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Undiagnosed diabetes and prediabetes in hypertensive and normotensive adults at the University College Hospital, Ibadan, Nigeria

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Abstract

Background: Essential hypertension is associated with an increased incidence of glucose intolerance (prediabetes and type 2 diabetes mellitus) but many persons with glucose intolerance remain undiagnosed for many years.

Aims: To determine the frequency of undiagnosed diabetes and prediabetes in a group of hypertensives and normotensives.

Methods: Anthropometry, blood pressure and standard oral glucose tolerance test (OGTT) were done in adult participants (hypertensive and normotensive controls) newly presenting to a General Outpatient Clinic of the University College Hospital, Ibadan.

Results: Using the OGTT, the frequency of undiagnosed diabetes was 10.4% and 4.3% in hypertensives and normotensives respectively (p=0.031) but was 5.2% and 2.6% in hypertensives and normotensives respectively using fasting plasma glucose (FPG) alone (p=0.308).Using the OGTT, impaired glucose tolerance (IGT) was diagnosed in 32.2% of hypertensives compared to 14.8% of normotensives (p=0.002) while impaired fasting glucose (IFG) was diagnosed in 5.2% of hypertensive and 2.6% of the normotensives (p=0.288). After adjusting for hypertension, age, level of education, body mass index and waist circumference, hypertensives and persons with a higher waist circumference had statistically significantly increased odds of having glucose intolerance: hypertension (OR 2.915; 95% CI 1.526-5.556) and waist circumference (OR 1.050; 95%CI 1.010-1.090).

Conclusion: Diabetes and prediabetes are commoner in hypertensive persons and such persons require close and frequent monitoring for the development of this disease. Screening with both fasting plasma glucose and post glucose load plasma glucose (OGTT) identifies more persons with glucose intolerance than fasting plasma glucose alone.

Keywords: *Hypertension, diabetes mellitus, impaired fasting glucose, impaired glucose tolerance, prediabetes, glucose intolerance*

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Résumé

Contexte: L'hypertension essentielle est liée à une incidence accrue de l'intolérance au glucose (prédiabète et de diabète de type 2), mais beaucoup de personnes souffrant d'intolérance au glucose ne sont toujours pas diagnostiquées pendant plusieurs années.

Objectifs: Déterminer la fréquence du diabète non diagnostiqué et le pré diabète parmi un groupe de patients hypertendus et normotendus.

Méthodes: L'anthropométrie, la pression artérielle et le test de tolérance au glucose oral standard (HGPO) ont été réalisées chez les participants adultes (le contrôle des hypertendus et des normotendus) nouvellement présentés à une policlinique du centre hospitalier universitaire d'Ibadan.

Résultats: En se servant du test HGPO, la fréquence du diabète non diagnostiqué était de 10,4% et de 4,3% chez les hypertendus et les normotendus respectivement (p = 0,031), mais elle était de 5,2% et de 2,6% chez les hypertendus et normotendus en utilisant respectivement la glycémie (p = 0,308). Avec l'usage du test HGPO, la tolérance au glucose (IGT) a été diagnostiqué chez 32,2% des hypertendus comparativement à 14,8% des sujets normotendus (p = 0,002), tandis que la glycémie (IFG) a été diagnostiqué chez 5,2% des hypertendus et 2,6% des sujets normotendus (p = 0,288). Après le contrôle de l'hypertension, l'âge, le niveau d'éducation, l'indice de masse corporelle et la largeur de la hanche, les hypertendus et les personnes ayant de plus large hanche a augmenté de façon statistiquement importante la chance de n'être probablement pas victime d'intolérance au glucose: l'hypertension (OR 2,915, IC 95% 1,526 à 5,556) et la largeur (OR 1,050, IC 95% 1,010 à 1,090).

Conclusion: Le diabète et le prédiabète sont plus fréquents chez les personnes hypertendues et ont donc besoin de fréquents contrôles afin d'éviter la gravité de cette maladie. Le dépistage à la fois par la glycémie et par le test HGPO identifie plus le nombre de personnes souffrant d'intolérance au glucose que par la glycémie seule.

Introduction

Diabetes mellitus is a metabolic disorder of multiple aetiology characterized by chronic hyperglycaemia

with disturbances of carbohydrate, fat and protein metabolism, resulting from defects in insulin secretion, insulin action or both [1]. Diabetes mellitus is a common endocrine problem that occurs worldwide and it is a well-known fact that its prevalence is rising globally. The International Diabetes Federation (IDF) estimated that in 2012 there were 371 million people worldwide with diabetes and that this figure is expected to rise to 552 million by 2030. The major part of the predicted increase is expected to occur in developing countries. Type 2 diabetes accounts for the vast majority of persons with diabetes mellitus worldwide [2].

The terms impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) refer to a metabolic stage intermediate between normal glucose homeostasis and type 2 diabetes and are regarded as categories of intermediate hyperglycaemia or prediabetes. IFG and IGT are considered to be stages in the development of type 2 diabetes and studies have indicated that they precede the development of type 2 diabetes mellitus [3,4]. Persons with IFG and IGT are at a higher risk of developing type 2 diabetes and macrovascular disease when compared with the general population [3,4]. The identification of persons with IFG or IGT can lead to the implementation of strategies aimed at the primary prevention of type 2 diabetes.

Essential hypertension is an established risk factor for the development of type 2 diabetes mellitus and a major risk factor for cardiovascular disease. Various studies have provided evidence for the co-existence of these two conditions [5,6].

Persons with diabetes mellitus in addition to hypertension are at an increased risk for microvascular and macrovascular disease. Thus, in persons with essential hypertension, early diagnosis of glucose intolerance would be of great importance, as it would allow for reduction of disease burden through early intervention and risk modification. It would also allow for implementation of strategies aimed at preventing or delaying the development of type 2 diabetes in those with prediabetes. This is of particular importance as persons with prediabetes and undiagnosed type 2 diabetes are often asymptomatic and may only be symptomatic after complications have developed. Screening would help in early diagnosis in such persons so as to implement appropriate management before complications of diabetes arise.

There is paucity of data regarding the burden and pattern of undiagnosed diabetes and prediabetes in Nigerians who have essential hypertension. This study aimed to determine the prevalence of undiagnosed diabetes and prediabetes in persons with essential hypertension in comparison with normotensive persons.

Materials and methods

Two hundred and thirty adults aged 35 years and above were studied. One hundred and fifteen consecutive persons with essential hypertension newly presenting to the General Outpatient Clinic of the University College Hospital, Ibadan formed the study subjects. The University College Hospital is a Tertiary Hospital located in Ibadan, a city in South-West Nigeria that provides all levels of health-care. One hundred and fifteen consecutive persons who did not have a history of hypertension or diabetes and whose measured blood pressures were normal (normotensives) formed the controls. Known persons with secondary hypertension, diabetes mellitus and pregnant women were excluded from the study. Ethical clearance was obtained from the UI/UCH ethics committee and written informed consent was obtained from all participants before participation. Baseline data on age, sex, tribe, level of education, occupation were obtained and entered into a questionnaire by trained assistants.

All participants had their physical measurements including weight, height, waist circumference, hip circumference and blood pressure measured using the World Health Organization (WHO) STEPS instrument as enunciated below. The weight of each of the subjects was measured in kilograms using a beam type scale without the subject wearing heavy clothes or shoes. The height was measured in meters with a stadiometer without the subject wearing shoes, caps or headgear and standing with the back to the measuring rod, and looking straight ahead. The waist circumference was measured with the use of a flexible inelastic tape measure with graduations at 0.1cm intervals. The measurement was taken midway between the inferior margin of the last rib and the crest of the ilium in the mid-axillary plane and the circumference measured in a horizontal plane at the end of normal expiration to the nearest 0.5cm. Hip circumference was taken with the arms relaxed at the sides and standing with their feet together. The measuring tape was placed around the maximum circumference of the buttocks. Measurement was read at this level to the nearest 0.5cm and the waist to hip ratio was then calculated. Blood pressure was measured with a mercury sphygmomanometer after the patient had rested for about five to ten minutes in a quiet room.

Following an overnight fast of 10-12 hours, 4ml of venous blood was drawn from each subject and

put into fluoride oxalate bottles for analysis of the fasting plasma glucose. A solution containing 75g of anhydrous glucose dissolved in 300ml of water was given to the subject to drink over about four minutes. Timing for the test started at the beginning of ingestion. Subjects remained seated and two hours after the ingestion of glucose another sample of venous blood was collected for glucose analysis. Plasma glucose was determined by a glucose oxidase method using 4 aminophenazone as oxygen acceptor as described by Trinder, with kits from Dialab Diagnostics, Austria.

Diabetes and prediabetes were defined according to the 1999 WHO diagnostic criteria. Diabetes was defined as FPG ≥7.0mmol/l (126mg/dl). IFG as fasting plasma glucose (FPG) between 6.1-6.9mmol/l (110-125mg/dl) while IGT was defined as FPG<7.0mmol/l (126mg/dl) and 2 hour post glucose load plasma glucose of 7.8- 11.0 mmol/L (140-199 mg/dl)

Data was entered into a computer with SPSS version 16. Summary statistics such as means, medians, frequencies and proportions were used to summarize variables depending on the type while bar charts were used for graphical presentation. Continuous variables were presented as mean (S.D.) and categorical variables as numbers (%). Comparison between means was done using the t test for two groups and analysis of variance (ANOVA) for more than two groups. Associations between two categorical variables were tested using the Chi square test. Adjustment for baseline differences (confounding variables) was done with the logistic regression for dichotomous outcomes and 95% confidence intervals were reported. Level of significance for all tests was p value less than 0.05.

Results

The mean BMI was 27.8(5.0)kg/m^2 and 26.3(5.0) kg/m^2 for hypertensives and normotensives respectively and this difference was statistically significant ($p<0.05$). The mean waist circumference was also significantly higher in the hypertensives 94.8 (14.9) cm compared to the normotensives 89.7(11.6)) cm. p=0.004 (table 1).

When separate analysis by gender was done, male participants had no significant differences in anthropometric indices in hypertensives compared with normotensives (table 2) but female hypertensives had significantly higher BMI (p=0.007) and waist circumference ($p<0.001$) compared to female normotensives. Female hypertensives also had higher waist hip ratio than the normotensives, but the difference was not statistically significant (p=0.176), (table 3).

Using the oral glucose tolerance test (result of two hour post glucose load), the frequency of diabetes was 10.4% and 4.3% in hypertensives and normotensives respectively (p=0.031) but was5.2% and 2.6% in hypertensives and normotensives respectively using fasting plasma glucose alone

Table 1: Comparison of anthropometric variables between hypertensives and normotensives

Parameters	Hypertensives (n=115) Mean (SD)	Normotensives (n=115) Mean (SD)	T	Pvalue
Weight (kg)	74.5(13.8)	72.4(15.4)	1.084	0.279
Body mass index (kg/m^2)	27.8(5.0)	26.3(5.0)	2.351	0.020*
Waist circumference (cm)	94.8(14.9)	89.7(11.6)	2.926	0.004*
Waist hip ratio	0.98(0.81)	0.87(0.1)	1.451	0.148

Table 2: Comparison of anthropometric variables between male hypertensives and normotensives

Parameters	Hypertensives (n=39) Mean (SD)	Normotensives (n=36) Mean (SD)	T	P value
Weight (kg)	72.6(12.9)	74.1(17.2)	0.418	0.677
Body mass index (kg/m^2)	25.3(3.9)	24.8(4.9)	0.507	0.614
Waist circumference (cm)	91.5(11.4)	91.9(15.2)	0.113	0.910
Waist hip ratio	0.93(0.05)	0.91(0.07)	1.571	0.120

Table 3: Comparison of anthropometric variables between female hypertensives and normotensives

Parameters	Hypertensives (n=76) Mean (SD)	Normotensives (n=79) Mean (SD)	T	P value
Weight (kg)	75.4(14.3)	71.6(14.6)	1.640	0.103
Body mass index (kg/m²)	29.1(5.0)	26.9(4.9)	2.748	0.007*
Waist circumference (cm)	96.5(16.2)	88.7(9.4)	3.706	<0.001*
Waist hip ratio	1.01(1.00)	0.85(0.11)	1.360	0.176

Table 4: Logistic regression analysis – strength of association of some risk factors with risk of glucose intolerance

	Odds ratio	95% CI OR	P value
Hypertension	2.915	1.526-5.556	0.001*
Age	1.015	0.980 – 1.051	0.418
Education	0.655	0.323 – 1.326	0.239
Occupation	0.800	0.410 – 1.561	0.514
Tribe	1.784	0.637 – 4.996	0.271
Body mass index	0.930	0.843 – 1.026	0.140
Waist circumference	1.050	1.010 – 1.090	0.013

(p=0.308). Prediabetes (IGT and IFG) was diagnosed in 37.4% of hypertensives and 17.4% of normotensives respectively (p<0.001). IGT was diagnosed in 32.2% of hypertensives compared to 14.8% of normotensives (p=0.002) while IFG was diagnosed in 5.2% of hypertensives and 2.6% of the normotensives (p=0.288).(figure 1).

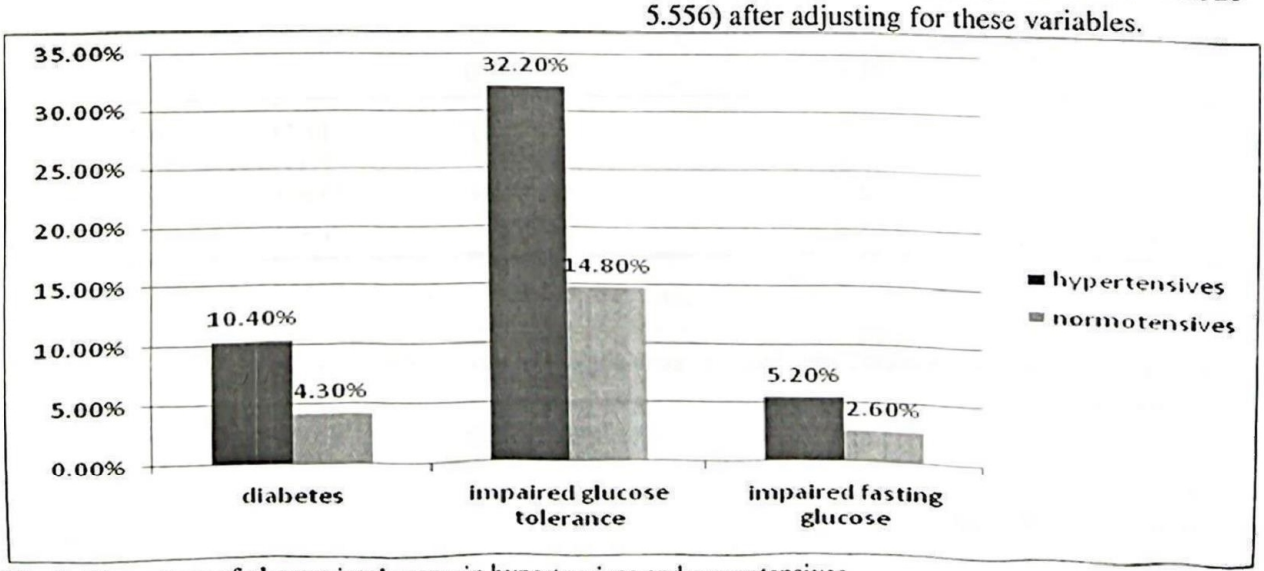

Fig. 1: The pattern of glucose intolerance in hypertensives and normotensives

The mean fasting plasma glucose was 92.9(17.8) mg/dl and 89.2(14.9) mg/dl for hypertensive and normotensives respectively (p=0.084), while the mean two hour post glucose load plasma glucose for both groups were 141.2(41.5) mg/dl and 121.8(29.5) mg/dl respectively (p <0.001).

Logistic regression showed that only hypertension and waist circumference remained significant independent predictors of glucose intolerance (table 4). Hypertensives were about 3 times (odds ratio =2.915) more likely than controls to have glucose intolerance (95% CI OR = 1.526 – 5.556) after adjusting for these variables.

Discussion

These results show that persons with essential hypertension have significantly higher frequencies of occurence of prediabetes and diabetes compared to normotensive persons. The frequencies of undiagnosed DM, IGT and IFG in persons with

essential hypertension in this study were 10.4%, 32.2% and 5.2% respectively.These figures are comparable to those of Stiefel and colleagues that showed that 38.5% of hypertensives in Spain had abnormal glucose tolerance (12.2% had type 2 DM, 22.2% had IGT while 2.1% had IFG [7] and those of Garcia-Puig *et al* who found that in hypertensives in Spain, 11.5% had undiagnosed type 2 DM, 22.5% had IGT while 11.2% had IFG [8].

Much higher frequencies were obtained in persons with essential hypertension in China, amongst whom prevalence rates of newly diagnosed diabetes and impaired glucose regulation (prediabetes) were 22.9% and 64.4% respectively. When compared with our study, Essien *et al* reported a lower prevalence of DM (4.6%) but similar prevalence of IGT (32.8%) among adult Nigerians with essential hypertension [9]. In a similar study in Northern Nigeria prevalences of 2%, 19% and 2% for DM, IGT and IFG respectively were reported in hypertensive [10]. The diagnosis of abnormal glucose tolerance in the above studies and this study were by oral glucose tolerance test (OGTT) and so there were no significant differences in methodology. The reason for the differences in prevalences of DM and IGT in these studies may be due to the differences in ethnicity and or socioeconomic status of the subjects studied as abnormal glucose tolerance has been known to vary across different ethnic groups and socioeconomic stata [11,12].

The significantly higher waist circumference in hypertensive subjects in this study could contribute to the higher prevalence of glucose intolerance seen in the hypertensive group compared with the normotensive group as truncal obesity has been associated with risk of hypertension and type 2 diabetes mellitus [13]. BMI was also significantly higher in the hypertensives which is not unexpected as overweight and obesity have been associated with hypertension and the metabolic syndrome [14].

The findings above have clearly shown that hypertensives have significantly higher frequencies of occurrence of glucose intolerance (Diabetes, IFG and IGT). Persons with diabetes are vulnerable to cardiovascular disease (heart disease, stroke, peripheral vascular disease) and microvascular disease (retinopathy, neuropathy, and nephropathy). Concomitant hypertension and diabetes increases this risk remarkably .

Therefore, early identification of diabetes in persons already known to have hypertension is essential in cardiovascular risk assessment and reduction.IFG and IGT are said to increase the absolute risk of type 2 DM by about 3-to 10-fold, with the risk varying in different populations [15]. Studies have shown that the complications of diabetes begin early in the progression from normal glucose tolerance to frank diabetes and that some people with prediabetes already have the characteristic microvascular and macrovascular changes resulting from diabetes [16,17].

Early identification and treatment of persons with IGT and IFG has the potential to reduce or delay the progression to diabetes and related cardiovascular and microvascular disease. In addition, persons with hypertension need education on non-pharmcological methods of prevention of type 2 diabetes such as a healthy diet, exercise and weight loss. In persons with prediabetes, randomized controlled trials with pharmacologic therapy such as metformin has proven to be beneficial in preventing or delaying the onset of type 2 diabetes, as well as reverting prediabetes to normal glucose tolerance. Its routine use in persons with prediabetes is however still being debated [15,18,19].

In the control (normotensive) group the frequency of diabetes (4.3%) was higher thanboth the 2010 IDF estimate for Nigeria (3.9%) and the prevalence rates obtained in rural Tanzania by McLarty *et al* [20] in 1989 (age-adjusted prevalence of DM and IGT of 1.1% and 8.4% respectively). It was also higher than prevalence rates obtained in a local study by Olatunbosun *et al* in 1998 (prevalence of DM and IGT of 0.8% and 2.2% respectively).

The diagnosis of glucose intolerance in the above studies and this study was by OGTT and thus no significant differences in methodology. The reason for the differences in prevalences of DM and IGT in these studies may be due to the differences in ethnicity and socioeconomic status of the subjects studied as the burden of abnormal glucose tolerance has been known to vary across different ethnic groups and socioeconomic status [11,12].

It could also be in keeping with the rising prevalence of diabetes world-wide, thought to be driven by the increasing adoption of a Westernised lifestyle and obesity [2], as the study by Olatunbosun *et al* was done over a decade ago. Another reason that could be adduced is that since some of the normotensives studied were first degree relatives of hypertensives, they may be at a higher risk for glucose intolerance than the normal population, since genes and a family history of hypertension have a role to play in the pathophysiology of hypertension and type 2 diabetes [21].

Another important finding is that more hypertensives had prediabetes diagnosed by the 2 hour post load plasma glucose than by IFG alone.

This is in keeping with the widely held belief that OGTT is more sensitive in detecting early abnormal glucose metabolism than fasting glucose alone, which is what is being done in many centers to screen hypertensives for glucose intolerance. It would therefore seem that fasting plasma glucose estimation alone is inadequate for screening for diabetes and prediabetes, especially in high risk persons such as persons with hypertension.

OGTT is said to be the 'gold standard' for diagnosing abnormal glucose tolerance. If fasting glucose alone is used as the screening tool, a third of subjects with diabetes will not be diagnosed [22]. Moreover, it is impossible to diagnose IGT without an OGTT. A sizable number of persons with hypertension would have abnormal glucose tolerance if screened by OGTT and it is clear that the risks and adverse consequences of high blood glucose occur at much lower glucose levels than those we currently define as diabetes. We hope that the findings from this study would prompt health care professionals to screen for glucose intolerance regularly in all hypertensives and would also prompt the implementation of various strategies known to delay the progression to overt diabetes and reduce vascular complications in those with abnormal glucose tolerance.

The strengths of this study are the use of a control population and the use of OGTT, a standardized method of identifying new cases of diabetes and asymptomatic preclinical phases of diabetes (IGT and IFG). We acknowledge that our study also has a few limitations: the relatively small study population and that it is Hospital-based.

Conclusion

Diabetes and prediabetes remain a major health challenge in Nigeria, as in the rest of the world. With the rather high prevalence of glucose intolerance in our subjects, further work needs to be done in screening larger populations, especially of hypertensives who are definitely at higher risk for glucose intolerance. In our environment where resources are scarce, and where most patients have to pay out of pocket, screening for prediabetes and diabetes needs to be targeted at persons at risk in order to institute lifestyle modifications which are known to delay or prevent development of glucose intolerance. OGTT would be be a better screning tool in detecting prediabetes than fasting plasma glucose alone in high-risk populations.

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