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DRUG RELATED PROBLEMS IN TYPE 2 DIABETIC PATIENTS WITH TUBERCULOSIS: A PROSPECTIVE STUDY

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ABSTRACT

Background and aim: Tuberculosis (TB) and diabetes mellitus (DM) are leading causes of morbidity and mortality in Nigeria. Patients with both diseases are often required to take multiple medications which increases the risks of developing drug-related problems (DRPs). This study aimed to identify and resolve DRPs encountered by TB and DM patients under a collaborative care model.
Methods: A prospective, observational study involving 52 TB and DM patients in two secondary care chest clinics in Lagos State, South-west Nigeria was carried out. Identification and classification of DRPs were based on the Pharmaceutical Care Network Europe classification version 7-0, and data statistically analysed. Number of DRPs were presented as frequencies and percentages. A bivariate logistic regression analysis identified determinants of DRPs at a statistical significance of $P \leqslant 0.05$.

Results: A total of 86 DRPs were reported in the study, averaging 1.5 DRP per patient. Adverse drug events (73.1%), untreated indications (46.2%) and suboptimal treatment (44.2%) were most commonly identified. Main causes were insufficient awareness of disease state (55.7%), new indications (46.2%), and wrong administration of medications (44.2%). Interventions carried out were accepted at patient (100%), prescriber (76.9%) and drug levels (46.2%). Sixty-three and half percent (63.5%) were accepted and fully implemented. DRPs were totally solved in 63.5% of instances. There were no significant association between patients' sociodemographic data and occurrence of DRPs ($P>0.05$).

Conclusion: The presence of DRPs in TB-DM patients is substantial. Early detection, patient education and prompt resolution will promote safe, effective and optimal treatment outcomes in TB-DM patients.

Key words: Tuberculosis, diabetes mellitus, tuberculosis and diabetes patients, drug-related problems, Nigeria

INTRODUCTION

According to the World Health Organisation and International Union against Tuberculosis and Lung Diseases' collaborative framework for care and control of tuberculosis (TB) and diabetes mellitus (DM), the increasing burden of DM contributes to sustained high levels of TB globally [1]. In 2019, about 463 million people were living with DM, this is estimated to increase to 578 and 700 million in 2030 and 2045, respectively [2]. Consequently, the proportion of TB cases attributable to diabetes globally is likely to increase. Both TB infection and DM are major global public health diseases and their co-morbidity is associated with significant morbidity and mortality, mutual negative interactions and exacerbations, as well as high pill burden from the use of multiple medications in their respective managements [1, 3]. About 10 million people are infected with TB disease annually, leading to an estimated 1.4 million deaths [4]. The International Diabetes Federation reports that 80% of people living with DM reside in low- and middle-income countries, Nigeria inclusive, where TB burden is predominant [5].

Multiple medications by patients (polypharmacy), is associated with an increased likelihood of developing drug-related problems (DRPs) [6]. DRPs occur when a patient experience, or is likely to experience a medical condition having an actual or suspected relationship with drug therapy. A drug-related problem is defined as an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes in patients [7]. Among the most common DRPs are: adverse drug reactions, adverse drug events, drug choice problem, dosing problem, drug-use problem and interactions [8]. DRPs are very common and may result in suboptimal treatment, increased morbidity and high health care costs, therapeutic failures or delays in achieving desired therapeutic outcomes. There are also the risks of increased hospital admission rates and unnecessary over prescription of drugs, or even occasional death [9, 10, 11]. It is important that DRPs are classified accordingly and prompt interventions given in order for patients to achieve desired therapeutic outcomes in the management of disease. Studies carried out in different countries reported the presence of DRPs in diabetic [11, 12, 13] as well as TB patients [12, 14, 15]. Commonly reported DRPs from these studies found in TB patients include drug-drug interactions, non-adherence and adverse drug reaction, while dosage and drug choice problems, untreated indications, and sub optimal treatment were reported for diabetic patients. However, there is paucity of data on the occurrence and presentation of DRPs when these two co-morbidities are present in a single patient. This study, thus set out to assess the occurrence and presentation of DRPs in TB patients who also have co-morbid DM, otherwise known as TB-DM patients. The specific objective of the study was to identify and resolve DRPs encountered by TB-DM patients when they are managed under a collaborative health care model.

METHODS

Study design setting: This study was a prospective observational study, carried out among patients with TB and DM co-morbidity (TB-DM), between June 2015 and January 2017, who were part of a larger study which evaluated drug-related management and TB treatment outcomes among TB and TB-DM patients in a collaborative health care model in Lagos State [16] located in South-West Nigeria. Although the smallest

State in Nigeria created in 1967, it has the highest urban population, home to about 24.6 million people and serves as the commercial nerve centre of the country [17]. The patients were registered in two chest clinics located on the Mainland and Island areas in the State. The two clinics run established Directly Observed Treatment, Short Course (DOTS) services and serve as both treatment and referral centers for diagnosed TB patients.

Study participants: The sample size for Cross‑Sectional, Cohort, and Randomised Clinical Trials at 95% confidence interval which was used to calculate the sample size for the larger study gave a sample size of 619 TB only and 52 TB-DM patients [16]. Thus, this present study included a total of fifty-two (52) TB-DM patients undergoing TB treatment. All the patients started TB treatment after diagnosis and were managed under DOTS therapy for TB. This consisted of fixed dose combinations (FDC) of a 2-month, initial phase, daily supervised combination of four drugs- Rifampicin (R), Isoniazid (H), Ethambutol (E) and Pyrazinamide (Z), followed by a 4-month, continuation phase (CP), comprising two drugs Rifampicin and Isoniazid (RH). The treatment regimen is commonly depicted as (2RHZE/4RH) [18]. The patients were also taking anti-diabetic medications which included either insulin, metformin, glimepiride and/or gliclazide.

Inclusion criteria into the study were newly diagnosed TB patients with or without previously diagnosed DM, aged 18 years and above, while TB patients less than 18 years of age, with known or suspected MDR‑TB cases and patients diagnosed with any disease condition other than TB and DM were excluded from the study.

Study procedure: Socio-demographic and clinical data for all patients were collected at first visit with the aid of pre-tested structured questionnaires and recorded. In addition to the procedures carried out in the larger study, the patients were evaluated for DRPs using the Pharmaceutical Care Network Europe (PCNE) Classification for drug related problems V 7.0 [8] during their first and subsequent visits. The basic classification of this tool consists of five sections: 3 primary domains for Problems encountered during the course of therapy, 8 primary domains for their causes, 5 primary domains for interventions made, 3 domains for acceptance of the intervention proposals, and 4 domains for status of the DRP after intervention.

Each patient received an assessment of all of their medications (anti-tuberculosis, antidiabetic, alternative, nutritional supplements), adherence to medications, symptoms, blood glucose monitoring, and adverse effects of treatment to determine the presence of DRPs. DRPs were identified as either sub optimal treatment– when the dose, dosing or duration of patient's medications were inadequate; untreated indication – when the patient had a medical condition that was not being treated or managed with any medication, no effect of drug treatment-when the patients' symptoms and blood glucose levels were not normalized with treatment; and adverse drug event – when patients had side or adverse effects of therapy.

When DRPs were identified, the types and their causes were noted and recorded in data collection forms modelled after PCNE V 7.0. The type of intervention administered per patient were also recorded – either at patient, prescriber, or at drug level. At patient level, patients and their families/ caregivers were counselled and educated about their disease, dosage of medications prescribed, adherence to medications, and the cause/s of the DRPs. A written information leaflet was deployed to this effect and given to them at the end of the counselling session. At prescriber level,

patients were referred back to the prescriber with recommendations to amend dosages, start new medications, add another medication to the patient's regimen where fasting blood glucose remains high, and schedule the diabetic patient for endocrinology clinic attendance. At drug level, changes made by the prescriber were initiated. Patients returned for monthly follow-up visits all through the six-month duration of TB treatment where resolution or reduction in levels of all encountered DRPs were determined. At the end of the six-month TB treatment, the intervention done, frequency of acceptance of intervention administered, and actual outcomes of identified DRPs experienced by the patients were determined and recorded.

Statistical analysis: Data from this study were analyzed using the IBM Statistical Product for Services Solution (SPSS) Statistics for Windows, Version 23.0 (IBM Corp, Version 23.0, Armonk, NY, USA). Descriptive statistics were used to summarise data. The number of DRPs and other categorical data encountered were presented as frequencies and percentages while continuous data were expressed as mean ± standard deviation.

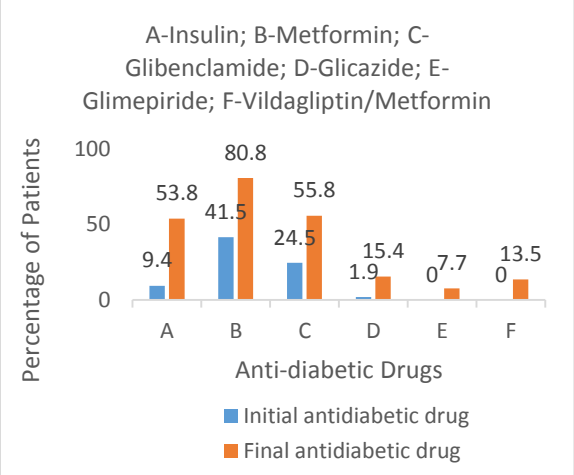
Ethical approval: Ethical approval for the study was obtained from the Health Research and Ethics Committee of Lagos University Teaching Hospital, LUTH (ADM/DCST/HREC/APP/665). Administrative approval was also obtained from Lagos State Health Service Commission (SHMB/728/Vol VI/). Recruited patients were required to fill an informed consent form, the contents of which were treated confidentially and anonymously.

RESULTSCharacteristics of Study Participants: A total of 52 patients with TB-DM co-morbidity participated in this study. Table 1 presents the socio- and clinical characteristics of respondents. Among the study participants, more than half, 28 (53.8%) were females with mean age 51.4±9.8 years. Majority of the participants, 29 (55.8%) were self-employed.

Clinical characteristics of respondents revealed that majority, 28 (53.8%) were known diabetics, while 24 (46.2%) were newly diagnosed at the onset of TB treatment. About a quarter, 15 (28.8%) had family history of DM. Majority of them, 29 (55.8%) were normal weighted while a quarter 13 (25%) were overweight. Also, slightly less than half of the respondents, 24 (46.2%) had hypertension. Mean random and fasting blood glucose were higher than normal (RBG > 200 mg/dL; FBG > 126 mg/dL).

Antidiabetic medications: Over 40% of study respondents were initially prescribed metformin at TB treatment initiation. Other antidiabetic medications initially prescribed were insulin, gliclazide and glibenclamide (Fig 1). At completion of TB treatment, the use of metformin about doubled, and that of insulin increased almost six-fold as over 80% and 50% of participants, respectively were placed on these therapies. Newer additions were vildagliptin-metformin and glimepiride (Fig. 1).

Figure 1: Antidiabetic medications prescribed



Characteristics	Sub-group	N (52)	Frequency (%)
Gender	Female	28	53.8
	Male	24	46.2
Age	< 40 years	4	7.7
	40-49 years	17	32.7
	50-59 years	20	38.5
	≥ 60 years	11	21.2
Status of Diabetes diagnosis	New	24	46.2
	Known	28	53.8
Family history of DM	Yes	15	28.8
Family history of TB	Yes	5	9.6
BMI	<18.5 (under-weight)	9	17.3
	18.5-24.99 (normal)	29	55.8
	25-29.9 (over weight)	13	25.0
	≥30 (obesity)	1	1.9
BP (mmHg)	Hypertension (≥140/90: SBP/DBP)	24	46.2
RBG (mg/dL)	Mean±SD	318.8±90.6	
FBG (mg/dL)	Mean±SD	207.4±80.3	

Table 1: Patients' socio-demographic and clinical and characteristics treatment initiation and completion

Identified Drug-Related Problems and causes in Study Participants:

In this study, a total of 86 DRPs with 100 causes were reported. DRPs were classified under two domains: Treatment effectiveness and Adverse drug event (Table 2). Treatment effectiveness was further divided into three sub-domains: untreated indication had the highest occurrence (46.2%), closely followed by sub-optimal treatment (44.2%) and no effect of drug treatment (1.9%). Adverse drug event accounted for 73.1% of DRPs.

The causes of DRPs were divided into five domains: Drug selection, dose selection, drug use/process, patient related causes and others. Insufficient awareness of disease state was the most common cause of DRP, with over half of the respondents (55.7%) in that category. This was followed by new indications that needed to be treated (46.2%) and wrong administration of medications (44.2%). Other causes were infrequent dosage regimen (13.5%), inability of patient to afford medications (9.6%), inappropriate timing of medications (9.6%), duplication of therapy (7.7%), forgetfulness on patient's part (1.9%), under administration of medications (1.9%) and no obvious cause (1.9%).

Interventions, acceptance of interventions and Status of Drug-Related Problems:

All patients were counselled and educated on disease and drug use and given written information to aid remembrance and facilitate implementation of what was learnt (100%) as depicted in Table 3. Participants with care-givers /family members were also educated (15.4%). Most patients (76.9%) were referred back to the prescriber where new drugs were prescribed (46.2%), some instructions for administration changed (15.4%) and one patient had dosages changed (1.9%). The acceptance and implementation of interventions made were also presented in Table 3. Interventions were accepted and fully implemented in most participants (63.5%), with a few (13.5%) partially implemented. Few cases were not implemented (11.5%) while some implementations were unaccounted for (11.5%).

With most TB-DM patients in this study having DRPs, over half (57.7%) were resolved. A quarter of the participants (25%) were uncooperative and some interventions were not effective (1.9%) hence, there was no resolution made. Few were partially resolved (11.5%) and the status of DRP for others was unknown.

Factors associated with occurrence of drug-related problems:

Evaluation of factors associated with occurrence of DRP in a bivariate analysis did not reveal any significant association between socio-demographic characteristics and presence of DRP ($P > 0.05$).

Table 2: Problems associated with drug therapy among TB-DM patients and their causes

Variable	Domain	Sub-domain	n (52)	Percentage (%)
DRP	Treatment effectiveness	Sub optimal treatment	23	44.2
		Untreated indication	24	46.2
		No effect of drug treatment	1	1.9
	Adverse drug event	Adverse drug event	38	73.1
		Total DRPs	86	
Causes	Drug selection	Inappropriate duplication of therapeutic group	4	7.7
		New indication for drug treatment presented	24	46.2
	Dose selection	Dosage regimen not frequent enough	7	13.5
	Drug use/process	Inappropriate timing of administration	5	9.6
		Drug under-administered	1	1.9
	Patient related	Patient administers drug in a wrong way	23	44.2
		Patient forgets to take drugs	1	1.9
		Patient cannot afford drug	5	9.6
	Other	Insufficient awareness of disease state	29	55.7

	No obvious cause	1	1.9
	Total causes	100	

Table 3: Interventions, frequency of acceptance of interventions and status of drug-related problems

DRP	Domain	Sub-domain	n (52)	Percent (%)
Interventions	**At patient level**	Patient counselling	52	100
		Written information provided	52	100
		Spoken to family member/ caregiver	8	15.4
		Patient referred to prescriber	40	76.9
	At prescriber level			
	At drug level	New drug started	24	46.2
		Dosages changed	1	1.9
		Instructions for use changed	8	15.4
Interventions accepted		Interventions accepted and fully implemented	33	63.5
		Interventions accepted and partially implemented	7	13.5
		Interventions accepted but not implemented	6	11.5
		Interventions accepted; implementations unknown	6	11.5
Status of DRP		Problem totally solved	30	57.7
		Problem partially solved	6	11.5
		Problem not solved, lack of co-operation of patient	13	25.0
		Problem not solved, intervention not effective	1	1.9
		Problem status unknown	2	3.8

DISCUSSION

This study set out to identify and resolve the occurrence of DRPs in TB patients who also have co-morbid DM in two chest clinics in Lagos State, Nigeria. A total of 86 DRPs were identified in the study. Majority of reported DRPs were the occurrence of adverse drug events (ADEs), untreated indications and sub-optimal treatment. The most common causes of DRPs were patient and drug selection related, thus, most interventions were carried out at patient and prescriber levels. At the end of the study, over sixty percent of the interventions done were accepted, fully implemented, and DRPs resolved.

More than three quarters (77%) of respondents in this study reported at least one DRP. This averaged 1.5 DRP per patient. No study till date has evaluated DRPs in TB-DM patients in our setting, making this study, to the best of our knowledge, the first investigation. However, two studies conducted among DM patients with co-morbid hypertension in Indonesia and Southwest Ethiopia reported mean DRPs of 2.88 and 1.65, respectively [13,19]. Other studies conducted among type 2 DM patients only in eastern Ethiopia reported at least one

DRP among respondents [12, 20]. The lower proportion of respondents reporting at least a DRP and the average number of DRP per patient in our study could have been as a result of different population of respondents, different co-morbidities presented by the patients and the collaborative health care offered to TB-DM patients in this study where they had access to care from the TB clinic, the endocrinology clinic as well as pharmacists' care [16]. Reported ADEs (73.1%) could have occurred as a result of use of anti-tuberculosis medications alone, or the concomitant use of anti-tuberculosis and antidiabetic medications by patients, and the attendant drug-drug interactions. A Brazilian study by Lopez et al [15] reported that 69.5% of DRPs recorded among TB patients were caused by safety issues in anti-tuberculous drugs. ADEs, directly or not directly related to medication use, could result in increased morbidity and affect therapeutic outcomes [21]. The proportion of untreated indications in our study (46.2%) was higher than reports from eastern Ethiopia among DM patients with comorbid hypertension (21.1%) [11]. This necessitated new indication for drug therapy, reported as a cause of DRP in our study (46.2%). This is consistent with the study in north-east Ethiopia where 40.3% of DM patients needed additional drug therapy [20], but higher than in south-west Ethiopia [19] and Indonesia [14] where only 29.3% of diabetic and 6.89% of tuberculosis patients respectively needed additional drug therapy. This difference may also be due to different populations being studied, different disease states as well as the fact that TB patients are managed under DOTS, where they are closely monitored thereby resulting lesser DRPs [14,19,20].

Suboptimal treatment accounted for 44.2% of total DRP in this study, that is, patient administering their medications in a wrong way. Suboptimal therapy, which can imply too high or too low dosage, duplicate therapy, missing dose or use of wrong medication [22] are common types of wrong administration of medications which leads to an increased risk of ADEs. The studies from eastern Ethiopia reported slightly higher (49.2%) and lower (36.2%) DRP values among DM/HTN and DM only patients, respectively [11,12] than this present study. Therefore, it can be deduced from this present study that presence of co-morbidities among DM patients increases the occurrence of DRPs. This might be due to the increased need for drug therapy to manage both co-morbidities than managing DM alone. According to our study, other causes of DRPs were mainly patient related. Over half of reported DRPs (55.7%) were caused by insufficient awareness of disease state. This was higher than reports from India among DM patients who also had cardiovascular disease [23], and TB patients only [24] where 5.54% and 21.75% of respondents, respectively reported insufficient awareness of health and disease state as causes of DRP. Again, this difference could have been as a result of different disease states and co-morbidities the patients had, or different study designs employed in the different studies. It could also have occurred as about half (46.2%) of respondents in our study were not aware they had DM and were newly diagnosed at the start of anti-tuberculosis therapy [16]. Insufficient knowledge of a disease state often leads to non-adherence to therapy. A study in Cameroon reported over half (54.4%) non adherence among DM patients [25]. It has been shown that actively engaging patients in their care by educating them, empowers them, encourages adherence and increased retention to care [26]. It also helped with the stigmatization associated with TB, addressed the awareness of patients about the disease states and right administration of medications which improved treatment outcomes [27], and resolved ADEs.

All newly diagnosed DM patients were referred by the pharmacist to the endocrinologist to commence antidiabetic medications in an attempt to resolve the problem of new indication for drug treatment. Choice of antidiabetic medications is dependent on factors such as cost, availability, ease of administration and safety [28]. With its relatively low risk of hypoglycemia, affordability and having no effect on body weight, metformin was the most commonly prescribed antidiabetic followed by Insulin and glibenclamide. This has probably further reduced blood glucose levels due to their hypoglycemic properties with close monitoring and counselling, especially with insulin use. This was similar to a study in India which revealed metformin as the most commonly used medication in the management of TB and DM patients [29].

Changes to drug therapy of previously diagnosed DM patients with TB was also addressed by referral to the endocrinologist. This addressed the issue of sub-optimal treatment and ADEs, thus possibly preventing microvascular complications such as retinopathy, neuropathy, nephropathy as well as cardiovascular complications and diabetic foot ulcers. Furthermore, this might reduce the risk of drug-disease interactions, preventing potential unnecessary pill burden used to manage these complications, ultimately leading to the resolution of untreated indications and suboptimal treatment. The difference in antidiabetic medications prescribed at the beginning and completion of TB treatment reflects the management choices of newly and previously diagnosed DM patients as metformin is considered first line drug in the management of type 2 DM patients with TB [3]. This would result in better prognosis, better TB treatment outcomes and prevent TB relapse.

All of the interventions done in this study were carried out with the patient as the focus. All the patients were counselled and educated, 76.9% referred to prescriber and also had interventions at drug levels - dosages were changed, instructions for use were corrected, and new drugs were started (46.2%). This is in agreement with Zazuli *et al* [13], where majority of interventions were predominantly at patient and care level. Over half (63.5%) of the interventions in our study were accepted and fully implemented, and the DRP were totally resolved in 57.7% of instances. The impact of pharmaceutical care was satisfactory for 73.9% of patients with a resolution rate of 77%. Lopez *et al*, [15] have similarly reported 73.9% satisfactory care for the respondents in their study. Partially implemented interventions pose a risk of becoming potential DRPs, and should be further addressed. In our study, there was no significant association between patients' socio-demographic characteristics and occurrence of DRPs ($P>0.05$). In contrast, Yimama *et al* [19], in the south-west Ethiopian study, reported age and the presence of co-morbidities as independent predictors of DRPs. Furthermore, Zazuli *et al* [13] reported number of medications as significantly correlated with the number of reported DRPs in an Indonesian study.

CONCLUSION

This study was carried out to identify and resolve DRPs in TB-DM patients using PCNE classification version 7.0, and a pharmacist initiated collaborative care. Over three quarters of the respondents reported at least one DRP, averaging 1.5 DRP per patient. The most common DRPs identified were ADEs, untreated indication and sub-optimal treatment which was resolved by patient counselling, referral to the prescriber, initiation of antidiabetic medications and modification of existing drug regimen. Early identification of DRPs led to a high level of interventions at patient, prescriber and drug

levels, which resulted into all interventions being accepted and fully implemented and DRPs resolved in more than half of instances. The authors of this study recommend caution in generalizing their findings to a larger population due to the small sample size employed in the study, and the lack of willingness of some patients to implement interventions. A small sample makes generalization of results to a larger population difficult and the unwillingness of patients shows the need for continuous counselling and follow up to increase the rate of resolutions of DRPs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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