Supervised Treatment with Glanil® and Gluformin® Obviates need for Insulin Therapy in Patients with poorly controlled Type 2 Diabetes Mellitus

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ABSTRACT

Objective: To determine the effect of supervised therapy with glibenclamide and metformin on glycaemic control in a selection of patients with poorly controlled type-2 diabetes mellitus in a Nigerian tertiary hospital.

Materials and Methods: A prospective uncontrolled open label design was used. Subjects were randomly selected on the basis of poor glycaemic control (Fasting plasma glucose > 150 mg/dl, 2-hour post prandial glucose>180mg/dl, HbA1c >7%) and maximal doses of glibenclamide and metformin (15-20 mg, 2-3g respectively). Patients were seen at regular intervals with analysis of plasma glucose, glycated haemoglobin and supervised treatment (drugs were provided and there was open access to consulting offices and counseling).

Results: There was significant reduction in the fasting plasma glucose, 2-hour post prandial plasma glucose and glycated haemoglobin at the end of the study. There were no adverse drug reactions recorded during the study and the drugs were well tolerated.

Conclusion: Supervised treatment with Metformin (Gluformin®) and Glibenclamide (Glanil®) significantly improves glycaemic control in patients with type-2 diabetes mellitus.

INTRODUCTION

The management of hyperglycaemia in patients with diabetes has undergone remarkable change in the past several years as a result of advances in the knowledge of the disorder and application of this knowledge to the development of new treatments and strategies.[1]

The understanding of the various pathophysiologic mechanisms involved in hyperglycaemia has led to the development of several therapeutic strategies in the drug treatment of type-2 diabetes mellitus.

The different major classes of oral antihyperglycaemic agents in current use can be divided into those that increase insulin secretion (insulin secretagogues: sulphonylureas, meglitinides), those that decrease insulin resistance (metformin and thiazolidinediones), and those that modify the rate of glucose entry from the cells (α glucosidase inhibitors).

More recently, glucagon like peptide-1 (GLP-1) has been introduced which acts by stimulating glucose dependent insulin secretion and synthesis.

Sulphonylurea drugs have been used in the treatment of type-2 diabetes since the early 1950's. They primarily act by increasing the late stage of insulin secretion. Glibenclamide is a second-generation sulphonylurea and currently the most widely prescribed (dosage 1.25–20mg). Its efficacy in reducing hyperglycaemia appears to be equal to that of other sulphonylureas though it is associated with significant hypoglycaemia that is higher than that of other sulphonylureas and a modest weight gain.[2]

Metformin, a biguanide has been used in the treatment of type 2 diabetes since the 1960s and exerts many physiologic effects that contribute to its ability to decrease hyperglycaemia in patients with type-2 diabetes. Treatment with metformin generally reduces hyperglycaemia by approximately the same magnitude as sulphonylurea treatment even though their mechanisms of action are entirely different.[3] Maximum effects occur at dosages of 1,750–2,000mg per day. The major complications associated with metformin use are gastrointestinal symptoms, which are transient and dose dependent. Studies comparing the effects of metformin and sulphonylureas in type-2 diabetes consistently show equivalence even though their modes of action are entirely different. Although the different antihyperglycaemic agents are effective as monotherapy in improving glycaemic control and lowering HbA1c, they are rarely able to restore glycaemia to near normal and improve HbA1c levels to less than 6.5% in patients with type-2 diabetes who present with fasting hyperglycaemia and HbA1c > 7%.[4] This is probably because of the different metabolic defects that have resulted in the hyperglycaemia.[5]

Combining agents with different modes of action produces additive effects on glycaemic control and also allows

use of sub-maximal doses of these drugs.

Glycaemic control is fundamental to the management of diabetes. Prospective randomized clinical trials have shown that achieving glycaemic control is associated with decreased rates of retinopathy, nephropathy, and neuropathy and reduction of cardiovascular disease. The goals of glycaemic control according to the American Diabetes Association are: Fasting plasma glucose; 90–130mg/dl, postprandial plasma glucose <180mg/dl.[6]

Poor glycaemic control despite maximum doses of oral agents could result from a number of factors which include; patient related factors: poor compliance with medical regimen, diet failure, intercurrent illness; natural history of type-2 diabetes with progressive beta cell failure which results in secondary failure of the oral agents. Insulin therapy is usually the therapeutic option at this stage.[7]

We set out to evaluate the effect of supervision of treatment with combination therapy of glibenclamide (Glanil®) and metformin (Gluformin®) in the treatment of type-2 diabetes mellitus in a selection of Nigerian patients with poor glycaemic control despite maximal doses of these drugs. The study lasted a six-month period.

Methodology

Subjects were selected from out-patients attending the Diabetes Unit of the Lagos University Teaching Hospital (LUTH) between January 2005–June 2005, who fulfilled the inclusion criteria: Confirmed type-2 diabetes; Age between 30–70 years; On combination therapy with maximum doses of glibenclamide (15–20mg/day) and metformin(2–3g/day) with poor glycaemic control (Fasting plasma glucose; FPG >150mg/dl or 2-hour post prandial plasma glucose; 2hPG >180mg/dl or Glycated haemoglobin; HbA1c > 7%. Patients with type-1 diabetes, significant renal or hepatic insufficiency, <30 or >70 years of age, on insulin therapy and patients with poor glycaemic control on sub-optimal doses of oral agents were excluded from the study. A signed informed consent was obtained from all patients recruited. There were a total of six visits.

At baseline, demographic characteristics were noted, anthropometric indices; weight, height, waist circumference, hip circumference were measured. Waist hip ratio was calculated and body mass index was calculated using the formula: weight in kilograms/height.[2] Laboratory estimation of fasting and post-prandial plasma glucose and glycated haemoglobin was done. Liver function tests, urinalysis and electrocardiogram were also done.

Physical examination with blood pressure measurements was performed at every visit with plasma glucose estimation and urinalysis.

During the last visit, glycated haemoglobin, lipid profile, liver function tests and electrocardiogram were repeated.
At each visit, patients had study medication dispensed and compliance was assessed by counting number of drugs returned by the patients.

Safety assessment was from spontaneously reported adverse events and serious adverse events were reported in the adverse event report form.

Patients were counselled at every visit on diet and exercise compliance. Concomitant drugs were noted.

A total of 37 subjects with type-2 diabetes and poor glycemic control (fasting plasma glucose ≥ 150mg/dl, 2 hour post prandial ≥ 180mg/dl or HbAlc ≥ 7%) were selected. One of the subjects had to discontinue oral drugs and changed over to insulin on the basis of confirmed secondary failure (no improvement in the fasting plasma glucose and glycated haemoglobin : FPG 275 mg/dl/214mg/dl; HbA1c 13.5% /13.4% at the beginning and after 12 weeks of commencement of the study respectively). He had a 14-year history of diabetes. An additional 5 subjects dropped out of the study. A total of 31 subjects completed the study.

The diagnosis of type-2 diabetes was based on the World Health Organization criteria.[6] The Hospital ethics committee approved the study protocol and informed consent was obtained from each patient prior to commencement of study.

Statistical Analysis:

Data are expressed as means plus or minus standard deviations. Statistical analyses were performed using ANOVA. A p-value <0.05 was regarded as statistically significant.

RESULTS

A total of 37 patients were recruited over the 6-month period out of which 31 patients completed the study. Fifteen males and 16 females were seen with a mean age of 57.1 ± 8 years, mean duration of diabetes 12.2 ± 6.6 years, mean BMI of 25.2 ± 4.7 kg/m² and mean waist hip ratio of 25.2 ± 4.7. Demographic characteristics are as shown on Table 1. Mean fasting plasma glucose at the beginning of the study was 176.5 ± 62.0 mg/dl, end of study 103.87 ± 47.4 mg/dl; mean 2-hour post-prandial plasma glucose 255.52 ± 81.7 mg/dl at the beginning of the study and 170.5 ± 79.4 mg/dl at the end of study. Mean HbA1c was 10.2 ± 2.2 and 8.3±2.0 at the beginning and end of study respectively. The mean reductions were statistically significant ($p < 0.05$). Table 2 shows the indices of metabolic control. Figure 1 and figure 2 show the decline in fasting plasma glucose and glycated haemoglobin respectively over time. There was also a significant reduction in the levels of triglycerides and low density lipoprotein cholesterol at the end of the study.

Table 1: **Demography of Subjects**

N	31
Male	15
Female	16
Age {Years}	57.1 ± 8
Age Range	40 – 70
Duration of Diabetes {Years}	12.2 ± 6.6
Duration of Diabetes (Range)	6 – 32
BMI {Kg/m²} Beginning	25.2 ± 4.7
BMI Range	17.3 – 36.0
BMI End	25.5 ± 4.7
Waist / Hip Ratio Beginning	0.94 ± 0.06
Waist Hip Ratio (range)	0.79 – 1.07
Waist Hip Ratio (end)	0.95 ± 0.06

Table 2: **Indices of Metabolic Control**

PARAMETERS	Beginning of Study	End of Study	P value
Fasting Plasma Glucose (mg/dl)	176.48 ± 62.0	103.87 ± 47.4	*0.0000
2-hour post prandial Glucose (mg/dl)	255.52 ± 81.7	170.50 ± 79.4	*0.0001
HbA1c (%)	10.2 ± 2.2	8.30 ± 2.0	*0.0008
Systolic Blood Pressure (mmHg)	136 ± 19.4	131.30 ± 20.1	0.27
Diastolic Blood Pressure (mmHg)	86.13 ± 14.7	80.80 ± 13.0	0.13
Plasma Cholesterol (mg/dl)	261.03 ± 59.0	229.06 ± 73.5	0.064
High Density Lipoprotein (mg/dl)	33.29 ± 6.5	39.70 ± 8.3	*0.006
Low Density Lipoprotein (mg/dl)	208.8 ± 55.0	171.30 ± 60.2	*0.013
Triglyceride (mg/dl)	96.22 ± 24.24	82.70 ± 24.0	*0.031

Values are expressed as means and standard deviations.

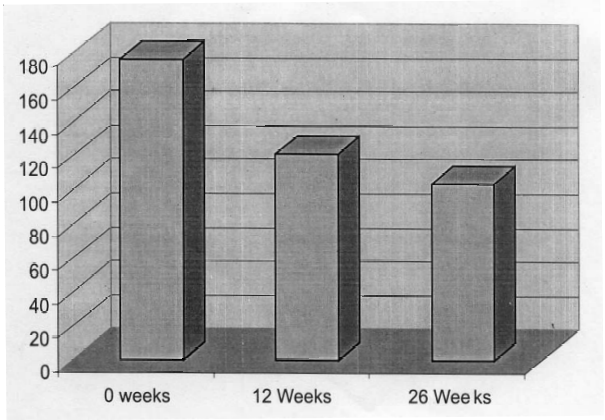

Fig. 1: **Distribution of mean fasting blood sugar over time.**

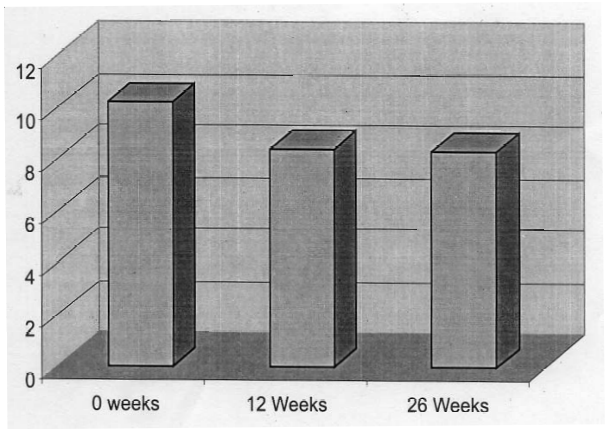

Fig 2: **Distribution of mean glycated haemoglobin (HbA1c) over time.**

DISCUSSION / CONCLUSIONS

A total of 31 patients, predominantly middle aged were seen in this study with a mean duration of diabetes of about 13 years. The mean body mass index of 25.2 ± 4.7 kg/m² shows a non-obese population. Obesity as defined by body mass index does not yet appear to be a major problem in our population of persons with diabetes.

Secondary failure of oral agents in the treatment of type 2 diabetes is said to occur after an initial response to an oral agent, decreasing effectiveness occurs thereafter and eventual failure to respond. For its diagnosis, it requires poor metabolic control after unequivocal diagnosis of diabetes, appropriate diet, exercise and use of maximum tolerated dose of the agents without intercurrent illness.[7]

Secondary failure developed in 5-10% of patients after about 10 years of diagnosis. The UKPDS demonstrated that in patients treated with sulphonylureas, an approximate linear failure rate (defined by the development of osmotic symptoms or a fasting plasma glucose >15 mmol /l) occurs with some 7% failing each year. Within six years, 44% of patients had failed on sulphonylurea therapy.[8]

In this study, with a mean duration of diabetes of about 13 years, it is not surprising that there was mean fasting plasma glucose of 176.48 ± 62mg/dl at the beginning of the study.

Secondary sulphonylurea failure could result from a number of factors which include patient related factors: poor compliance with medical regimen, diet failure and lack of exercise; natural history of type 2 diabetes with progressive beta cell failure and progressive insulin resistance.[7]

One patient in this study had definite secondary failure with no improvement in the fasting plasma glucose and glycated haemoglobin over a 12 week period despite supervised care.

The role of patient related factors has been illustrated in this study. The improvement in indices of metabolic control (reduced mean fasting plasma glucose, post-prandial plasma glucose and glycated haemoglobin) after intervention (supervision of care with free provision of drugs, unrestricted regular access to care providers, counselling on diet and exercise) suggest they were possibly non-compliant which contributed to their initial poor glycaemic control as reflected by the mean indices of control at the beginning of the study.

Other authors have noted the role of supervision of care. Rheeder and colleagues[9] concluded that the introduction of a physician education programme and a structured consultation schedule improved the quality of care in a tertiary care diabetes clinic. In this study, after a baseline audit of care, there was significant improvement in process outcomes in the intervention

group after introduction of physician education and structured consultation schedules.

In a systematic review of interventions to improve the management of diabetes in health care settings, Renders *et al* noted that multifaceted professional interventions and organizational interventions that facilitated structured and regular review of patients were effective in improving process of care.[10]

At the end of this study, we noted a significant reduction in the low density lipoprotein cholesterol (LDL-c) and triglycerides with a significant increase in the high density lipoprotein cholesterol (HDL-c). Metformin has been shown to have effects on modifying cardiovascular risk profiles in patients with type-2 diabetes.

In a study on the effect of metformin on lipids in patients with secondary failure, Fanghanel *et al* noted a reduction in the total cholesterol and triglycerides.[11] In a similar study, Giugliano *et al* noted a significant decrease in total cholesterol, triglycerides, and fibrinogen whereas high-density lipoprotein cholesterol increased.[12] The finding of an increased HDL-c is as noted in our study. There was no change in total cholesterol in this study.

Metformin has also been found to modify other alterations associated with insulin resistance such as being overweight and arterial hypertension.[11,12] We found no significant changes in BMI and blood pressures at the end of this study.

In the management of patients with poor glycaemic control despite maximal doses of two oral glucose lowering agents, treatment options include addition of a third agent from another class of drugs or insulin therapy. Insulin therapy could be the addition of overnight basal insulin to existing oral agents or the substitution of oral therapy with a more intensive twice daily or multiple injection regimens.

Supervision of care has obviated the need for insulin therapy in this cohort of patients who would have been regarded as secondary drug failure. In our type of practice environment where the introduction of insulin therapy is not often acceptable, closer supervision with education on drug compliance, counselling on exercise and diet is likely to improve control.

The need for the multidisciplinary approach to diabetes care with diabetes educators and specialist nurses cannot be overemphasized.

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