FASTING PLASMA GLUCOSE CONTROL AMONG NIGERIANS WITH METABOLIC SYNDROME.

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Abstract

Introduction: Metabolic Syndrome consists of many diseases that predispose to cardiovascular events including type 2 diabetes mellitus, systemic hypertension, central obesity, dyslipidaemia, endothelial dysfunction and inflammation. Hence, glycaemic management of these cluster of diseases might take a different pattern compared with only type 2 diabetes mellitus.

Objective: To determine the levels of fasting plasma glucose (FPG) and the type of oral antidiabetic drugs patients with metabolic syndrome are receiving. To relate the FPG to the type of medications the patients were using.

Materials and Methods: One-hundred and ninety-two patients with type 2 DM attending Diabetic clinic of the Lagos University Teaching Hospital (LUTH), Lagos were randomly enrolled for the study. Ninety-six of the patients had metabolic syndrome X (presence of hypertension and obesity in addition to type 2 DM), while the rest had only type 2 DM. History was obtained through a questionnaire and they were physically examined. Blood samples were obtained twice for plasma glucose estimation.

Results: There were more metabolic syndrome subjects on combination of sulponylurea and metformin (80%) than the controls (28%), (<0.01). While many of the control subjects were on sulphonylurea alone (56% vs 7%, <0.01), none was on metformin alone. The mean fasting plasma glucose were comparable among the groups (5.63.8mmol/l vs 5.52.9mmol/l), =0.36.

Conclusion: Insulin resistance seems to plays a more prominent role in MS and patients benefited more from either combination therapy or metformin alone whereas cells dysfunction may be more important among patients with T2DM alone and they benefited more from sulphonylurea.

Introduction

Hyperglycaemia in Type 2 Diabetes Mellitus (T2DM) results from the combination of insulin resistance (IR) and cells dysfunction[1]. IR is a diminished ability of insulin to exert its biologic action across a broad range of concentrations. Persons with IR secrete abnormally high amounts of insulin to compensate for this defect to properly stimulate glucose transport in muscle and fat cells, and suppress hepatic glucose production[2]. During the initial phase of IR, the cells of the pancreas compensate by increasing the secretion of insulin to maintain euglycaemia. This, however, fails as the disease progresses when the pancreas can no longer cope with the insulin requirement to overcome the resistance. The latter is called cell dysfunction[2].

Metabolic Syndrome (MS) on the other hand consists of type 2 diabetes mellitus or impaired glucose tolerance, systemic hypertension, central obesity, dyslipidaemia, endothelia dysfunction and inflammation[1]. IR has been agreed upon as the main pathogenic factor in the development of MS[3-5]. This study was

designed to see which of the two abnormalities play a more important role in the FPG control of those who had MS as compared to those with T2DM alone (without obesity and hypertension) using their FPG levels and the types or the number of the medications required to achieve that glycaemic levels.

Insulin sensitizers like metformin and thiozolidinedione have been documented to reduce IR[6]. Sulphonylurea on the other hand stimulates insulin secretion thereby ameliorating cell dysfunction[7]. The type and/or the number of the medication a patient in either group is/are on may give some information as to which of the two pathogenesis is more prominent.

Kinnear[8], Ibadan in 1963 and Oviasu[9], Benin in 1973 used absence of hypoglycaemia and hypoglycaemia to determine glycaemic control among patients with T2DM. However, there is paucity of report on the type of oral antidiabetic drugs that will more beneficial to either patients with T2DM alone and those with MS. A study of this nature is to assist clinician on which medication will be more useful to each group of patients. Haemoglobin A1c is the gold standard for the determination of glycaemic control, however, this was not done due to financial constrain.

Materials and Methods

One hundred and ninety-two patients with T2DM between the ages of 30-70 years attending Diabetic Clinic of Lagos University Teaching Hospital (LUTH), Lagos were randomly selected for the study. Half of the population selected had MS while the other half had only T2 DM (control subjects). History was obtained from them through the questionnaire and they were physically examined. All the patients had the diabetes for at least 6 months and had been on either lifestyle modification alone or with oral antidiabetic drugs. The diagnosis of MSX was made in the presence of systemic hypertension (BP 140/90 or patients on anti-hypertensive medication) and obesity (body mass index [BMI] 30kg/m^2) and/or waist hip ratio [WHR] in male 0.9, in female 0.85) in addition to the presence of T2 DM[1]. The control subjects had only T2DM without systemic hypertension and obesity. Blood samples were collected twice to determine fasting plasma glucose (FPG) levels and an average value of the two was used. FPG was said to be satisfactory at values between 4.4 6.1mmol/l and unsatisfactory at values outside this range[10]. Trinder's analytic method was used for glucose estimation[11]. Patients on insulin were excluded from the study because of the initial study design to measure plasma insulin. The information obtained was analyzed using the statistical software Epi info 6.

Results

Among the study groups, females were 61 and 47 for MS and control subjects, respectively. The mean duration of T2DM were 7.5 4.8 years and 6.3 4.3 years for MS and control subjects respectively. The characteristic features of both groups are shown in Fig1. However, more patients with MSX (80%) were on combination therapy out of which 75% had satisfactory glycaemic control, than the controls (28%) ($p< 0.01$) out of which 48% had satisfactory glycaemic control (Fig 1). While many of the control subjects were on sulphonylurea alone (56% vs 7%, <0.01), none was on metformin alone. However, fewer patients with MS (7%), and 10% were on sulphonylurea alone and metformin alone, respectively. Two percent of patients with MSX were on dietary management alone for their glycaemic control compared with the control subjects (16%), <0.05 (fig 2).

The mean FPG were comparable among the MS and the control subjects (5.6 3.8 vs 5.5 2.9 mmol/l respectively). Many patients with MS (75%) and controls (69%) had satisfactory glycaemic control. There were many patients with MS (84%)] and the controls (68%)] that had short term (=10years) DM with satisfactory glycaemic control. The glycaemic control was generally comparable among patients with MSX and controls ($\chi^2 = 1.86$).

Table 1: Characteristics of the Study Population .

	MSX (m + sd))	Control (m + sd)	ρ
Age (yr)	58±12.3	52.2±14.8	<0.001
BMI (kg/m^2)	28.6±2.1	22.7±1.8	<0.001
WC (cm)	94.4±3.1	75±1.6	<0.001
FPG (mmol/l)	5.6±3.8	5.5±2.9	0.706
SBP (mmHg)	163±14.8	126±10	<0.001
DBP (mmHg)	92.6±13.3	72.1±7.4	<0.001
DM Duration (yr)	7.5±4.8	6.3±4.3	<0.001

Table 1. Glycaemic control among patients with metab olic syndrome X and controls according to the type of treatment for DM

	MSX Subjects(%)			Controls (%)			P values	
Therapy (1)	N 2)	Satisfactory (3)	Unsatisfactory (4)	N (5)	Satisfactory (6)	Unsatisfactory (7)	P_1 (3 v 6)	P_2 (4 v 7)
0	2	2 (100)	0 (0)			3 (20)		0
1	7	4 (57.1)	3 (42.9)	15	12 (80)	13 (24.1)	0.01	0.02
2	10	8 (80)	2 (20)	54	41 (75.9)	0 (0)	<0.01	0
3	77	58 (75.3)	19 (24.7)	0	0 (0)	14 (51.8)	0	0.52
Total	96	72	24	27	13 (48.2)	14	<0.01	
				96	66			

0; Diet only 1; Sulphonylurea 2; Metformin 3; combination therapy of s ulphonylurea and metformin

Discussion

It was observed that subjects with MSX and those with T2DM alone had good and comparable glycaemic control (5.6 3.8 and 5.5 2.9 mmol/l respectively). About 80% of patients with MSX required a combination of metformin and sulphonylurea for their glycaemic control as compared with 28% of those with T2DM alone. In addition, it was observed that about 60% of patients with T2DM alone were controlled on sulphonylurea only while none of them was on metformin alone.

Good glycaemic control in a major goal in the management of T2DM in order to prevent or limit complications, disabilities and mortality. The American Diabetes Association (ADA) has recommended a preprandial plasma glucose level of 4.4 6.7mmol/l (80 120mg/dl) and a bedtime level of 5.6 7.8mmol/l (100 140mg/dl) for patients with T2DM[12]. However, the American College of Endocrinology, American Association of Clinical Endocrinologist (AACE) and International Diabetic Federation proposed a more stringent target of a preprandial of <6.1mmol/l (110mg/dl) and a 2-hour postprandial of <7.8mmol/l (140mg/dl)[13]. The good glycaemic control seen among the study subjects might be a reflection of the quality of management being offered to them since the study was carried out in a tertiary care institution where there were adequate facilities for the management of diabetes. However, the HbA_{1c} assay, which could not be performed in this study due to financial constraint, gives a better information on glycaemic control than FPG. It was reported by the UKPDS group 35 that for every 1% reduction in HbA_{1c} there was a 21% reduction in death from diabetes mellitus, 14% from heart attack, 37% from microvascular

complications and 43% from peripheral vascular disorder[14].

The fact that 10% of patients with MS and none with T2DM alone required only metformin for their glycaemic control may be attributable to the prominent role of insulin resistance among patients with MS than in T2DM alone. Metformin is considered an insulin sensitizer. It reduces hepatic glucose production and enhances peripheral glucose disposal by decreasing glucotoxicity[15, 16]. Furthermore, metformin has been found to be able to cause a significant reduction in the weight of the patients, decreases lipid levels especially the LDL-cholesterol and triglyceride[6], reduces the plasminogen activator inhibitor 1 (PAI1) [17] as well as ameliorating vascular reactivity and endothelial dysfunction[18] all of which are the constituents of MS. In the UKPDS, patients treated with metformin compared with those on sulphonylurea or insulin had 32% reduction in any diabetes-related end points (= .02), 42% reduction in diabetes-related deaths (= .02) and a 36% reduction in all-cause mortality (= .01) [19]. When compared with the conventional group, patients on metformin had a reduction in myocardial infarction by 39% (= .01) and all macrovascular end points by 30% (= .02) [19]. These findings may suggest that the ways through which glucose are lowered by antidiabetic medications might uniquely influence the outcomes. Lastly, metformin has been shown to improve ovulatory function in insulin-resistant woman with polycystic ovarian syndrome.

Conversely, cell dysfunction may play a more dominant role in those with T2DM alone and so, may depend more on sulphonylurea for their glycaemic control. Sulphonylurea by closing the voltage-dependent potassium adenosine triphosphate channels, facilitating the cell membrane depolarization, calcium entry into the cell and then causes insulin secretion[7]. It is worthy of note that this drug can lead to weight gain in the patients on it thereby worsening the insulin resistance[7]. Patients on sulphonylurea are also at the risk of hypoglycaemia[7]. In the UKPDS, when compared with the conventional therapy, sulphonylurea was associated with reduction in microvascular end points by 25% (< .001), in any diabetic-related end points by 12% (= .03) [19]. There was no significant effects on diabetes related death or on the all-cause mortality; and only a small effect on the risk of myocardial infarction (-16%), = .05 [19]. One might infer that that the improvement seen in glycaemia did not decrease the macrovascular risk because of the opposing effect of hyperinsulinaemia. Furthermore, 80% of patients with MS were on combination therapy as against 28% of those with T2DM alone. This may be due to more rapid worsening of glycaemic control among the former group than the latter.

It is imperative to note that dietary and lifestyle modifications still remain the backbone of diabetic management. All the patients studied in this case were on such management.

Maintenance of good glycaemic control is bedeviled by a number of limitations which include progressive severity of the disease, limitation of the current monotherapy, dose-limiting side effects and sub optimal compliance with therapy. Turner et al[20] observed that about 50% of patients with T2DM required multi therapy within 3 years of management to achieve good glycaemic control and 75% within 9 years. In the UKPDS, it can be concluded that no treatment studied prevented deterioration in glycaemic control and deterioration in cell function[19]. Traditional treatment options do not primarily target the underlying disease pathophysiology. It is therefore good to approach the management of T2DM and indeed, MS with combination therapy with different and additive mechanism of action that addresses the underlying pathophysiology. This will help in achieving effective and sustainable glycaemic control.

Conclusion: From this study, it can be inferred that IR plays a prominent role in MS and patients benefitted more from either combination therapy or metformin alone whereas cells dysfunction is more important among patients with T2DM alone and they

benefitted more from sulphonylurea. This may help the clinicians in making a quick decision on which drug/s will be of utmost benefit to any patient depending on the group they fall into. The better way of assessing glycaemic control is the use of HbA_{1c}, however, this could not be used because of financial constraint. In the future, HbA_{1c} should be used to assess glycaemic control of the subjects. Other drugs like glyburide, rosiglitazole and insulin should be included in the study design.

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