPG and fasting insulin were considered together in the Cox regression model. 2hPG was significantly associated with CHD incidence in the unadjusted model [HR = 1.28 per quartile increase (95% CI: 1.11–1.46); P = 0.004 for trend]. There was a non-linear association between 2hPG and CHD incidence in the fully adjusted model (P = 0.18 for trend), and the HRs for developing hard CHD events by
increasing quartiles of 2hPG were 1.0, 1.31 (95% CI: 0.90–1.92), 1.28 (0.85–1.93) and 1.64 (1.03–2.61), respectively. There was a significant association between fasting plasma insulin and CHD incidence with an HR of 1.18 (per quartile increase; 95% CI: 1.06–1.32) in model 4, indicating an 18% increased chance of a CHD event with every one-quartile increase in fasting plasma insulin level. Additional adjustments for HbA1c did not alter this association [HR = 1.18 per quartile increase (95% CI: 1.06–1.32); \( P = 0.001 \) for trend]. In contrast, FPG was not an independent predictor of CHD.

Table 4 presents the results of Cox regression analyses of hard CHD events by quartiles of HOMA-IR and HOMA-\( \beta \). The interaction term between gender and HOMA-\( \beta \) was significant, and the results are categorized by gender (\( P = 0.01 \)). HOMA-IR predicted CHD events in both unadjusted and fully adjusted models [HR = 1.15 (95% CI: 1.04–1.28) and HR = 1.19 (1.07–1.34); \( P < 0.001 \) for trend, respectively]. HOMA-\( \beta \) was not significantly associated with CHD incidence in women whereas, in the unadjusted model, HOMA-\( \beta \) showed a significant association with hard CHD events in men [HR = 1.20 (95% CI: 1.06–1.37)], although this was attenuated to null and became non-significant after further adjusting for other risk factors.

A test for interactions between gender and FPG, 2hPG, fasting insulin and HOMA-IR quartiles for incident CHD was not significant (\( P > 0.05 \)), suggesting that the effect of gender on incident CHD did not differ according to values of FPG, 2hPG, fasting insulin and HOMA-IR. Also, no significant interaction was detected between HbA1c and either 2hPG or fasting insulin.

4. Discussion

The main finding of the present study is that elevated fasting insulinaemia is significantly related to risk of CHD in patients with T2D independently of fasting glucose, 2hPG and HbA1c levels. Furthermore, 2hPG is also associated with risk of incident CHD in such patients. Obesity is known to be associated with
both IR and CHD. Indeed, in the present study, the association of fasting insulin and 2-h glucose with incident CHD remained significant when adjusted for BMI.

Our results are consistent with those of previous studies showing an association between IR and CHD. Hyperinsulinaemia, a surrogate marker of the presence of IR, has been linked to both the development and extent of atherosclerosis [29–31]. Fasting insulinaemia was also able to predict CVD in some [32,33], but not all [34–38], studies. However, the majority of these studies analyzed samples from the general population and, to our knowledge, only a few previous studies focused specifically on patients with diabetes [39,40]. In addition, in the study by Bonora et al. [39], their mean prospective follow-up duration was only 52 ± 6 months, compared with 7.2 years in our present study, and fasting insulin concentration was not associated with incident CVD. Thus, to our knowledge, the present study is one of the few investigations to show a significant association between fasting insulin concentration and incident CHD in patients with T2D.

In terms of pathophysiological mechanisms, insulin receptors are expressed at the surface of both endothelial and vascular smooth muscle cells. The main steps in the activation of insulin receptors include phosphorylation of several insulin receptor substrates (IRS), which leads to downstream activation of phosphoinositide 3-kinase (PI3-kinase) and Akt [41]. Another pathway, the mitogen-activated protein (MAP) kinase pathway, remains responsive to insulin even in patients who are insulin-resistant [42]. As a consequence, this pathway remains stimulated in patients with T2D who are insulin-resistant, with compensatory endogenous chronic insulin hypersecretion. The MAP kinase pathway is involved in inflammation, and cell growth and proliferation, as well as in furthering the development and/or progression of atherosclerosis [41]. Furthermore, other non-metabolic insulin-signaling pathways may also regulate the production and secretion of potent vasoconstrictor endothelin-1 in endothelium [43]. The activities of these pathways, and their possible imbalances, may therefore play a role in the development of CHD in patients with T2D.

Nevertheless, it should be noted that the antiatherogenic effects of insulin have also been reported by other studies [44,45]. Thus, the precise role of insulin in the progression of atherosclerosis remains a subject of intense debate [29].

Beyond the role of IR, the specific influence of non-fasting hyperglycaemia on the incidence of CHD in T2D was recently highlighted by epidemiological and genetic studies [46,47]. There is also evidence showing that postprandial glucose levels and hyperglycaemic excursions are independent risk factors.

### Table 2
Hazard ratios (HRs) for coronary heart disease (CHD) events according to quartiles of fasting plasma glucose (FPG), 2-h post-load glucose and fasting insulin (not mutually adjusted).

<table>
<thead>
<tr>
<th></th>
<th>FPG</th>
<th>2-hPG</th>
<th>Fasting insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>1.07 (0.96–1.8)</td>
<td>1.19 (1.07–1.33)</td>
<td>1.15 (1.04–1.27)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.04 (0.94–1.16)</td>
<td>1.14 (1.02–1.27)</td>
<td>1.19 (1.08–1.32)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.10 (0.99–1.22)</td>
<td>1.19 (1.07–1.33)</td>
<td>1.15 (1.03–1.28)</td>
</tr>
<tr>
<td>Model 4</td>
<td>1.09 (0.98–1.21)</td>
<td>1.18 (1.06–1.32)</td>
<td>1.17 (1.05–1.30)</td>
</tr>
<tr>
<td>Model 5</td>
<td>0.98 (0.86–1.10)</td>
<td>1.09 (0.96–1.23)</td>
<td>1.18 (1.05–1.31)</td>
</tr>
</tbody>
</table>

Model 1: unadjusted; model 2: adjusted for gender; model 3: additionally adjusted for systolic and diastolic blood pressures, low-density lipoprotein cholesterol and body mass index; model 4: additionally adjusted for family history of CHD, smoking and medication use; model 5: additionally adjusted for HbA1c.

Each parameter was tested separately; HRs are calculated using Cox proportional hazard regression with hard CHD events as outcomes (defined in main text); patients’ attained age was used as time scale; all changes per one-quartile increase in values.

*  P < 0.05.
**  P < 0.01.
***  P < 0.001.

### Table 3
Hazard ratios (HRs) for coronary heart disease (CHD) events by quartiles of fasting plasma glucose (FPG), 2-h post-load glucose (2hPG) and fasting insulin (mutually adjusted).

<table>
<thead>
<tr>
<th></th>
<th>FPG</th>
<th>2hPG</th>
<th>Fasting insulin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>0.93 (0.81–1.06)</td>
<td>1.28 (1.11–1.46)</td>
<td>1.17 (1.06–1.30)</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.94 (0.82–1.08)</td>
<td>1.21 (1.05–1.39)</td>
<td>1.21 (1.09–1.34)</td>
</tr>
<tr>
<td>Model 3</td>
<td>0.98 (0.86–1.12)</td>
<td>1.22 (1.06–1.40)</td>
<td>1.16 (1.04–1.30)</td>
</tr>
<tr>
<td>Model 4</td>
<td>0.98 (0.86–1.12)</td>
<td>1.21 (1.05–1.39)</td>
<td>1.18 (1.06–1.32)</td>
</tr>
<tr>
<td>Model 5</td>
<td>0.92 (0.80–1.06)</td>
<td>1.15 (1.00–1.32)</td>
<td>1.18 (1.06–1.32)</td>
</tr>
</tbody>
</table>

Model 1: unadjusted; model 2: adjusted for gender; model 3: additionally adjusted for systolic and diastolic blood pressures, low-density lipoprotein cholesterol and body mass index; model 4: additionally adjusted for family history of CHD, smoking and medication use; model 5: additionally adjusted for HbA1c.

HRs are calculated by Cox proportional hazard regression with hard CHD events as outcomes (defined in main text as quartile-specific HRs); patients’ attained age was used as time scale; all changes per one-quartile increase in values.

*  P < 0.05.
**  P < 0.01.
***  P < 0.001.

### Table 4
Hazard ratios (HRs) for coronary heart disease (CHD) events by quartiles of HOMA-IR and HOMA-β.

<table>
<thead>
<tr>
<th></th>
<th>Insulin resistance (HOMA-IR)</th>
<th>Insulin secretion (HOMA-β)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Model 1</td>
<td>1.15 (1.04–1.28)</td>
<td>1.20 (1.06–1.37)</td>
</tr>
<tr>
<td>Model 2</td>
<td>1.19 (1.07–1.32)</td>
<td>1.12 (0.98–1.29)</td>
</tr>
<tr>
<td>Model 3</td>
<td>1.17 (1.05–1.30)</td>
<td>1.14 (0.99–1.31)</td>
</tr>
<tr>
<td>Model 4</td>
<td>1.19 (1.07–1.32)</td>
<td>1.06 (0.91–1.23)</td>
</tr>
<tr>
<td>Model 5</td>
<td>1.19 (1.07–1.34)</td>
<td>1.06 (0.91–1.23)</td>
</tr>
</tbody>
</table>

Model 1: unadjusted; model 2: adjusted for systolic and diastolic blood pressures, body mass index and low-density lipoprotein cholesterol; model 3: additionally adjusted for smoking, medication use and family history of CHD; model 4: additionally adjusted for HOMA-IR (homeostasis model assessment for insulin resistance) in models investigating effects on beta-cell function or for HOMA-β (homeostasis model assessment for beta-cell function) in models investigating HOMA-IR effects.

HRs are calculated by Cox proportional hazard regression with hard CHD events as outcomes (defined in main text); patients’ attained age was used as time scale; all changes per one-quartile increase in values.

*  P < 0.01.
**  P < 0.001.
of CVD, with stronger effects than those observed for fasting glucose levels [48–50]. One particular example is the diabetes epidemiology: collaborative analysis of diagnostic criteria in Europe (DECODE) study, which found that the 2-h post-load glucose is a better predictor of all-cause and CVD mortality compared with FPG [47,51].

In fact, a greater incidence of hard CHD events in the upper quintiles of postprandial glucose compared with the lower quintiles was reported more than a decade ago [32]. In the Diabetes Intervention Study, a prospective 11-year population-based study of 1139 newly diagnosed patients with diabetes deemed well controlled with diet alone, baseline postprandial glucose levels predicted all-cause mortality, whereas FPG concentrations did not [52]. In a 5-year study of 529 patients attending a diabetes clinic, baseline post-lunch glucose levels, but not FPG or HbA1c, were significant predictors of CVD [53]. In addition, post-meal glucose peaks have been associated with carotid subclinical atherosclerosis in patients with T2D [54].

The HbA1c value is recognized as the gold-standard method of overall glycaemic control [55]. In our present study, 2-h post-challenge hyperglycaemia had a significant impact on CHD incidence, independent of IR and FPG. While no interaction was observed between HbA1c and our variables of interest, the 2hPG effect was attenuated after the introduction of HbA1c into the model. This indicates a confounding effect and implies that at least some of the risk due to postprandial glycaemic excursions may be explained by HbA1c itself. The attenuation in HRs was also far more evident for 2hPG (HR decrease from 1.19 to 1.09 in non-mutually adjusted models and from 1.28 to 1.15 in mutually adjusted models) compared with fasting insulin (from 1.15 to 1.18 in non-mutually adjusted models and from 1.17 to 1.18 in mutually adjusted models).

However, one disadvantage of cohort studies is the failure to control for all covariates. There was also the matter of missing data and the potential for participants to be lost to follow-up, which prompted the training of research assistants to contact and follow-up each participant. The probability of CHD underestimation and recall bias, as patients were required to report any CHD event, can be considered further limitations of our study.

In conclusion, our present findings provide evidence of a significant association between 2-h post-load glucose levels and incident CHD in patients with T2D that is beyond the conventional cardiovascular risk factors and independent of IR. Interventional trials to test the effects of controlling post-meal glucose excursions on incident CVD in T2D patients are now needed to assess the specific influence of this parameter. In addition, our results suggest that raised fasting insulin concentrations could be helpful for identifying patients with T2D at high risk of subsequent CVD.

Disclosure of interest

The authors declare that they have no competing interest.

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