Contents available at ScienceDirect

Diabetes Research and Clinical Practice

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

International Diabetes Federation

Clinical characteristics of people experiencing biochemical hypoglycaemia during an oral glucose tolerance test: Cross-sectional analyses from a UK multi-ethnic population

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ARTICLE INFO

Article history:
Received 11 October 2013
Received in revised form
21 January 2014
Accepted 19 February 2014
Available online 4 March 2014

Keywords:
Diabetes screening
Hypoglycaemia
Insulin resistance
Insulin sensitivity

ABSTRACT

Aims: People who experience biochemical hypoglycaemia during an oral glucose tolerance test (OGTT) may be insulin resistant, but this has not been investigated robustly, therefore we examined this in a population-based multi-ethnic UK study.

Methods: Cross-sectional data from 6478 diabetes-free participants (849 with fasting insulin data available) who had an OGTT in the ADDITION-Leicester screening study (2005–2009) were analysed. People with biochemical hypoglycaemia (2-h glucose <3.3 mmol/l) were compared with people with normal glucose tolerance (NGT) or impaired glucose regulation (IGR) using regression methods.

Results: 359 participants (5.5%) had biochemical hypoglycaemia, 1079 (16.7%) IGR and 5040 (77.8%) NGT. Biochemical hypoglycaemia was associated with younger age ($P < 0.01$), white European ethnicity ($P < 0.001$), higher HDL cholesterol ($P < 0.01$), higher insulin sensitivity ($P < 0.05$), and lower body mass index ($P < 0.001$), blood pressure ($P < 0.01$), fasting glucose ($P < 0.001$), HbA1C ($P < 0.01$), and triglycerides ($P < 0.01$) compared with NGT and IGR separately in both unadjusted and adjusted (age, sex, ethnicity, body mass index, smoking status) models.

Conclusions: Biochemical hypoglycaemia during an OGTT in the absence of diabetes or IGR was not associated with insulin resistance, but instead appeared to be associated with more favourable glycaemic risk profiles than IGR and NGT. Thus, clinicians may not need to intervene due to biochemical hypoglycaemia on a 2-h OGTT.

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http://dx.doi.org/10.1016/j.diabres.2014.02.013

1. Introduction

Biochemical hypoglycaemia is a relatively common finding on oral glucose tolerance tests (OGTTs) in population based screening for Type 2 Diabetes Mellitus (T2DM) and is thought to be potentially linked with increased T2DM risk [1,2]. Despite this common perception, there is very little data considering this association, but data suggest that there may be a link with insulin resistance [3,4] and most, but by no means all, clinicians anecdotally believe that biochemical hypoglycaemia during an OGTT is associated with insulin resistance.

In insulin resistant states, such as T2DM and polycystic ovary syndrome (PCOS), insulin resistance leads to basal fasting hyperinsulinemia. This hyperinsulinemia then causes desensitisation of beta cells to alteration in glucose levels. This desensitisation results in a blunted first phase insulin response to the postprandial rise in glucose levels and a subsequent exaggerated compensatory second phase insulin response leading to hypoglycaemia [5,6]. Therefore, the occurrence of post-challenge hypoglycaemia may be an indicator of early beta cell dysfunction and insulin resistance and when it occurs in the absence of overt diabetes or impaired glucose tolerance could potentially be an early indicator of future diabetes. Biochemical hypoglycaemia on an OGTT is similar to, but not the same as, reactive hypoglycaemia, which is hypoglycaemia after a high carbohydrate or glucose load and requires Whipple's Triad for diagnosis. OGTTs alone are not suitable to detect reactive hypoglycaemia.

To date, there is limited evidence to support such a mechanism. This evidence comprises a recent study showing a prevalence of post-prandial hypoglycaemia of 50% among women with PCOS, an insulin resistant state [7], and case reports showing an association between reactive hypoglycaemia, insulin resistance and future risk of T2DM [3,4]. However, an association between insulin resistance and reactive hypoglycaemia or biochemical hypoglycaemia during an OGTT has not been shown previously in epidemiological studies. This might be because until recently there were only two existing studies, one of which has only been published as a conference abstract, and both of which had relatively small sample sizes of fewer than 600 participants [1,2]. This is further compounded by the considerable variation in the definitions used for biochemical hypoglycaemia across the world and across various laboratories [8,9]. Conversely, a recently published study suggests that biochemical hypoglycaemia may be associated with insulin sensitivity, rather than insulin resistance [10].

If biochemical hypoglycaemia on an OGTT is associated with insulin resistance, and thus is potentially an early precursor of diabetes, then these people could be targeted for early intervention in order to reduce the burden of T2DM. This issue is particularly pertinent at present as the use of OGTTs to screen for diabetes is becoming less common, with diagnosis using HbA1c becoming increasingly popular, thus it is important to know whether this will result in a missed opportunity to identify an at risk population early in the development of diabetes. Therefore, the aim of these analyses of a population-based study was to determine whether biochemical hypoglycaemia on a 2-h screening OGTT in the absence of T2DM or impaired glucose regulation (IGR) in people who do not necessarily have any hypoglycaemia or T2DM symptoms is associated with biochemical or phenotypic insulin resistance. These are a secondary analysis of study data collected for another purpose.

1.1. Subjects

These analyses used data from the population-based ADDITION-Leicester study, the rationale and design of which have been described previously [11]. Briefly, 6749 participants from a multi-ethnic population had an OGTT as a part of a systematic screening programme for diabetes (Fig. 1). People aged 40–75 years inclusive (White European ethnicity) or 25–75 years inclusive (other ethnic groups) were invited for screening from 20 general practices in urban and rural Leicestershire, UK (2005–2009). Participants were excluded if they had pre-existing diabetes, a terminal illness, an inability to provide informed consent or were pregnant or lactating. Consecutive participants were additionally invited to participate in a sub-study involving fasting insulin at their baseline visit (n = 987). Participants were excluded from these analyses if their fasting or 2-h plasma glucose levels were within the diabetes range as defined by WHO 1998 criteria [12], or if data on 2-h glucose levels were missing as it was not possible to determine whether these people had biochemical hypoglycaemia. The study received ethical approval from local research ethics committees, and all participants gave written informed consent.

2. Materials and methods

2.1. Data collection

Before attending the screening visit, participants were asked to fast for 8 h, consume their regular evening meal and snacks before fasting, and refrain from alcohol consumption [11]. Fasting blood tests were taken for glucose, lipid profiles and HbA1c. An OGTT was then performed using a standard 75 g glucose dose, with bloods taken 2 h after the OGTT for measurement of plasma glucose. The taking of samples was postponed if in the preceding three days instructions to follow a normal unrestricted diet were not followed or participants reported fever or unusual physical activity. Furthermore, participants were asked not to run to their appointment or to smoke until after the test.

Fasting and 2-h plasma glucose samples were taken in fluoride oxalate test tubes and placed immediately in a portable 4 °C refrigerator. Samples were processed within a maximum of 2 h via the hexokinase method using an Abbott Aeroset clinical chemistry analyzer. This machinery has an imprecision coefficient of variation of 1.61%. HbA1C was analysed using the Bio-rad variant II HPLC system (Bio-Rad Laboratories, Hemel Hempstead, UK). All tests were analysed by the accredited pathology laboratory at the University Hospitals of Leicester. Samples were measured in duplicate and repeat testing was done if the coefficient of variance was $\geq$20%. Serum total cholesterol, triglycerides and HDL cholesterol were measured