

Frequency of impaired glucose tolerance and diabetes mellitus in subjects with fasting blood glucose below 6.1 mmol/L (110 mg/dL)

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تواتر خلل تحمل الغلوكوز والسكري لدى من يقل غلوكوز الدم على الريق لديهم عن 6.1 ميلي مول/ لتر (110 ميلي غرام/ ديسي لتر)
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الخلاصة: لا يوجد اتفاق على تشخيص السكري وفق المعايير المتاحة، ويعتمد إلى حد كبير على نتائج غلوكوز الدم الصيامي (على الريق). وقد أجرى الباحثون هذه الدراسة في عامي 2010 – 2011، وتهدف لقياس تواتر خلل تحمل الغلوكوز والسكري لدى 127 شخصاً يقل لديهم غلوكوز الدم الصيامي عن 7 ميلي مول/ لتر، وكذلك لقياس التوافق بين معايير التشخيص القياسية المختلفة. ووضع الباحثون المراجعين للمختبر من أجل تحليل غلوكوز الدم الصيامي أمام تحدٍ بالغلوكوز الفموي مقداره 75 غراماً على مدى ساعتين، من أجل استبعاد تشخيص السكري؛ فوجدوا أن مجمل 40.6% من المراجعين الذين كان مستوى غلوكوز الدم الصيامي لديهم يصل إلى 5.6 – 6.0 ميلي مول/ لتر كان لديهم تنظيم غير سوي للغلوكوز وفقاً للمعيار الذهبي للتحدي بالغلوكوز. وكان التوافق بين معايير الجمعية الأمريكية للسكري ومنظمة الصحة العالمية مقبولاً (كبا = 0.32). ويرى الباحثون أن حالات اضطراب استقلاب الغلوكوز بما فيها خلل تحمل الغلوكوز، والسكري يمكن أن تُصادف ضمن مجموعة نتائج غلوكوز الدم الصيامي التي تقل عن 6.1 ميلي مول/ لتر (110 ميلي غرام/ ديسي لتر).

ABSTRACT The diagnosis of diabetes mellitus by the available criteria is controversial and relies heavily on fasting glucose results. This cross-sectional study in 2010–2011 aimed to measure the frequency of impaired glucose tolerance and diabetes mellitus in 127 subjects having fasting blood glucose < 7.0 mmol/L and to measure the agreement between different standard diagnostic criteria. Subjects presenting to a laboratory for analysis of fasting blood glucose for excluding diabetes mellitus underwent a 2-hour 75 g oral glucose challenge. A total of 40.6% of subjects with fasting blood glucose from 5.6–6.0 mmol/L had abnormal glucose regulation on the basis of the gold standard glucose challenge. Agreement between American Diabetes Association and World Health Organization diagnostic criteria was only fair (kappa = 0.32). Abnormalities of glucose metabolism including impaired glucose tolerance and diabetes mellitus can exist at fasting blood glucose results < 6.1 mmol/L (110 mg/dL).

Fréquence de la diminution de la tolérance au glucose et du diabète chez des sujets ayant une glycémie à jeun inférieure à 6,1 mmol/l (110 mg/dl)

RÉSUMÉ Le diagnostic du diabète selon les critères disponibles est controversé et repose principalement sur les résultats de la glycémie à jeun. La présente étude transversale menée en 2010 et 2011 visait à mesurer la fréquence de la diminution de la tolérance au glucose et du diabète chez 127 sujets présentant une glycémie à jeun inférieure à 7,0 mmol/l et à mesurer la concordance entre différents critères diagnostiques standard. Les sujets se présentant au laboratoire pour une analyse de la glycémie à jeun visant à éliminer un diagnostic de diabète ont passé une épreuve d'hyperglycémie provoquée par voie orale deux heures après l'ingestion de 75 g de glucose. Au total, 40,6 % des sujets ayant une glycémie à jeun entre 5,6–6,0 mmol/l présentaient une régulation anormale de la glycémie selon les critères de référence de l'épreuve d'hyperglycémie. La concordance entre les critères diagnostiques de l'*American Diabetes Association* et de l'Organisation mondiale de la Santé était seulement passable (kappa = 0,32). Les anomalies du métabolisme du glucose telles que la diminution de la tolérance au glucose et le diabète sont possibles avec des résultats de la glycémie à jeun inférieurs à 6,1 mmol/l (110 mg/dl).

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Introduction

Diabetes mellitus (DM) is one of the leading global causes of mortality and is a growing epidemic [1]. While the causes of the disease, i.e. sedentary lifestyles, higher intake of refined carbohydrates and saturated fatty acids, synergize to add to the disease burden, the situation is aggravated by the unavailability of any curative treatments [2]. Added to this, delays in diagnosis make subjects vulnerable to various complications of the disease [3].

The diagnosis of DM relies on the demonstration of raised glucose levels in the patient's blood. However, this is more complex than it seems due to existence of multiple diagnostic criteria. Traditionally an oral glucose tolerance test (OGTT) was used to diagnose DM [4]. The latest World Health Organization (WHO) criteria, however, recommended a 2-step strategy, i.e. an initial fasting glucose test and, if levels are between 6.1–6.9 mmol/L, followed by a 2-hour OGTT [5]. The 2003 American Diabetic Association (ADA) guidelines proposed a fasting glucose result with an upper cut-off of 5.6 mmol/L [6]. Moreover, the published data dealing with the labelling of hyperglycaemia suffer from the problems of different diagnostic cut-offs and prevalence rates for DM [7,8].

Apart from the lack of consensus regarding the diagnosis of DM, other controversies exist. First, clinical practice suggests that subjects having fasting glucose levels < 6.1 mmol/L or even < 5.6 mmol/L may receive a diagnosis of DM in an OGTT and vice versa [9]. Secondly, the evidence also suggests a definite lag in the diagnosis of DM, resulting in subjects being at risk of various DM-related complications from the outset [10]. Thirdly, the literature has highlighted the risks associated with a decision based on a single reading of fasting blood glucose on account of patient non-compliance with fasting or laboratory-related inaccuracies [11].

Finally, older subjects may be normoglycaemic, but can become glucose intolerant on exposure to a glucose load [12].

This study in Karachi, Pakistan was therefore designed to measure the frequency of impaired glucose tolerance (IGT) and DM in subjects having fasting blood glucose < 7.0 mmol/L and to measure the agreement between the ADA and the WHO diagnostic criteria for DM.

Methods

Study setting and sample

This cross-sectional study was carried out at the department of pathology at PNS Rahat and Shifa hospitals, Karachi, from March 2010 to June 2011.

All subjects who presented to the laboratory for analysis of fasting blood glucose for excluding DM were eligible for the study. Subjects were initially interviewed for clinical details (e.g. history of hypertension, DM and ischaemic heart disease). Subjects who gave a history of intake of medicines, were known diabetics, were not observing proper medical fasting, were inpatients, were pregnant or had some physical or mental stress were excluded from the study.

Data collection

After explanation of the study prerequisites and obtaining a signed written consent, 172 subjects were sampled for fasting blood glucose. After the blood samples were taken subjects were requested to undergo a complete a 2-hour 75-g glucose challenge. They were asked to drink the glucose solution (300 mL) over 5 minutes. Starting from the time of intake of glucose, subjects were advised to return for the 2-hour sample for glucose. All samples were analysed within 3 (\pm 1) hours. Glucose was analysed by the hexokinase method on a random access clinical chemistry analyser (Hitachi-902).

Subjects were grouped into 5 groups according to their fasting blood glucose results: < 5.0 mmol/L (< 90 mg/dL); 5.0–5.5 mmol/L (90–99 mg/dL); 5.6–6.0 mmol/L (100–108 mg/dL); 6.1–6.9 mmol/L (110–125 mg/dL); or > 6.9 mmol/L (125 mg/dL).

Subjects were defined from 2-hour OGTT results as: normal glucose tolerance < 7.8 mmol/L (< 140 mg/dL); IGT 7.8–11.0 mmol/L (140–199 mg/dL); or DM > 11.0 mmol/L (> 199 mg/dL).

Statistical analysis

All data were entered into SPSS, version 15. Measures of central tendency and dispersion i.e., mean and standard deviation (SD) was calculated for age. Frequencies by sex were also calculated. Frequency of normal glucose tolerance, IGT and DM based upon the 2-hour OGTT readings were measured at various levels of fasting blood glucose defined cut-offs by utilizing descriptive statistics. The differences in 2-hour post-75-g glucose challenge based diagnosis, i.e. normal, IGT and DM across various levels (defined groups), were compared by 1-way ANOVA. Level of agreement between WHO and ADA criteria was measured by the kappa statistic.

Results

The mean age of our study population was 43.7 (SD 10.8) years. Out of the evaluated subjects, 139 were male and 33 were females.

Participants with IGT and DM based on the 2-hour OGTT results spanned all the ranges of fasting blood glucose results (Figure 1). An increasing frequency of diagnosis of IGT and DM was seen after the fasting blood glucose results crossed the level of 5.6 mmol/L.

Table 1 shows that the mean 2-hour OGTT results crossed the WHO and

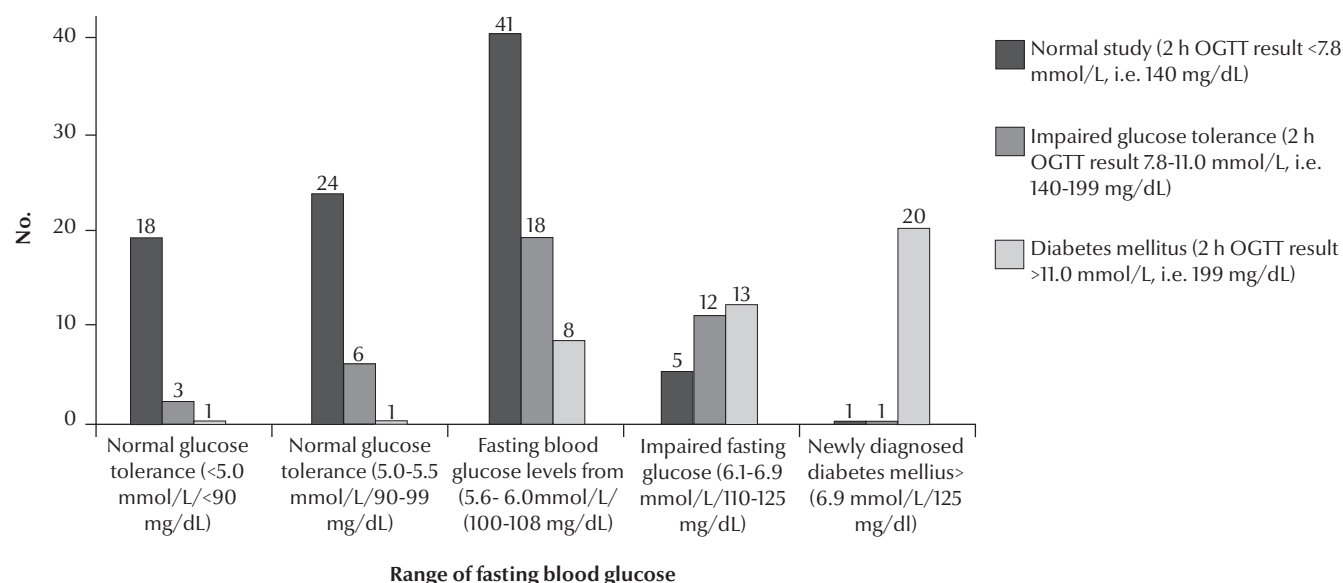


Figure 1 Frequency distribution of normal glucose tolerance, impaired glucose tolerance and diabetes mellitus based on the 2-hour oral glucose oral glucose tolerance test results across fasting blood glucose groups ($n = 172$ patients)

ADA defined cut-off of 7.8 mmol/L in subjects having fasting blood glucose results > 5.6 mmol/L.

The relative percentage of diagnosis rates of IGT and DM based upon 2-hour OGTT increased with age (Figure 2).

A total of 40.6% of subjects (29.7% IGT and 10.9% DM) with fasting blood glucose between 5.6–6.0 mmol/L had abnormal glucose regulation on the basis of the gold standard 2-hour OGTT results (Figure 3). The agreement between the ADA and the WHO diagnostic criteria was only fair ($\kappa = 0.32$, $P < 0.001$).

Discussion

Our study has shown that subjects having fasting blood glucose < 6.1 mmol/L can have biochemically abnormal response in terms of glucose intolerance after subjecting them to a glucose load. A review of the literature revealed other studies that agree with our findings [11,13]. We also showed that even subjects in the normal range of fasting glycaemia, i.e. fasting blood glucose < 5.6 mmol/L, can have glucose dysregulation demonstrated during a 2-hour glucose challenge test. Therefore the current diagnostic approach may

miss as many as 40% of cases with abnormal glucose metabolism as depicted by a 2-hour OGTT reading, i.e. IGT and DM. Similar results have been shown by studies in which subjects with normal glucose levels and abnormal 2-hour glucose load readings [14]. Richard et al. showed no reliable cut-off for fasting glucose was sensitive enough to rule out DM, and concluded that OGTT testing must be maintained for the diagnosis of DM [8].

The possible reasons for such findings could be multifold. First, fasting and post-glucose challenge results demonstrate 2 different processes; the

Table 1 Differences of mean 2-hour oral glucose tolerance test (OGTT) blood glucose results across fasting blood glucose groups

Fasting blood glucose level (mmol/L)	No. of patients	2-hour OGTT blood glucose level (mmol/L)
		Mean (95% CI)
< 5.0 (normal glucose tolerance)	22	6.7 (6.0–7.5)
5.0–5.5 (normal glucose tolerance)	31	7.2 (6.6–7.8)
5.6–6.0 (fasting blood glucose)	67	8.0 (7.6–8.5)
6.1–6.9 (impaired fasting glucose)	30	10.5 (9.4–11.5)
> 6.9 (newly diagnosed diabetes mellitus)	22	17.3 (15.1–19.6)

$P < 0.001$, 1-way ANOVA.
CI = confidence interval.

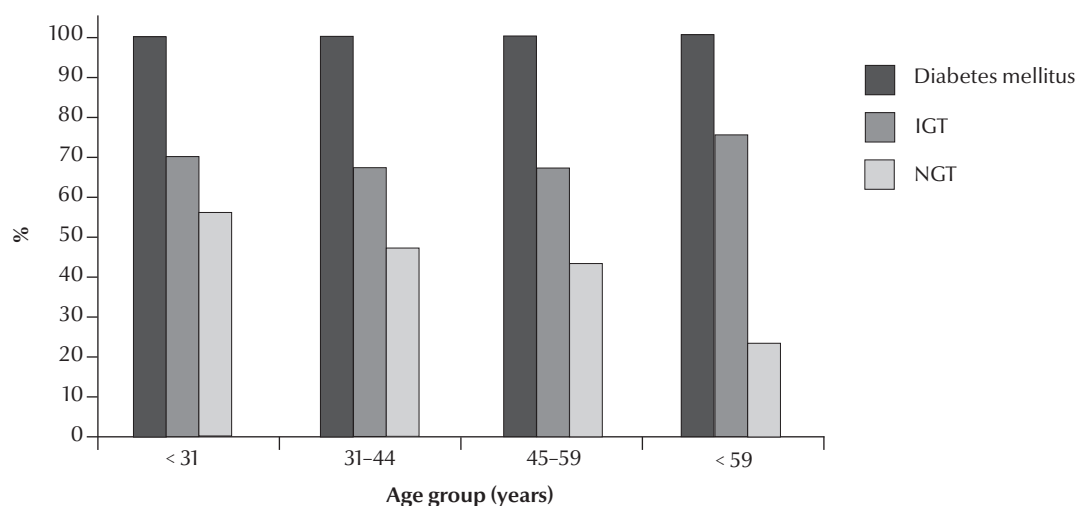


Figure 2 Percentage distribution of normal glucose tolerance (NGT), impaired glucose tolerance (IGT) and diabetes mellitus based on the 2-hour oral glucose tolerance test results across various age groups ($n = 172$ patients)

former may reflect the glycaemic baseline being influenced by the amount of fasting and associated physical and psychological state, while the later reflects a stimulated response from the beta cells of pancreas after glucose loading [15]. Traditionally, stimulated or dynamic glucose testing has been referred as the gold standard. So both glucose results represent different dimensions to the diabetogenic processes [15–17]. Secondly, the trade-off between sensitivity and specificity of the test is the underlying consideration once decisions are required for screening or devising a confirmatory methodology

[18]. Our results suggest that sole reliance on fasting blood glucose will compromise sensitivity due to the high number of false negative cases. Once a 2-hour OGTT reading is used, it not only adds strength to the diagnosis but also adds to the sensitivity by identifying subjects with glucose intolerance who have underlying atherosclerosis-related complications [19]. Thirdly, 2-hour readings have been shown to be better correlated with markers of glycation including glycosylated haemoglobin and fructosamine [20]. So why not incorporate a single 2-hour reading to screen subjects suspected

of having DM? The quality and cost added by early diagnosis of DM can be weighed against the cost of late initiation of treatment. Already the literature recommends the use of OGTT in the detection of undiagnosed DM in certain disease categories such as stroke and myocardial infarction [21,22]. Philips et al. have recommended a glucose challenge test to improve the diagnostic sensitivity for undiagnosed DM [23]. The question arises as to why wait for the development of complications whose treatment cost greatly exceeds the screening cost? Finally, a review of certain regional literature on

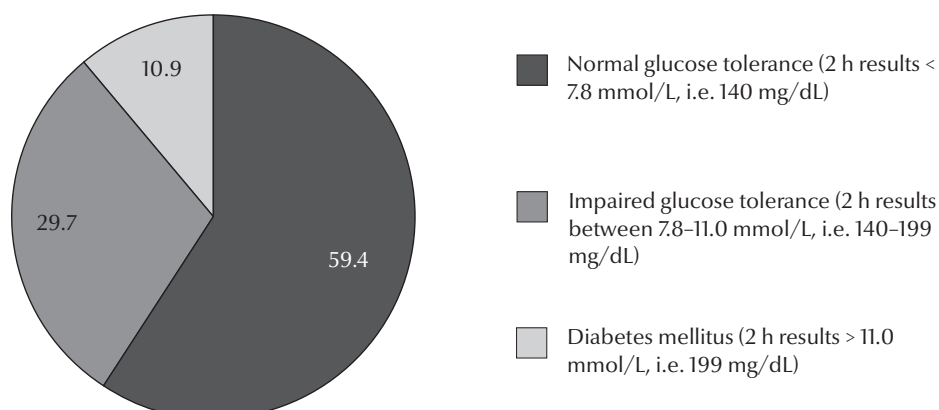


Figure 3 Percentage distribution of normal glucose tolerance, impaired glucose tolerance and diabetes mellitus based on the 2-hour oral glucose tolerance test results in subjects having fasting blood glucose between 5.6–6.0 mmol/L ($n = 67$ patients)

diabetes screening highlights the varying recommendations about screening in our population in contrast to their non-Asian counterparts [12,24]. More regional literature do exist recommending a lower threshold of screening for DM in our population [24–26]. Thus racial and regional differences in the pattern of diabetes could be another reason for subjects demonstrating glucose intolerance during glucose loading.

Comparing WHO criteria for diagnosis of diabetes with ADA criteria shows minimal agreement between the 2 definitions of similar disease. The available literature review does suggest comparable results [7,8,27]. In the opinion of the authors, the lower cut-offs may be more compatible with the screening concept for diagnosing DM, while subjects having a slightly higher degree of clinical suspicion may be further confirmed by adopting the 2-hour OGTT test as per WHO recommendations. There may also

be an argument for further lowering the cut-offs for our population, but prospective clinical trials must address this issue [18].

We have also observed that ageing is related to post-glucose load intolerance. Choi et al. reported similar findings [12]. The reason could be the age-related deterioration in the functioning of beta cells of the pancreas or the development of insulin resistance which appears later in life [12,28].

There are some limitations to our study which should be noted. First, stress hyperglycaemia is a known entity. Attempts were made to exclude subjects with any degree of physical ailments, but a psychological stress evaluation was not carried out among our subjects. Secondly, the results may have been confounded by the presence of obesity, hypertension or ischaemic heart disease.

This study was clinically important because it highlighted controversies associated with the diagnostic criteria

for DM. At present clinical practice suggests labelling of individuals as normoglycaemic based on a fasting blood glucose result. However, in the light of our findings it can be suggested that a patient can have DM when the fasting blood glucose result is normal. Interpretation of fasting blood glucose results must include consideration of a patient's age and clinical information. Moreover, a 2-hour OGTT reading should also be considered as a screening test after a necessary cost–benefit analysis and consensus among the authorities.

Conclusion

Abnormalities of glucose metabolism including impaired glucose tolerance and DM can exist at fasting blood glucose results < 6.1 mmol/L (110 mg/dL). WHO and ADA criteria showed poor agreement between each other for the diagnosis of DM.

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Note from the Editor

We wish to draw the kind attention of our potential authors to the importance of applying the editorial requirements of the EMHJ when preparing their manuscripts for submission for publication. These provisions can be seen in the Guidelines for Authors, which are published at the end of every issue of the Journal. We regret that we are unable to accept papers that do not conform to the editorial requirements.