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Original Research Article

Clinical Investigation of Treatment Failure in Type 2 Diabetic Patients Treated with Metformin and Glibenclamide at a Hospital in Northwestern Nigeria

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Abstract

Purpose: *To examine body mass index (BMI), occupation, sex, age, and duration of therapy as contributory factors in treatment failure in type 2 diabetic patients taking metformin and glibenclamide in a tertiary hospital in Northwestern Nigeria.*
Method: *A retrospective case control study was employed where variables (age, sex, body mass index, tribe, duration of therapy, glycaemic profile and occupation) for a total of 520 type 2 diabetic patients that took metformin and glibenclamide for a minimum of 1 year were examined. Patients were classified into two groups based on progression to triple oral therapy or a switch from metformin and glibenclamide therapy.*
Results: *Of the 520 patients analysed, 276 failed treatment. Over 90 % of the patients were > 40 years while 61 % had been on treatment for > 4 years. The subjects' mean age was 53.22 ± 9.03 years. The mean population body mass index (BMI) was 27 kg/m^2. Housewives comprised more than half of the population (55.5 %). The mean fasting blood glucose and 2 h post prandial blood glucose levels of group 1 were 5.99 ± 0.67 mmol/L and 8.76 ± 2.19 mmol/L respectively while the corresponding values for group 2 were 12.55 ± 4.12 mmol/L and 18.42 ± 5.3 mmol/L, respectively.*
Conclusion: *Progressive deterioration in pancreatic ß-cell function, BMI > 28 kg/m^2, advancing age, and young age at diagnosis were identified as contributory factors to the development of secondary failure in type 2 diabetics receiving metformin and glibenclamide.*

Keywords: *Diabetes, Glibenclamide, Metformin, Pancreatic ß-cell function, Treatment failure*

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INTRODUCTION

Type 2 diabetes mellitus comprises about 90 % of people with diabetes around the world and is often associated with obesity [1]. According to a report of the World Health Organization, risks for type 2 diabetes and dyslipidaemia are greatly increased in obese subjects (relative risk, more than three times), [2]. Glycaemic control reduces the risk of blindness, renal failure, neuropathy, and other microvascular complications in type 2 diabetes [3].

Good glycaemic control has become even more important with earlier diagnosis and more aggressive cardiovascular prevention and treatment. In order to monitor and treat complications promptly, regular re-examinations are essential to type 2 diabetic patients [4]. Glycaemic control reduces the risk of

neuropathy, blindness, renal failure and other microvascular complication in type 2 diabetes [3].

EXPERIMENTAL

Study setting and design

A total of 520 type 2 diabetic patients who attended the diabetic clinic at the Medical Outpatient Department of Ahmadu Bello University Teaching Hospital (ABUTH), Shika, Zaria, in northwestern Nigeria were used for the study. Ethical clearance was obtained for the study from the Department of Medicine Ethical Committee of ABUTH (ref no.A374) and the research was conducted according to the International Ethical Guidelines for Biomedical Research Involving Human Subjects prepared by the Council for International Organizations of Medical Sciences (CIOMS) in collaboration with the World Health Organization, Geneva [5].

The patient folders comprising those that failed and those that did not fail treatment with metformin and glibenclamide combination were obtained from the Medical Records Department. Secondary failure was defined as progression to triple oral therapy or a switch from metformin and glibenclamide therapy [6,13]. A total of 276 type 2 diabetic patients were identified to have failed treatment with a combination of metformin and glibenclamide at their maximum doses while 244 type 2 diabetic patients receiving similar drugs but considered responding to treatment were used as the control group.

Classification of patients

The control group (those that did not fail) was classified as group 1 and those that were considered to have failed treatment were classified as group 2. The data collected from patients' folders included age, sex, body mass index (BMI), tribe, duration of therapy and occupation. The glycaemic profile defined as fasting blood sugar and 2 h post prandial glucose level were taken from the patients' folders. Patients with farming, trading and teaching as their occupation were considered as physically active and those that are civil servants, house wives and pensioners were considered physically inactive.

Selection criteria

The criteria used for the selection of the patients included having established type 2 diabetes, and receiving combination of metformin and glibenclamide for a minimum of one year. Others were having a fasting blood sugar level of 7.0 mmol/L and above or a 2 h post prandial (PP) glucose level of 10 mmol/L and above for failed group as well as having a fasting blood glucose level below 7.0 mm/L or 2 h post prandial sugar level below 10.0 mmol/L for group responding to treatment.

Age and sex distribution, plasma sugar concentration (fasting and 2 h PP), ethnic group distribution, anthropometry (body mass index) and patients' occupation of the patients were then studied.

Data analysis

The bio-data collected were processed, coded and analyzed using SPSS version 16 and was presented as mean ± standard deviation. Comparison of means was done using independent sample t-test (continuous variable) while proportions of independent variables was determined using Pearson chi square test (categorical variables). Values of $p < 0.05$ were considered significant.

RESULTS

The mean age of patients studied was 53.22 ± 9.03 years with a range of 30 to 70 years. There was no significant difference between the mean age of males and females. The mean population BMI was 27.0 kg/m^2 with female having significant higher BMI than males. The mean duration of therapy was 6.7 ± 5.08 years (Table 1).

Table 1: Gender differences in age and BMI of the study population

Gender	Age (years) (mean ± SD)	BMI (kg/m^2) (mean ± SD)
Male	54.27 ± 8.78	24.86 ± 3.87
Female	52.52 ± 9.14	28.22 ± 5.28*
Both	53.22 ± 9.03	27.00 ± 5.05

*$p < 0.05$

General characteristics of the study population

Type 2 diabetes mellitus was more commonly diagnosed in people older than 40 years with a peak in people older than 60 years. Females made up 64.6 % of the patients (Table 1). The BMI of 28 kg/m^2 and above is shown to contribute to increased insulin resistance leading to treatment failure. About 40 % of the patients had BMI of 28 kg/m^2 and above. Over 90 % of the patients are older than 40 years and about 61 % of the patients have been on treatment for

Table 2: Frequency distribution of demographic profile of diabetic patients attending the clinic

Parameter	Value	Frequency (N)	%
Sex of patients	Male	184	35.4
	Female	336	64.6
BMI (kg/m^2)	≥28	200	38.5
	<28	320	61.5
Age of patients (yrs)	≥40	488	93.8
	<40	32	6.2
Duration of treatment (yrs)	>4	320	61.5
	≤4	200	38.5
Occupation	Active	116	22.2
	Inactive	404	77.8

more than 4 years (Table 2). About 77 % of the patients have occupations that make them physically inactive.

Of the 520 patients studied, 276 (53.1%) were identified to have failed treatment with combination of metformin and glibenclamide.

Occupational distribution of the patients

Housewives comprised more than half of the population (55.5 %), farmers were the least with only 3 % of the population. Others included civil servants (18.2 %), business persons (8 %), traders (6 %), teachers (5.5 %), and pensioners (4 %).

Ethnic group distribution of the total population

Five major tribes in the study area including Hausa-Fulani (49.2 %), Yoruba (13.8 %), Igbo (5.4 %), Egbira (2.3 %), Idoma (4.6 %) and other minor tribes classified as others (24.6 %) were represented, Hausa-Fulani comprised of about 50 % of the patient's population with Egbira having the least percentage.

Analysis of blood glucose concentration for the two groups of patients

Fasting blood sugar (FBS) and 2 h post prandial (2HR PP) plasma glucose level were used as markers of glycaemic control. The mean FBS and 2HR PP of group 1 was 5.99 and 8.76 mmol/L as shown in Table 3. This is within the normal range and is an indication for good response to treatment. However, the respective values for group 2 are significantly higher than group 1 (Table 3). These higher values of glycaemic indices due to poor plasma glucose control puts the patient at increased risk of diabetic complications.

Table 3: Glycaemic profile for the two groups of patients

Parameter	Group 1 (mean±SD)	Group 2 (mean±SD)
FBS (mmol/L)	5.99 ± 0.67	12.55 ± 4.12*
2HR PP (mmol/L)	8.76 ± 2.19	18.42 ± 5.30*

Group 1: Non failed group, Group 2: Failed group SD = standard deviation, FBS: fasting blood sugar, 2HR PP: 2 hour post prandial blood glucose

Age, duration of therapy and BMI analysis for failed and non-failed groups

The mean age of patients in the failed group was 52.81 ± 9.07 years as against 51.13 ± 7.56 years for non failed group. However, there is no significant difference in the mean age between the two groups as shown in Table 46. No statistically significant difference was found in the duration of treatment between the two groups (Table 4).

The mean BMI for the failed group was 27.48 ± 4.85 kg/m^2 while the non-failed group had a BMI of 23.94 ± 4.16 kg/m^2. This as shown in table 4 is statistically significant ($p < 0.05$).

Table 4: Difference in age, duration of treatment and BMI for failed and non-failed group

Variable	Group 1	Group 2	Population
Age ± SD (years)	51.13 ± 7.56	52.81 ± 9.07	52.49 ± 8.73
BMI ± SD (kg/m^2)	23.94 ± 4.16	27.48 ± 4.85*	26.74 ± 4.14
Duration of treatment ± SD (yr)	7.56 ± 5.29	6.54 ± 5.06	6.73 ± 5.08

Group 1: Non-failed group; Group 2: Failed group; SD = standard deviation

Females in the failed group had significantly higher BMI when compared to males. There is no statistically significant difference between the mean age of Groups 1 and 2.

Occupation of patients with treatment failure

Housewives contributed over 50 % of the patients within the failed group, followed civil servants with 16 %. Farmers, traders and pensioners had the least percentage of 3.7 as shown in figure 1a. However, no relationship was found between occupation of patients and treatment failure ($p > 0.05$).

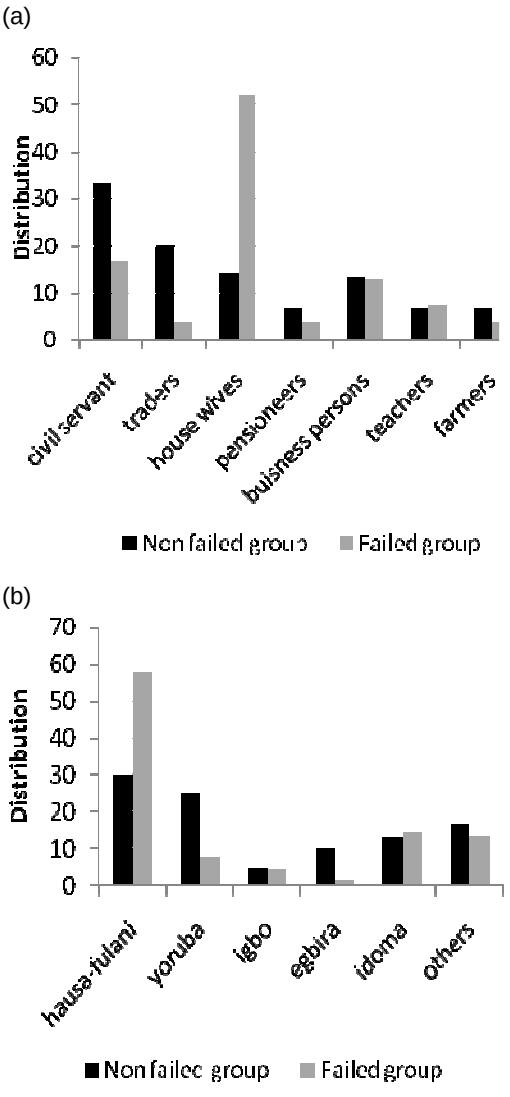

Fig 1: Occupation (a) and tribal (b) distribution of the patients

Tribal distribution of patients with secondary failure

Hausa-Fulani comprised of about 50 % of the failed group as against the 30 % of the non failed group (Figure 1b). The minority tribes contribute up to 24 % of the failed group with Egbira having the least percentage among the failed group.

DISCUSSION

In the present study, we found out that young age at diagnosis, duration of treatment, change in body weight and increased BMI were responsible for the development of secondary failure in diabetes. Most of these factors were reported in a prospective cohort study done by Ishikawa-Takata *et al* [7]. Lack of exercise and physically inactive jobs are established risk factors for the development of treatment failure in type 2 diabetes [8].

Pearson *et al* [8] in an investigation identified pharmacogenetics as a possible cause of treatment failure in diabetes, which affects patients' response to anti-diabetic agents. Genetic variation in Transcription Factor 7 Like-2 (TF7L-2) was shown by Pearson *et al* [9] to result in clinically significant difference in the therapeutic response to sulphonylurea leading to treatment failure in some type 2 diabetes patients. Retman and Schadt [10] have identified a variant gene for Organic cation transporter-1 (OCT-1) in patients that failed to respond to treatment with metformin. OCT-1 is an enzyme responsible for metformin entry into hepatocytes and enterocytes, thus reducing the amount of metformin that ultimately reaches the site of action [11].

In the present work, the patient parameters that were studied are age and sex distribution, duration of therapy, BMI, tribe and occupation of patients. The mean age of the whole population is within the normal age for diabetic patients. No significant difference was found in age and duration of therapy between group that failed and those responding to treatment. This finding is not in agreement with the findings of Sesti *et al* [12] where they showed relationship between age and duration of treatment with treatment failure. This could be as a result of the fewer number of patients used in this study as compared to the earlier work.

Although 64.6 % of the patients in the failed group were females, there was no relationship found between sex and treatment failure. This was in consistence with the result of Eurich *et al* [13], where they also found no relationship between sex and secondary failure.

BMI is a measure of total body mass particularly the fat deposit. Higher BMI has been implicated in the development of both type 2 diabetes and secondary failure during treatment [12]. Patients with higher BMI above 28 kg/m^2 are shown to be at increased risk of developing secondary failure [8]. The analysis of BMI carried out revealed that the group with secondary failure has significantly higher BMI than those responding to treatment. This is in agreement with the work of Sesti *et al* [12]. Within the failed group, females had significantly higher BMI than males. Since there was no relationship between sex and secondary failure, the possible explanation to this finding could be due to the fact that females, generally, have higher fat deposit than their male counterpart. Furthermore, they live more sedentary life style as they usually stay at home and are not very active [14].

Although Hausa-Fulani tribe contributed a significant percentage of the failed group, there was no sufficient evidence to suggest relationship between tribe and treatment failure. The explanation for the large percentage of this tribe in the failed group may be due to the fact that Hausa-Fulani is the dominant tribe in the study area.

Earlier studies have shown relationship between physical activity and treatment failure [8]. Exercise and occupation with physical activity is shown to increase insulin sensitivity and reduce the progression of pancreatic β-cell function deterioration [15]. Similarly, sedentary life style or occupations that are not physically active are shown to increase risk of developing secondary failure in diabetic patients.

The findings that house wives and civil servants which are considered to be physically inactive constitute over 60 % of the failed group could relate occupation and treatment failure. However, no association was found between occupation and treatment failure in these patients.

Limitations of the study

Some of the patients who were considered to be physically active or inactive based on their occupation might in few cases be the opposite. Furthermore, the presence of other disease conditions which could have contributed to treatment failure were not considered during selection of subjects.

CONCLUSION

Progressive deterioration in pancreatic β-cell function, BMI greater > 28 kg/m^2, and advancing age are identified in this study identified as possible contributory factors to the development of secondary failure in type 2 diabetes.

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