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Patterns of drug use among type 2 diabetic patients with comorbidities attending a tertiary centre in Lagos, Nigeria

ABSTRACT

Background. Diabetes care involves the use of drugs to control hyperglycaemia and the treatment of comorbid disorders to prevent cardiovascular morbidity and other complications. This study investigated patterns of comorbidities and drug use among diabetic patients at a tertiary centre in Lagos, Nigeria.

Methods. This was a cross-sectional study carried out among 216 patients with type 2 DM attending the Diabetes Clinic of a tertiary centre. Data was captured by using a questionnaire that documented biodata, number of comorbidities, number and combination of drugs for each participant and analysed using SPSS version 18.

Results. Comorbidities were present among 215 out of 216 (99.54%) participants and hypertension and dyslipidaemia were the most common comorbid disorders. The number of pills consumed per patient ranged from 1 to10 with a mean of 4.78 ± 1.73 and 57.4% were on 5 pills or more. A fixed-dose combination was used in 37 (17.1%) of the patients. The majority of the patients were on metformin as monotherapy or in combination therapy. Antihypertensive most prescribed were renin-angiotensin system (RAS) blockers which were prescribed in 73% of participants. Antiplatelet drugs were used for both primary and secondary prevention of CVDs. Statin was used in less than 50% of the population. Double RAS blockade was also observed in 6% of participants.

Conclusions. Comorbidities were common in the diabetic population. Pill load was high but appropriate in most patients. Statin uptake was suboptimal while there was increased uptake of antiplatelet drugs among participants. (Clin Diabetol 2021; 10; 4: 342–348)

Key words: diabetes mellitus, comorbidities, antidiabetic drugs, type 2 DM, antihypertensive drugs

Introduction

Type 2 Diabetes mellitus (T2DM) is one of the most common cardiovascular risk factors and is associated with high morbidity and mortality globally. It is a chronic disease characterized by relative or/and absolute insulin deficiency and insulin insensitivity which results in deficient metabolism of carbohydrate, protein, and lipids [1]. International Diabetes Federation (IDF) 2019 reported Diabetes prevalence in Nigeria as 3%, but this is probably underestimated because a systematic review by Uloko and colleagues published in 2018 found the prevalence of DM in Nigeria to be 5.77% [2, 3].

The complications arising from diabetes mellitus (DM) are major contributors to increased hospitalization and mortality. Complications from DM include atherosclerotic cardiovascular diseases such as coronary

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heart disease, cerebrovascular disease, or peripheral arterial disease (PAD) presumed to be of atherosclerotic origin and microvascular complications such as chronic kidney disease, retinopathy, and neuropathy [4]. Appropriate management of DM helps to prevent these complications.

The management of DM addresses glycaemic control and the prevention and management of complications. It also involves the treatment of comorbid cardiovascular risk factors like hypertension, dyslipidaemia, obesity [4, 5]. Consequently, patients with DM often require a relatively high number of drugs to achieve therapeutic goals.

The high pill load among this population calls for caution because of the increased risk of drug-drug interactions and drug-disease interaction which may lead to reduced drug efficacy or adverse drug effects especially in the elderly [6]. This is a result of declining organ function and multiple comorbid conditions that occurs with ageing. Furthermore, the prevalence of DM is disproportionately higher in the older population because of increasing life expectancy especially in developing countries and this emphasises the need to address drug use patterns among individuals with diabetes. Increased mortality in hospitalised elderly patients has been associated with drug reactions [7]. Therefore, the use of appropriate drug therapy is imperative in diabetic care.

Evidence-based guidelines have been developed to optimize treatment outcome and improve the quality of care among patients with DM. These guidelines provide recommendations for managing hyperglycaemia as well as the management of comorbidities and complications. Guidelines used in DM care include publications from the International Diabetes Federation (IDF), the American Diabetes Association (ADA), the American Association of Clinical Endocrinologists (AACE) and the Diabetes Association of Nigeria (DAN) [2, 4, 5, 8]. Studies have shown gaps in implementing guidelines in the management of patients with chronic diseases [9, 10].

Most studies have evaluated the use of glucose-lowering drugs among persons with DM, with little attention paid to the management of comorbid conditions among this population. Poor management of comorbidities and inappropriate drug combinations may obliterate the gains from glycaemic control. Therefore, it is important to evaluate the presence and treatment of comorbidities to improve clinical outcome in Diabetic care. This study investigated comorbidities and assessed the pattern of drug use concerning the presence of comorbid disorders in out-patient Type 2 diabetic patients.

Material and methods

Study site

The study was conducted at the diabetes out-patient clinic of the Department of Medicine, Lagos University Teaching Hospital (LUTH).

Study design

This was a cross-sectional study carried out among patients with type 2 DM for three months after obtaining approval from the LUTH Health Research Ethics committee. A total of 216 patients who consented were included in the study.

Inclusion criteria were men and women aged 18 years and above with a diagnosis of type 2 diabetes mellitus (T2DM). Exclusion criteria are Type 1 diabetic and gestational diabetes. Questionnaires were administered by Medical House officers, who were blinded to the aims of the study. Patients were interviewed using a standard questionnaire and case notes were used to corroborate medications orders. Data was collected for demographic details (names, age, and sex of patients), diagnosis and comorbidities. The comorbidities assessed in this study include hypertension, dyslipidaemia, obesity, diabetes mellitus foot syndrome (DMFS), chronic kidney disease (CKD) and stroke. These comorbidities were ascertained based on patients' report or a diagnosis of the specific comorbidity in the case note. The prescribed drug, including the branded and generic name of all drugs used by patients (both prescription and non-prescription drugs), dose, dose frequency and route of administration were also recorded. Data were analysed using IBM SPSS version -18. Data were presented as frequencies, percentages, mean and standard deviation.

Results

A total of 216 patients between the ages of 34 to 89 years were recruited for the study. The duration of DM ranged from 1-46 years. At least one comorbidity was present in 99.54% of the population. Other demographic and comorbidity patterns are shown in Table 1.

Patterns of drug use

The number of pills consumed per patient was from 1 to10 with a mean of 4.78 ± 1.73 (Fig.1). The majority (57.4%) were on 5 pills or more. A fixed-dose combination was used in 37 (17.1%) of the patients.

Drugs commonly used are represented in figure 2 below. Antidiabetic was used by 215 out of 216 diabetic patients, one patient was on dietary therapy. A total of 167 (77.31%) patients were on antihypertensive drugs against 153(70.8%) patients who reported hypertension. Statins were utilized in 116 (53.7%) of the

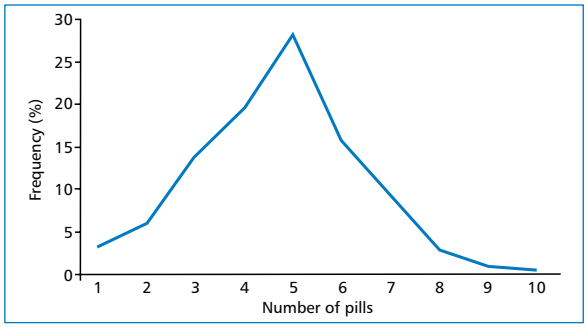

Figure 1. Pill count among participants

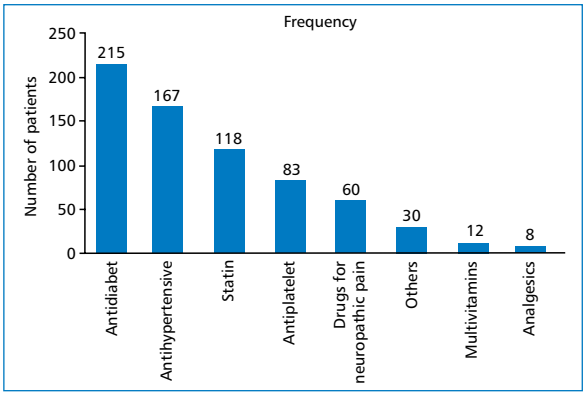

Figure 2. Classes of drug use among participants

participants whereas a total of 106 (49.1%) patients reported dyslipidaemia.

Other drugs such as antacids, sildenafil, antiviral drugs, proton pump inhibitors, tamsulosin, antifungal, steroids and antiandrogen were used in less than 14%. Analgesics include tramadol, didydrocodeine and diclofenac, celecoxib. This is shown in figure 1.

Sulphonylureas (SU) used were long-acting glibenclamide, and glimepiride and short-acting gliclazide. Dipeptidyl peptidase-4 (DPP4) inhibitors included vildagliptin, sitagliptin, linagliptin. Glucagon-like peptide-1 (GLP-1) receptor agonists used was liraglutide while the only thiazolidinedione used was pioglitazone (See supplementary Table 1).

An inappropriate combination of two drugs from the sulphonylurea class was observed in 3 patients and double RAS blockade was also observed in about 13 (5%) patients (see supplementary Tables 1 and 2).

Discussion

The study represented a population of type 2 diabetes mellitus in a tertiary health centre, the majority of the patients were 40 years and above and comorbidities were common. Hypertension and dyslipidaemia were the most common comorbid conditions seen in the population. This study findings are similar to that of a multicentre study in sub-Saharan Africa which reported high rates of comorbid conditions, hypertension was the most common which was reported in 71% of the population. This was followed by dyslipidaemia which was observed in 34% [11].

The study shows that the pill load among participants was quite high, the majority (57.4%) of the participants were on 5 or more pills. This agrees with previous reports of a high drug burden among indi-

Table 1. Demography and comorbidity patterns

Parameter	n	%
Age (years)		
34–39	6	2.8
40–59	157	72.7
60 and above	53	24.5
Gender		
Male	87	40.3
Female	129	59.7
Level of education		
None	11	5.1
Primary	37	17.1
Secondary	69	31.9
Tertiary	99	45.9
Duration of diabetes mellitus in years		
Less than 10	104	48.1
10–19	78	26.2
20 and above	34	15.7
Number of comorbidities		
0	1	0.46
1	1	0.46
2	7	3.24
3	56	25.93
4	91	42.13
5	60	27.78
Comorbidities		
Hypertension	153	70.8
Chronic kidney disease	15	6.9
Stroke	17	7.9
Obesity	68	31.5
Dyslipidaemia	106	49.1
DMFS	27	12.5

Table 2. Antidiabetic drug use among study participants

Drug Class	n	%
Biguanide (Metformin)	183	84.7
Sulphonylurea	113	52.3
Glibenclamide	8	3.6
Glimepiride	70	31.8
Gliclazide	35	15.9
Insulin analogues	54	25
DPP4I	47	21.8
Thiazolidinediones	7	3.2
GLP-1 receptor analogue	2	0.9
No of drugs		
One	63	29.0
Two	106	48.8
Three	31	14.1
Four	2	0.9

DPP4I: dipeptidyl peptidase-4 inhibitors; SU: sulphonylureas; GLP: glucagon-like peptide-1 (GLP-1) receptor agonists

Table 3. Antihypertensive use pattern among participants

Drug Class	n	%
CCB	87	40.3
ACEI	78	36.1
ARB	58	26.9
Diuretics	68	31.5
BB	25	11.6
ALPHA AGO	2	0.9
No of drugs		
One	79	36.6
Two	59	27.3
Three	27	12.5
Four	10	4.6
Seven	1	0.5

CCB: calcium channel blockers; ACEI: angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; BB: beta-blockers; ALPHA AGO: and centrally acting alpha agonists. Two diuretics include combinations of indapamide + frusemide, hydrochlorthiazide + frusemide, spironolactone + torsemide and hydrochlorthiazide + spironolactone

viduals with T2DM [12–14]. The use of a high number of drugs has been associated with the presence of multi-morbidities among diabetes patients [15]. Multi-morbidities in DM may occur from the presence of other co-morbid cardiovascular risk factors and/or complications of DM.

Generally, the concomitant use of several drugs in a patient which is termed polypharmacy is discouraged because of the increased risk of drug-related problems such as poor drug adherence, drug-drug interaction, drug-disease interaction, adverse effects, and increased cost of medications [16]. Most studies have used an arbitrary number of five drugs to define polypharmacy and have described the use of five or more drugs as irrational drug use. While the fear of polypharmacy is rational, it has been recommended that rational drug use should be judged based on the appropriateness of therapy rather than an absolute pill count [17].

Although the population studied are on polypharmacy, the drug use pattern appears to be appropriate for the majority of the patients in this study. The use of fewer than five drugs in this population may result in under-treatment because the majority of the patients had co-morbid diseases.

The classes of drugs used in this study correlate with the patterns of co-morbidity seen in the population (Fig. 1). The most commonly prescribed antidiabetic drug in the study was metformin, which was used in two-thirds of the patients on monotherapy and in over 90% of the patients on polytherapy (Table 3). This is in line with the DAN, AACE/ACE and ADA guidelines that recommend the use of metformin as the first-line drug and as add-on therapy in those who need a second antidiabetic drug in type 2 DM provided there is no contraindication to the use of metformin [4, 5, 8]. Metformin is effective in lowering HBA1C, weight and showed reduced CVS mortality compared to SU [18].

Other studies have also reported a preference for metformin as a first-line drug and also used frequently in combination therapy [19]. The use of DPP4I and alpha-glucosidase inhibitors as preferred first-line drugs have been documented in other regions for instance a study reported the use of alpha-glucosidase inhibitors in Beijing, China [20].

SUs were the second most prescribed drugs either in monotherapy or in combination with other drugs. This pattern has been described in other studies in Nigeria [21]. The most used SU in this study was glimepiride with a relatively shorter half-life compared to glibenclamide. This conflicts with previous reports of a high uptake of glibenclamide which has a long half-life [22]. SU with shorter half-lives are associated with a lower incidence of hypoglycaemia and are therefore preferred especially in the elderly who are more prone to hypoglycaemia.

Other drug classes used among participants in this study include insulin analogues in 25%, DPP4I in 21.8%, GLP-1 agonist in 0.5%, and thiazolidinedione in 0.5%. ADA guidelines recommend the early introduction of insulin in patients with glycated HB above

Table 4. Statin and antiplatelet use among participants

Drug	n	%
Statin use	**118**	**54.6**
High-Intensity Statin	14	6.5
Medium Intensity Statin	92	42.6
Low-Intensity Statin	2	0.9
Antiplatelet	**82**	**38**
Clopidogrel	11	5.1
Aspirin	71	32.9

Statins used include atorvastatin, rosuvastatin and simvastatin

10% to reduce cardiovascular morbidity [4] AACE on the other hand recommended the addition of insulin when HbA1c is above 9% with symptoms [5]. The high rate of insulin use observed in this study may reflect higher baseline HBA1c or more advanced B-islet cell failure in the population. An increasing trend towards the use of DPP4I was also observed and may be due to its lower risk of hypoglycaemia and weight naïve effect compared to SU [21, 22].

Overall, antidiabetic drug use in this population complies with available guidelines, although the prescription was limited to four classes of antidiabetic drugs. This may be related to tolerability, cost, availability, and physician's preference. Consideration for drugs classes like SGLT is important because of its benefit in patients with heart failure [4].

Antihypertensive drugs were used in 79.2 % of the population. This is disproportionately higher compared to the number who had hypertension. The higher rates may be attributed to the use of these drugs in other conditions, for example, ACEI or ARB are used in the management of proteinuria and beta-blockers in arrhythmias. Drugs used in monotherapy include calcium channel blockers (CCB), angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), diuretics and beta-blockers (BB). The use of CCB and thiazide diuretics as initial monotherapy follows the JNC 8 guideline which recommends the use of CCB and thiazide diuretics as first-line agents in black diabetic patients with co-morbid hypertension. This is because these classes of drugs have been associated with a more favourable cardiovascular outcome when compared to other classes of hypertensive drugs among blacks with DM [22]. Other guidelines have however recommended the use of ACEI or ARB as the preferred first-line in diabetics because of the protective effect on nephropathy and retinopathy [4, 5, 8]. A large proportion of the participants are on either ACEI or ARB. Further comparative study on antihypertensive drugs is needed to provide robust evidence guiding the use of the first-line antihypertensive drug in blacks with DM.

An inappropriate combination of antihypertensive was observed in the participants and was associated with polypills. About 6% were on double RAS blockade. Initially, dual angiotensin blockade was advocated because the combination was shown to improve proteinuria compared to a single agent from either class but recent evidence from randomised controlled trials showed higher risks of adverse effects like hyperkalaemia and declining renal function [24, 25]. As a result, the use of double RAS blockade in hypertension is no longer recommended [24]. A regular review of the medication is important to correct such practices even though many of these patients attend multiple clinics (nephrology, cardiology, and neurology) due to their co-morbid states.

Statins are indicated for the treatment of dyslipidaemia and the prevention of macrovascular complications in patients with DM [4, 5, 8]. The ADA recommends the use of statin in all patients between 40 - 75 years irrespective of CVS risk and levels of cholesterol whereas statin use is recommended in the other guidelines based on risk stratification and cholesterol goals [5, 8]. There is a uniform consensus on the use of high-intensity statins for secondary prevention of atherosclerotic cardiovascular disease (ASCVD).

In this study, only 54.6% of the participants were on statin, of these only 6.5% were on a high-intensity statin. This appears low considering that 49.1% had dyslipidaemia, 7.9% had a stroke and 12.5% had diabetes mellitus foot syndrome. DMFS may also suggest ASCVD because the condition occurs secondary to atherosclerotic peripheral vascular disease, peripheral neuropathy and infections. Presented findings suggest that statins were prescribed in patients who had dyslipidaemia and ASCVD. Comparing with the ADA guideline, statin uptake is low since more than 95% of the population were 40 years and above. Low statin uptake has been reported in other studies, a study evaluating statin use among high-risk patients showed only about half of the patients 47.5% were on statin therapy [26].

Antiplatelet therapy using aspirin at a dose of 75–162 mg/day is recommended for the secondary prevention of ASCVD in DM patients with a history of atherosclerotic cardiovascular disease [4]. Clopidogrel is recommended in patients with aspirin allergy [4]. There is no uniform consensus on the use of antiplatelet in primary ASCVD prevention. Antiplatelet drugs were used in 38% of the population and this is disproportionally high compared to ASCVD prevalence. The number of patients on antiplatelet exceeds the number of

participants with stroke and DMFS. This suggests that antiplatelet were used in both secondary and primary prevention of ASCVD. Risk stratification and discussion with the patient is advised or essential if aspirin is considered for primary prevention [4].

Pregabalin and gabapentin were used in about a tenth of the population for the treatment of neuropathic pain. The pattern of drug treatment largely complies with the ADA guideline which recommends the use of pregabalin, gabapentin and duloxetine for treating neuropathic pain in DM (ADA) [4]. A few patients were on nutritional supplements, supplements are not recommended unless there are specific indications [4].

Although several studies have been carried out on drug use in diabetes, most of these only documented the use of antidiabetic or antihypertensive drugs, to the best of the authors' knowledge, this study is one of the few studies that investigated all drug classes used in DM patients. It has been identified that a high drug load was appropriate in the majority of the patients.

Conclusion

This study reported comorbidities and drug use pattern among diabetic patients and a tendency to use a large number of drugs which is appropriate because of the presence of co-morbid conditions. It also identified inappropriate drug combination patterns. There is a need to continue regular review of medications to optimize patient care.

Conflict of interest

The authors report no competing interests.

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