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Research Article

Prevalence and Risk Factors for Angiotensin Converting Enzyme Inhibitor Induced Cough among Diabetic Patients in a Tertiary Institution in Southeast Nigeria

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Abstract

Introduction: The prevalence of diabetes mellitus (DM) is increasing worldwide, with the attendant cardiovascular morbidity and mortality especially heightened by co-existing hypertension and proteinuria. The renin-angiotensin system (RAS) has been a drug target of particular interest because of its involvement in the cardiovascular and renal disease progression. The ACE inhibitors (ACEI) have been proven effective for reducing cardiovascular events and mortality in patients with cardiovascular disease. However, these medications are associated with cough in certain subjects which could lead to poor drug adherence and increased cardiovascular morbidity and mortality. This study sought to determine the prevalence of ACEI-induced subjects in DM patients.

Methodology: A total of 100 patients who fit eligibility criteria were included in the study. A questionnaire was administered on subjects who were on ACEI while data was abstracted from the medical records of subjects who had been on the medication in the preceding two years.

Results: The prevalence of ACEI-induced cough was 20%. Female gender ($p=0.022$) and prolonged use of the medication ($p=0.017$) positively correlated with cough among DM subjects who had received ACEI in the preceding 2 years, or were on the medication at the time of this study. There was no correlation between the type of ACEI, anthropometry, and glycaemic control and the prevalence of cough among the subjects.

Conclusion: Our study suggests that the prevalence of cough among patients with diabetes mellitus who have been exposed to ACEI is substantial.

Keywords: ACE inhibitors; cough; diabetes mellitus.

INTRODUCTION

Diabetes mellitus is a non-communicable disease characterised by hyperglycaemia, with increasing prevalence all over the world ¹. Hypertension and diabetes, which often occur together, are two of the leading risk factors for atherosclerosis and its complications ². The development of hypertension in diabetic individuals not only complicates treatment strategy and increases healthcare costs but also heightens the risk for macrovascular and microvascular complications considerably ³. Angiotensin II (AT₂), the main effector peptide of the renin angiotensin system (RAS), plays an active role in the evolution of the cardiovascular risks associated with diabetes and hypertension ⁴. Angiotensin-converting enzyme inhibitors (ACEI) are effective antihypertensive agents that have been shown to reduce the risk of cardiovascular and renal events ^{4,5,6}. Although they are well-tolerated medicines, almost one-fifth of patients discontinue their treatments due to side effects, especially cough ⁷. ACEI-induced cough may develop within hours after the first dose or even weeks or months later ⁸. It is an idiosyncratic reaction which only occurs in susceptible individuals independent of the dose of the drug ⁹. These medications have also been found useful in the management of diabetic subjects without hypertension especially in the presence of proteinuria, which is a major risk factor for

cardiovascular and end stage kidney disease ^{10, 11}. Our study sought to determine the prevalence of cough among diabetic subjects who have been exposed to ACEI, and to know if there is any link with their age, gender, anthropometry, type of ACEI and duration of treatment, as well as glycaemic control. There is paucity of data on this subject hence the need for this study, considering the fact that studies have shown that diabetes is also a risk factor for ACEI-induced cough ^{12, 13}.

MATERIALS AND METHODS

This cross-sectional study was conducted in the Endocrine and Diabetes clinic of ESUT Teaching Hospital Parklane, Enugu Nigeria from August to November 2021. Diabetic patients who are currently taking ACE inhibitors were interviewed about occurrence of dry cough, its characteristics, measures taken and adherence to their medication. Data was also extracted from the medical records of patients who had been on any ACEI in the preceding 2 years. The latter and out-patients currently on the medication, aged 18 years and above, were included as study subjects. The sample size required for the study was determined using the formula for single population proportion by considering the prevalence rate of cough 10% and 5% margin of error at 95% confidence level and finally adjusting for finite population correction, a sample of 100 patients were selected. The patients on ACE inhibitors were

recruited consecutively. Data on age, sex, occupation, duration of DM and duration of hypertension, type of ACEI, HbA1c and Anthropometric indices were obtained. Patients who had cough were asked about its characteristics in terms of onset, nature, severity and duration; temporal relation with initiation of their medications; relieving or provocative factors; effect of drug discontinuation or re-introducing (if any) and impact on adherence. Subjects with conditions associated with cough were excluded from the study. They included patients with heart failure, bronchial asthma, chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis, tuberculosis, pneumonia, gastro-oesophageal reflux disease and smokers.

Operational definitions Causality: Cough associated with the use of ACE inhibitors was classified based on the World Health organizations (WHO) causality scale ¹⁴. The following criteria were used to classify cough causality: temporal relationship of cough to initiation of treatment, absence of drug or diseases that can cause cough, discontinuation effect and re-introducing effect. • **Certain:-** All of the four criteria are fulfilled. • **Probable:-** All of the criteria are fulfilled except re-introducing effect. • **Possible:-** All of the criteria are fulfilled except discontinuation and re-introducing effect. • **Unlikely:-** None of the four criteria are fulfilled. **Nonadherence:** A patient missed at least two doses of his/her treatments in the last month. The study was conducted on consenting subjects, after ethical approval was obtained from the ethics committee of the hospital. Data collated was analyzed using SPSS version

26.0. Descriptive statistics which include frequency and percentages were used to summarize categorical variables while means and standard deviations were obtained for continuous variables. Associations between categorical variables were done using logistic regression and Chi square while means of continuous variables were compared using t test. P-value < 0.05 was considered statistically significant. Results were presented in tables and charts.

RESULTS

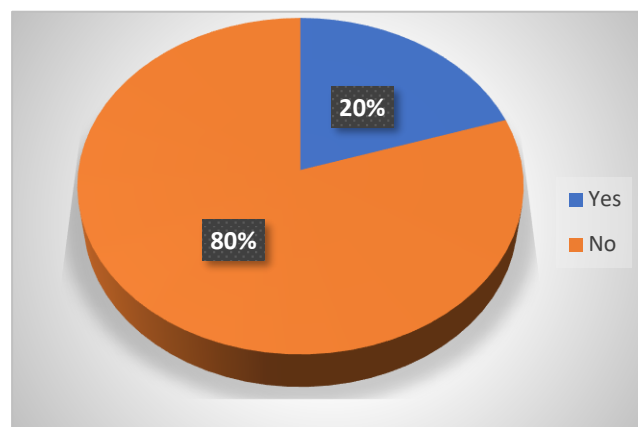


Figure 1: Prevalence of cough

A fifth of the studied subjects had ACEI-induced cough

Table 1: Demographic characteristics of the patients

	Frequency	Percent
Sex		
Male	34	34.0
Female	66	66.0
Age group		
<45	4	4.0
45 – 64	73	73.0
≥65	23	23.0
Occupation		
Civil servant	32	32
Farmer	25	25.0
Business/trader	23	23.0
Artisan	7	7.0
Retired	13	13.0

Two thirds of the studied subjects were female, while about three quaters were in the middle age category. There were more civil servants among the patients studied.

Table 2: Association between ACEI type and cough

ACEI type	Cough		χ^2	P value
	Yes n (%)	No n (%)		
ENALAPRIL	3 (13.6)	19 (86.4)	2.283	0.516
LISINOPRIL	11 (19.3)	46 (80.7)		
RAMIPRIL	1 (16.7)	5 (83.3)		
THIAPRIL	5 (33.3)	10 (66.7)		

Lisinopril was the most prescribed ACEI, while ramipril was the least prescribed.

Table 3: Association between demographic characteristics and cough

	Cough		χ^2	P value
	Yes	No		
	n (%)	n (%)		
<i>Sex</i>				
Male	7 (20.6)	27 (79.4)	0.011	0.916
Female	13 (19.7)	53 (80.3)		
<i>Age group</i>				
<45	1 (25.0)	3 (75.0)	0.174	0.917
45 – 64	15 (20.5)	58 (79.5)		
≥65	4 (17.4)	19 (82.6)		
<i>Occupation</i>				
Civil servant	6 (20.0)	24 (80.0)	1.789	0.878
Teacher	1 (50.0)	1 (50.0)		
Farmer	6 (24.0)	19 (76.0)		
Business/trader	4 (17.4)	19 (82.6)		
Artisan	1 (14.3)	6 (85.7)		
Retired	2 (15.4)	11 (84.6)		

Out of the subjects studied, 66% were females while 73% of the respondents were between the aged of 45 to 64 years. The mean age was 58.25 ± 9.49, about a third of the patients were civil servants and a quarter were farmers.

Table 4: Comparison of mean age, HbA1c and anthropometry between patients with and without cough

	Cough		T	P value
	Yes Mean ± SD	No Mean ± SD		
Age	56.65 ± 9.02	58.65 ± 9.62	0.841	0.402
Height	1.72 ± 0.06	1.71 ± 0.06	0.682	0.497
BMI	28.11 ± 3.43	28.44 ± 5.39	0.263	0.793
WC	94.45 ± 7.74	95.48 ± 7.44	0.547	0.586
Weight	84.75 ± 10.95	83.10 ± 14.19	0.484	0.629
HbA1c	7.11 ± 0.85	7.66 ± 1.68	1.402	0.164

Table 5: Association between gender and cough

Sex	Cough		P value	OR	95% C.I for OR
	Yes n (%)	No n (%)			
Female	17 (25.8)	49 (74.2)	0.022	6.000	1.302 – 27.649
Male	3 (8.8)	31 (91.2)			

Eighty five percent of the subjects who had cough were female

Table 6: Association between nutritional status and cough

Nutritional status	Cough		χ^2	P value
	Yes n (%)	No n (%)		
Normal	3 (16.7)	15 (83.3)	0.152	0.927
Overweight	11 (20.8)	42 (79.2)		
Obese	6 (20.7)	23 (79.3)		

About half subjects studied were overweight, while a third were obese.

Table 7: Association between glycemic control and cough

HbA1c	Cough		χ^2	P value
	Yes n (%)	No n (%)		
<7	10 (29.4)	24 (70.6)	2.852	0.091
≥ 7	10 (15.2)	56 (84.8)		

About two thirds of the subjects had poor glycaemic control.

Table 8: Association between duration of DM, HTN, ACE-I and cough

	Cough		χ^2	P value
	Yes	No		
	n (%)	n (%)		
<i>Duration of DM</i>				
<5	9 (17.6)	42 (82.4)	0.650	0.722
5 –10	6 (20.0)	24 (80.0)		
>10	5 (26.3)	14 (73.7)		
<i>Duration of HTN</i>				
<5	10 (19.6)	41 (80.4)	0.018	0.991
5 – 10	6 (20.0)	24 (80.0)		
>10	4 (21.1)	15 (78.9)		
<i>Duration ACE-I</i>				
<1 year	12 (35.3)	22 (64.7)	8.166	0.017
1 – 2 years	6 (15.4)	33 (84.6)		
>2 years	2 (7.4)	25 (92.6)		

About half of the subjects have had DM and HTN for <5years, More pateints used ACEI for 1-2years.

DISCUSSION

The prevalence of cough in this study was 20%, similar to the finding in another study done on hypertensive patients attending an outpatient cardiology clinic in Nigeria ¹⁵. However, this is higher than the prevalence of 9-11% in the west ^{16, 17} and 7% in Pakistan ¹⁸. The incidence is lower than the 44% found in Chinese subjects ¹⁹, the 61.3% found in Brazil ²⁰, and the 27-30% found in other studies done in Western Nigeria ^{21, 22}. This varying prevalence may be related to environmental, racial and genetic differences ^{19, 21, 23, 24, 25}.

The prevalence of cough was found to be more common among women than men in this study (25.8% vs 8.8%). This is similar to findings in other studies in Nigeria ^{15, 21}, Poland ²⁶ and Baghrain ²⁷.

Studies have shown that women are generally more prone to adverse drug reactions (ADRs) compared to men, and 60% of patients admitted to hospital with an ADR are women ^{28, 29}. Several factors have been adduced for this discrepancy in the incidence of ADR in both sexes. These include differences in pharmacokinetics and pharmacodynamics between women and men, making women in general more susceptible to dose-dependent ADRs ^{28, 30, 31}. Numerous factors influence the bioavailability and distribution of drugs, such as the ratio of lean to fat tissue, circulating plasma volume, and the amount of plasma proteins binding the drug ³². On average, the body composition in women includes higher percentage of body fat and a lower body mass ^{33, 34}; consequently, lipid soluble drugs with a longer half-life and water soluble drugs may yield

higher exposure in women. Furthermore, renal clearance is usually higher in men than in women, which could lead to drug accumulation and the emergence of ADR ³³. Moreover, women may respond to cardiovascular medication differently than men ³⁵, and sex differences in pharmacodynamic responses may include both increased and decreased effects as well as adverse effects in women compared to men.

Duration of ACEI use was found to positively correlate with the presence of cough in this study. This is similar to the finding among subjects in Pakistan ³⁶ but differs from the finding by Sato et al which noted a reduced incidence of cough reported with continuous use of ACEIs ³⁷. Genetic and ethnic differences in handling ACEIs ^{19, 38}, as well as the possible incidence of long delay in onset of cough in some subjects taking the drug may account for this variation ³⁹.

There was no positive relationship between the presence of cough and the type of ACEI in the studied subjects. This is similar to the findings in Malaysia and Ethiopia ^{40, 41}, while another study in Pakistan ³⁶ found that Enalapril is the most common cause of cough among ACEIs. Similarly, Tumanan-Mendoza et al found a 2-fold higher incidence of cough in patients undergoing enalapril therapy (22%) compared with perindopril treatment (11%) ⁴², while Yeşil S et al found that cough was commoner during treatment with captopril and enalapril than perindopril and lisinopril ⁴³. Santoni et al also found that cough was two times commoner in subjects who were receiving captopril than those on perindopril ⁴⁴. These differences may be from the fact that perindopril, which causes the least cough among ACEIs, was hardly used in our

centre, and was therefore not compared with others unlike the studies mentioned. Glycaemic control did not correlate with cough in our subjects. There is paucity of data on the effect of good glycaemic control, represented by HbA1c <7%, on the prevalence of cough in ACEI treated subjects with DM. More studies are needed in this regard. There was no relationship between the occurrence of cough and BMI in our study. Similar findings were found in a prospective study done on newly diagnosed hypertensive subjects in two primary healthcare centres in Bahrain ²⁷, and in a cross-sectional observational study in a referral centre in Bahia, Brazil [20]. In contrast, other authors in Pakistan ⁴⁵ and Sweden ⁴⁶ found that BMI positively correlated with the incidence of cough due to ACEI administration. This difference could be attributed to genetic factors.

CONCLUSION AND RECOMMENDATIONS

ACEI-induced cough is very common among diabetic subjects in our centre. We advise clinicians to be on the lookout for this and either switch to an ARB or perindopril, since the latter has been found to cause the least cough among the ACEIs. This will engender drug adherence so as to prevent the cardiovascular consequences of poor blood pressure control and proteinuria in DM patients.

CONFLICT OF INTEREST

We declare no conflict of interest

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