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Isolated post-challenge hyperglycaemia predicts increased cardiovascular mortality

Guenther Silbernagel [a,b], Harald Sourij [c], Tanja B. Grammer [d], Marcus E. Kleber [a,d], Bríain ó Hartaigh [e,f], Bernhard R. Winkelmann [g], Bernhard O. Boehm [h], Winfried März [d,i,j,*]

[a] LURIC Study Nonprofit LLC, Freiburg, Germany
[b] Division of Endocrinology, Diabetology, Nephrology, Vascular Disease, and Clinical Chemistry, Department of Internal Medicine, Eberhard-Karls-University Tübingen, Tübingen, Germany
[c] Division of Endocrinology and Metabolism, Department of Internal Medicine, Medical University of Graz, Graz, Austria
[d] Institute of Public Health, Social and Preventive Medicine, Mannheim Medical Faculty, University of Heidelberg, Mannheim, Germany
[e] Public Health, Epidemiology and Biostatistics, University of Birmingham, Birmingham, United Kingdom
[f] School of Sport and Exercise Sciences, University of Birmingham, Birmingham, United Kingdom
[g] Cardiology Group Frankfurt-Sachsenhausen, Frankfurt, Germany
[h] Division of Endocrinology and Diabetes, Department of Internal Medicine, Ulm University, Ulm, Germany
[i] Synlab Services GmbH, Mannheim, Germany
[j] Clinical Institute of Medical and Chemical Laboratory Diagnostics, Medical University of Graz, Graz, Austria

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ABSTRACT

Objective: The American Diabetes Association (ADA) has revised the criteria for the diagnosis of diabetes in 2010. Glycated haemoglobin at a cut-point of ≥6.5% has been included in the diagnostic algorithm. We aimed to investigate whether there is still the need to perform oral glucose tolerance tests (OGTT).
Methods: We studied 2002 people referred for angiography who did not have a history of diabetes. OGTT were performed in all 1772 subjects with fasting glucose <126 mg/dl. Participants were prospectively followed for all-cause and cardiovascular mortality over a mean duration (±standard deviation) of 7.7 ± 2.0 years.
Results: Using the ADA 2010 criteria 618 individuals were categorised as having new-onset type 2 diabetes. Among these, 167 had isolated post-challenge hyperglycaemia. A total of 346 participants died during follow-up. Cardiovascular death occurred in 202 cases. Those with elevated fasting glucose ≥126 mg/dl and/or glycated haemoglobin ≥6.5% had increased all-cause (hazard ratio [HR]: 1.63, 95% confidence interval [95%CI]: 1.28–2.08, $p < 0.001$) and cardiovascular mortality (HR: 1.66, 95%CI: 1.21–2.29, $p = 0.002$) compared to subjects without diabetes according to the ADA 2010 definition. Isolated elevation of post-challenge glucose independently predicted increased cardiovascular mortality (HR: 1.57, 95%CI: 1.02–2.43, $p = 0.041$). All-cause and cardiovascular mortality were not significantly different between subjects with increased fasting glucose and/or glycated haemoglobin and those with isolated elevation of post-challenge glucose.
Conclusions: Performing OGTT will identify a high risk group for cardiovascular mortality undetected by fasting glucose or glycated haemoglobin.

1. Introduction

Diabetes mellitus is a well-established cardiovascular risk factor [1–3]. The American Diabetes Association (ADA) in the past has recommended the use of fasting and post-challenge glucose for the diagnosis of diabetes [4]. In 2010, glycated haemoglobin at a threshold of ≥6.5% was introduced as an additional diagnostic criterion [5].

Glycated haemoglobin, a stable measure of average blood glucose [6,7], is a determinant of microvascular disease [8].

Abbreviations: ADA, American Diabetes Association; LURIC, LUdwigshafen RIsk and Cardiovascular health; OGTT, oral glucose tolerance tests.

* Corresponding author. Synlab Services GmbH, Synlab Academy, Gottlieb-Daimler-Straße 25, D-68165 Mannheim, Germany. Tel.: +49 621 43179432; fax: +49 621 43179433.
E-mail address: winfried.maerz@synlab.de (W. März).

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However, several studies including the Hoorn Study, the CHARM program, and the EPIC-Norfolk Study have demonstrated that glycated haemoglobin is also associated with macrovascular complications [9–11]. Moreover, recent evidence from the ARIC and LUdwigshafen RIsk and Cardiovascular health (LURIC) studies have highlighted that glycated haemoglobin is a superior measure compared to fasting glucose for predicting cardiovascular endpoints [12,13]. Further data from the LURIC cohort have proposed that individuals with isolated elevation of glycated haemoglobin ≥6.5% are at greater risk of dying from cardiovascular causes [14].

Since glycated haemoglobin appears to be a feasible tool for diagnosing diabetes [15] and for estimating prognosis [9–14] the following question arises: Do we still need to perform oral glucose tolerance tests (OGTT)? Undoubtedly, numerous investigations such as the DECODE Study, the Euro Heart Survey, the AusDiab Study, the ADDITION-Leicester Study, and an Austrian collective have all confirmed that post-challenge hyperglycaemia is associated with an adverse outcome in subjects with fasting glucose <126 mg/dl [16–22]. Nevertheless, it is unclear whether OGTT will improve cardiovascular risk stratification in persons with both, fasting glucose <126 mg/dl and glycated haemoglobin <6.5%. Notably, a considerable amount of individuals exhibiting post-challenge hyperglycaemia ≥200 mg/dl will be categorised diabetic due to a concomitant elevation of glycated haemoglobin ≥6.5% [23,24].

Based on the previously mentioned novel guidelines, we sought to investigate whether isolated elevation of post-challenge glucose ≥200 mg/dl is predictive of increased all-cause and cardiovascular mortality. We report on data from the LURIC study. This large prospective clinical trial was planned to serve as a resource for analysing clinical, biochemical, and genetic predictors of hard cardiovascular outcomes and death from any other causes [25].

2. Methods

2.1. Study design, participants and clinical characterization

A total of 3316 patients, who were referred for coronary angiography to Ludwigshafen Heart Center in South-West Germany, were recruited between July 1997 and January 2000 [25]. Inclusion criteria were: German ancestry, clinical stability except for acute coronary syndromes, and the availability of a coronary angiogram. The indications for angiography in individuals in clinically stable condition were chest pain and/or noninvasive test results consistent with myocardial ischaemia. Individuals suffering from any acute illness other than acute coronary syndromes, chronic non-cardiac diseases, or malignancy within the five past years, and those unable to understand the purpose of the study were excluded. Subjects with a history of diabetes and 684 subjects with incomplete determination of the gluco-metabolic phenotype (missing OGTT despite fasting glucose <126 mg/d) were additionally ruled out resulting in a sample size of 2002 (60.4%) out of 3316 LURIC participants for the present study. Death certificates were not available for 11 individuals. Hence, the analytic sample for the calculations on cardiovascular mortality was 1991 subjects. The study was approved by the ethics committee at the "Ärztekammer Rheinland-Pfalz" and was conducted in accordance with the "Declaration of Helsinki". Informed written consent was obtained from all participants [25].

Diagnostic criteria for diabetes: According to ADA 2009 criteria subjects with increased fasting (≥126 mg/dl) and/or post-challenge (2 h after the 75 g glucose load ≥200 mg/dl) glucose are considered diabetic [4]. Using the ADA 2010 guidelines persons with elevated glycated haemoglobin (≥6.5%) are additionally categorised as having diabetes [5]. OGTT were performed in all 1772 subjects with fasting glucose <126 mg/dl.

Hypertension was diagnosed if the systolic and/or diastolic blood pressure exceeded 140 and/or 90 mm Hg or if there was a history of hypertension, also evident through the use of antihypertensive drugs [25].

Coronary artery disease was diagnosed if coronary angiography revealed stenosis of one or more vessels ≥50%. The severity of coronary artery disease was quantified with the Friesinger score which was broken down to quartiles (group 1: score 0–1, group 2: score 2–4, group 3: score 5–8, group 4: score 9–15) [26]. Maximum luminal narrowing was estimated by visual analysis as described previously [25].

Cerebrovascular disease was defined clinically by documented history of a previous cerebrovascular disease event (transient ischaemic attack, prolonged ischaemic neurological deficit, cerebral infarction with or without a remaining neurological deficit) and/or by documented carotid plaques (≥50% luminal obstruction) [25].

Peripheral vascular disease was defined by a history of intermittent claudication, angiographic documentation of atherosclerotic luminal obstruction of the peripheral arteries and/or a history of a peripheral arterial intervention for atherosclerotic disease (angioplasty and/or surgery) [25].

Comorbidity was assessed using the Charlson comorbidity index. This is a weighted score that takes into account the number and the seriousness of comorbid disease. We formed 3 groups (group 0: 0 score points, group 1: 1 score point, and group 2: 2 or more score points) [27].

Physical activity was assessed using a questionnaire with a scoring system ranging from 1 "sedentary" (avoid walking or exertion) to 11 "regular heavy exercise". The study participants were grouped into the following 3 categories of physical activity (below average: scores 1–3, average: scores 4–7, and above average: scores 8–11).

2.2. Follow-up

There was a follow-up for all-cause and cardiovascular mortality. The mean (±standard deviation) duration of the follow-up was 7.7 ± 2.0 years. Information on the vital status was obtained from local person registries. Using death certificates, two experienced clinicians independently classified the causes of death. Both were masked to any other data belonging to the study participants. In a case of disagreement or uncertainty concerning the coding of a specific cause of death, classification was confirmed by a principal investigator of the LURIC study (W. M.) who was also masked to any other data belonging to the study participants [25].

2.3. Laboratory analyses

The standard laboratory methods have been described [25]. Glucose was measured enzymatically on a Hitachi 717 analyzer (Roche, Mannheim, Germany). Glycated haemoglobin was measured with immunoassay (haemoglobin A1c UNIMATE 5; Hoffmann-LaRoche, Grenzach-Whylen, Germany). Lipoproteins were separated using a combined ultracentrifugation–precipitation method and measured on a WAKO 30 R analyzer (WAKO Chemicals GmbH, Neuss, Germany). Triglycerides were quantified with an enzymatic colour assay on a Hitachi 717 analyzer (Roche). Creatinine was measured with the Jaffé method on a Hitachi 717 analyzer (Roche).

2.4. Statistical analysis

Three groups were formed (category A: subjects without diabetes according to the ADA 2010 definition; category B: subjects