

Incidence and Determinants of Reported Hypoglycaemia among Patients with Type 2 Diabetes Mellitus in a Tertiary Health Institution in Nigeria

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Abstract

Introduction: Hypoglycaemia is a frequent and serious adverse effect of anti-diabetic therapy associated with both immediate and delayed adverse clinical outcomes. However, it continues to be a neglected complication with limited study of its burden, knowledge, determinants and preventive measures adopted by type 2 diabetics. **Methods:** Patients with type 2 diabetes who presented at Diabetes Clinic of a University teaching hospital and fulfilled selection criteria were recruited. The information obtained included sociodemographic, clinical details with hypoglycaemic symptoms and laboratory measurements. **Results:** There were 113 participants with a mean age of 60.94 ± 11.95 years. The majority of the patients had fair knowledge of hypoglycaemic symptoms and also knew what actions to take to ameliorate the symptoms when it occurs. The incidence of hypoglycaemia was 45.1% and most commonly occurred in the afternoon before lunch. The commonest symptoms reported by patients were shivering (76.1%), hunger (71.7%) sweatiness (71.5%) and weakness (69.9%). Almost one-fifth (19.6%) of those who reported hypoglycaemia had severe symptoms, of which 16.1% had hospital admission for its management. Use of insulin, duration of diabetes, age and possession of glucometers were some of the determinants of hypoglycaemic symptoms. **Conclusions:** The burden of reported hypoglycaemia among type 2 diabetics is significant. Hence, diabetics at risk should always be asked about symptoms at each clinic visit. Early recognition of hypoglycaemia risks,

self-monitoring of blood glucose (SMBG), appropriate education programs for both health care providers and patients with diabetes are the major ways to minimize risks of hypoglycaemia.

Keywords

Diabetes Mellitus, Epidemiology, Hypoglycaemia, Knowledge, Predictors, Risk Factors

1. Introduction

Diabetes mellitus (DM) is a chronic disease that requires continuous medical care and patients' management education to prevent acute complication and reduce the risk of long-term complications [1]. Hypoglycaemia is an important complication in the treatment of type 2 diabetes mellitus (T2DM), because it causes morbidity, and is sometime fatal [2]. Achieving target glycaemic goals while avoiding hypoglycaemia is a major challenge in the management of patients with T2DM [3]. Hypoglycaemia is the limiting factor in the management of the vast majority of people with diabetes [4] [5].

Although landmarks studies like Diabetes Complications Control Trial (DCCT) and United Kingdom Prospective Diabetes Studies (UKPDS), demonstrated the benefits of intensive glycaemic control in type 1 and type 2 diabetes respectively [6] [7], the associated increased frequency of hypoglycaemia has limited the clinical implementation of such intensive therapy because of pharmacokinetics imperfection of available medications [7] [8] [9].

Hypoglycaemia is a medical emergency which requires prompt recognition, and treatment to prevent organ damage, especially the brain. Severe untreated hypoglycaemia can cause a significant economic and personal burden; therefore, identification and prevention can reduce diabetes burden by the prevention of hypoglycaemic complication. The UK Hypoglycaemia Study showed that in patients with type 2 diabetes, the risk of severe hypoglycaemia is low in the first few years (7%) and that increases to 25% later in the course of diabetes [10]. However, the prevalence of T2DM is about 20-fold higher than that of type 1 diabetes, and many patients with T2DM finally requiring treatment with insulin. Hence, most episodes of hypoglycaemia occur in patients with T2DM [11].

Hypoglycaemia is a common and serious complication of diabetes treatment especially in patients who do not have knowledge of the condition and personal glucose meters. It is the rate limiting complication in the achievement of strict glycemic control in diabetes management. Significant episodes of hypoglycemia and its attendant counter-regulatory hormonal response lead to poor glycemic control. The former may also be associated with cardiovascular and cerebrovascular morbidities [12]. Large trials (Action to Control Cardiovascular Risk in Diabetes (ACCORD), Veterans Affairs Diabetes Trial (VADT)) have shown that

there was a higher mortality in the group that had hypoglycemia (intensively treated arm) [13] [14]. Hence, the American Diabetes Association (ADA) guidelines emphasize on individualizing targets and reducing risk of hypoglycemia in patients with long duration of diabetes and comorbidities [15].

The symptoms of hypoglycemia are varied. The symptoms may be nonspecific with intensity decreasing with increasing age. Thus, it is very important that the subjects are able to recognize and identify the symptoms onset at an early stage in order to manage the episode effectively and take steps to prevent the recurrence.

Patients with very good drug compliance are at greater risk of developing hypoglycaemia. Sometimes hypoglycaemia among patients on antidiabetic agents could be symptomatic or asymptomatic [16].

Although hypoglycaemia is a common complication among treated type 2 diabetic patients, especially those on insulin either alone or in combination with oral anti-diabetic agents mostly the insulin sensitizers like sulphonylureas, there is little information about the burden and risk factors among Nigerians with type 2 diabetes. Hence, this study was aimed at assessing the knowledge of hypoglycaemic symptoms, burdens and predictors of hypoglycaemia among type 2 diabetics.

2. Materials and Methods

This study was done among type 2 diabetes mellitus patients attending the Diabetes Clinic of the Endocrinology, Diabetes and Metabolism Unit of LAUTECH Teaching Hospital, Ogbomoso.

Patients with T2DM whose diagnosis was made at the age of 30 years or older, and were on treatment with either oral anti-diabetic agents or insulin, or both, were recruited as a convenient sample size over a period of 6 months (January - June 2017). Patients with Type 2 diabetes who were not on medications or those with Type 1 diabetes or pregnant women were excluded. Also excluded were those with T2DM complicated by major organ dysfunctions like heart failure, renal failure or liver dysfunctions. Information obtained from each of the patients included age, gender, educational status, duration of diabetes, and types of anti-diabetic agents used. Information obtained regarding hypoglycaemic symptoms included knowledge of hypoglycaemia, previous experience of hypoglycemia, methods of managing hypoglycaemia and possession of glucometers and frequency of self-monitoring of blood glucose (SMBG). Patients were asked if they have had any of the common symptoms suggestive of hypoglycemia in the past 6 months. The symptoms suggestive of hypoglycemia asked included, sweating, shivering (tremors), hunger, weakness, palpitation, headache, light headedness, anxiety, dizziness, blurred vision, and/or disturbance of consciousness, among others. Since most of the patients did not possess a glucometer to measure plasma glucose concentration especially during the occurrence of above or similar symptoms, they were asked if they ate something immediately

following those symptoms and whether they were relieved of the symptoms. Also, all clinical suspicions of hypoglycemia were considered as occurrence of hypoglycemia especially if there were constellation of symptoms, even if unconfirmed with either laboratory blood glucose test or SMBG. Physical and biochemical measurements like weight, height, and average fasting plasma glucose were checked in each of the patients.

The study was approved by the Institutional Ethics Committee of the hospital (LTH/OGB/EC/2018/031) and each participant gave informed consent.

3. Data Analysis

Data were analysed using Statistical Package for Social Sciences version 21.0 software (SPSS Inc, Chicago, IL, USA). Continuous variables were presented as means \pm standard deviation while categorical variables were presented as frequencies and percentages. The factors associated with occurrence of reported hypoglycaemia were identified and test for association. All the factors that showed a significant association with the risk of developing hypoglycaemia on bivariate analysis were put into a multiple logistical regression model. Risk of developing hypoglycaemia was considered to be the outcome variable and the variables showing significant association as co-variants. The odds ratios and the 95% confidence intervals (CI) were calculated. A p value < 0.05 was considered as significant for all analysis.

4. Definition of Operational Terms

For the purposes of the analysis,

Mild hypoglycaemia: defined as patient report of typical symptoms of hypoglycaemia (eg, sweating, tremulousness, hunger, and/or dizziness) that were relieved by eating, or patient report of home glucose monitoring values of less than 60 mg/dl (<3.3 mmol/L).

Severe hypoglycaemia: defined as loss of consciousness or other major alteration of mental status caused by hypoglycaemia that required the assistance of another person to manage the condition.

Asymptomatic hypoglycaemia: defined as low blood glucose values < 60 mg/dl (3.3 mmol/L) but with no symptoms.

5. Results

Of the 113 participants, about 59.3% were females and the mean age of study participants was 60.94 ± 11.95 years. More than half of the participants had at least secondary school education. The prevalent occupation of the participants was trading (34.5%) and civil service (32.7%). Majority of the participants make less than N20,000 per month (56 USD, at 1 USD to N360). Sixty eight (60.2%) were on oral anti-diabetic drugs only while 15 (13.3%) were on insulin alone. The other distribution concerning sociodemographic and other indices are as shown in [Table 1](#).

Table 1. Sociodemographic characteristics and clinical data of the study participants (n = 113).

Variable	Frequency	Percentage
Sex		
Male	46	40.7
Female	67	59.3
Education		
None	19	16.8
Primary	35	31.0
Secondary	11	9.7
Tertiary	48	42.5
Occupation		
Farmer	14	12.4
Trader	39	34.5
Artisan	9	8.0
Professional	6	5.3
Civil Servant	37	32.7
Others	8	7.1
Monthly Income (₦)		
<10,000	48	42.5
10,000 - 20,000	22	19.5
20,000 - 50,000	12	10.6
50,000 - 100,000	20	17.7
>100,000	11	9.7
History of Hypertension		
Yes	84	74.3
No	29	25.7
Diabetes Treatment		
Diet alone	1	0.9
OAD	68	60.2
OAD + Insulin	29	25.6
Insulin alone	15	13.3
If OAD		
Metformin	28	24.8
Metformin + SUs	49	43.4
Metformin + SUs + Pioglitazone	1	0.9
Metformin + DPP4-inhibitor	1	0.9
Metformin + Pioglitazone	1	0.9
SUs	2	1.8
DPP4-inhibitor	2	1.8
Age (Mean ± SD) Years		60.94 ± 11.95
BMI (Mean ± SD) Kg/m ²		29.07 ± 11.23
FPG (Mean ± SD) mmol/L		9.05 ± 3.48

OHA = Oral Hypoglycaemic Agent, SU = Sulfonylurea, DPP4 = Dipeptidyl Peptidase, BMI = Body Mass Index, FPG = Fasting Plasma Glucose.

Regarding knowledge of hypoglycaemia, 95.2% had good knowledge of hypoglycaemia as they were able to identify or recognize hypoglycaemic symptoms. Less than half of the participants, 56 (45.1%) had experienced hypoglycemia in

the last 3 months. The incidences of hypoglycaemic symptoms reported by the participants are as shown in **Figure 1**.

The commonest symptoms identified to be symptoms of hypoglycaemia were shivering (76.1%), sweatiness (73.7%), hunger (71.7%) and weakness (69.9%). Less study participants knew that aggression (32.7%), convulsion (37.2%) and anxiety (38.1%) could be symptoms of hypoglycaemia. Among the participants, 70 (61.9%) owned glucometers but only 30/56 (53.6%) had ever tested their blood glucose to confirm hypoglycaemia before managing symptoms suspected to be hypoglycaemia. Taking timely meals was the measure adopted by 72.5% of patients with hypoglycaemia to relieve the symptoms. Approximately 10.6% of participants regularly took table sugar, soft drink, glucose tablets or other forms of glucose with them while going out.

The frequency and times of hypoglycaemic symptoms occurrence among study participants are as shown in **Figure 2**. Most symptoms of hypoglycaemia in the Study occurred in the afternoon before lunch (28.3%), and least occurred at night. Almost a quarter of participants (23.5%) developed both daytime and nocturnal hypoglycaemia. Almost all spouses 108 (95.6%) of diabetic participants know of the diabetic status of their spouses, more wives know about the diabetic status of their husbands compared with husbands knowing the diabetic status of their wives.

Most of the patients who reported hypoglycaemic symptoms, 36 (64.3%) perceived that the main cause of hypoglycaemic symptom was missed/delayed or inadequate meal intake rather than excessive/unaccustomed exercise or overdose of anti-diabetic medications.

The incidence of hypoglycaemia subtypes in this study was mild/moderate hypoglycaemia reported by 45/56 (80.4%) and severe hypoglycaemia reported by 11/56 (19.6%) patients. Hospital admission for hypoglycaemia symptoms was reported by 9/56 (16.1%) patients of which 2 (3.6%) had more than 2 hospital admissions (**Table 2**).

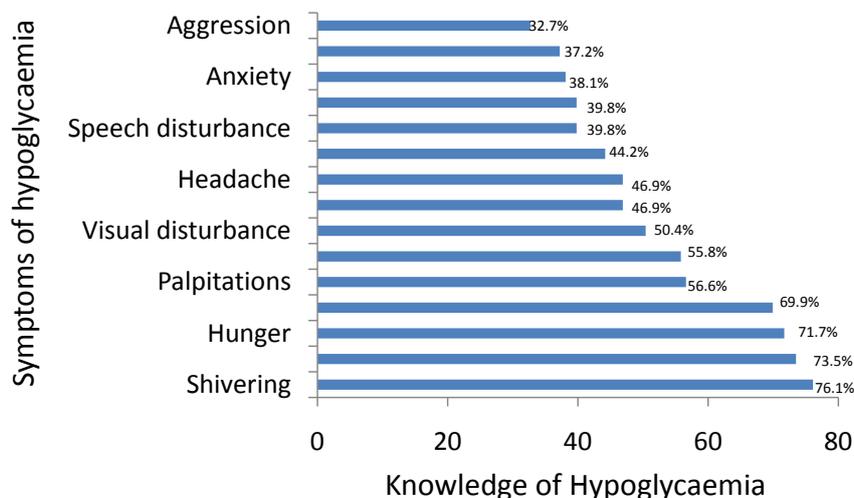


Figure 1. Prevalence of hypoglycaemic symptoms among type 2 diabetic patients.

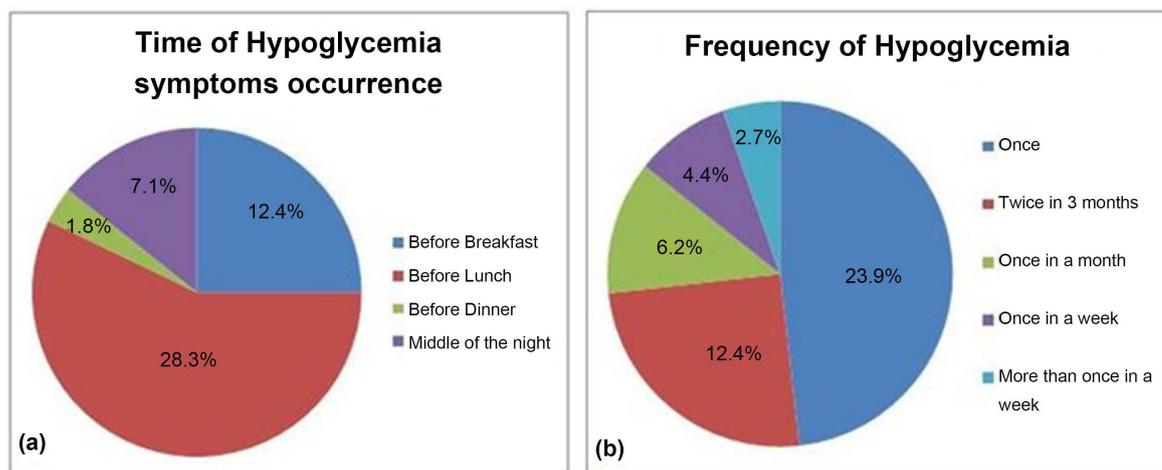


Figure 2. Time and frequency of hypoglycaemic symptoms occurrence among type 2 diabetic patients.

Table 2. Patterns of hypoglycaemia occurrence among the study participants.

Variable	N = 113		
	Frequency	Percentage	
Cause of hypoglycaemia	Missed/delayed meal	36	64.3
	Over medication or insulin regimen	18	32.1
	Acute illness	1	1.8
	Alcohol intake	0	0.0
	Vigorous exercise	1	1.8
Possession of glucometer	Yes, <i>Do you use glucometer when symptomatic?</i>	70	61.9
	Yes	30	26.5
	No	40	35.4
Frequency of blood sugar check	No	43	38.1
	Once	30	26.5
	2 - 3 times	13	11.5
	4 - 5 times	39	34.5
	Everyday	12	10.6
Does your spouse know you have diabetes?	Never to occasionally	19	16.8
	Yes, <i>Can they recognise symptoms?</i>	108	95.6
	Yes, <i>Do they know what to do?</i>	59	52.2
	Yes	51	45.1
Regular meals	No	8	7.1
	No	49	43.4
	No	5	4.4
Do you carry cubes of sugar or other forms of glucose around when going out?	Yes	80	70.8
	No	33	29.2
	Yes	12	10.6
Hospital admission due to hypoglycaemia	No	101	89.4
	Yes, <i>How many times?</i>	9	8.0
	Once	7	6.2
	2 - 3 times	2	1.8
No	104	92.0	

As shown in **Table 3**, multivariate logistic analysis revealed that older age, longer duration of diabetes, possession of a glucometer and use of insulin were associated with higher odds of hypoglycaemia. Participants who were on insulin had 4.5 times higher odds of hypoglycaemia compared with those who were not. There was no independent association between report of hypoglycaemia symptoms by participants and fasting blood sugar and carriage of sugar around, respectively.

6. Discussion

This descriptive study was done to assess the incidence of occurrence of hypoglycaemia symptoms among type 2 diabetics individuals, their knowledge of hypoglycaemia and their practices with respect to managing reported hypoglycaemia.

The findings in this study suggest that there is a significant risk of hypoglycaemia in patients who are on anti-diabetic agents. The risk was particularly moderate for symptomatic hypoglycaemia (19.6%). More than three-quarter (80.4%) of the study participants reported one or other symptoms of hypoglycaemia. Shivering, sweatiness and hunger were the most common symptoms reported by diabetic patients.

Approximately half of diabetic patients in this study had experienced hypoglycaemic symptoms. This shows that hypoglycaemia is an important complication that should always be explored and addressed. The reported risk of hypoglycaemia in this study, 45.1% is similar to 43.3% reported by Fritsche *et al.* [17], and 45% reported by Donnelly *et al.* [18] but lower than 64% by Henderson *et al.* [19] and 75.3% reported by Dhuha *et al.* [20]. It is encouraging to know that the majority of the patients were able to recognize hypoglycaemic symptoms, as well as understand the hypoglycaemia action plan. This suggests that the education they received on diabetes during the clinic visits is effective in covering this aspect of diabetes care. This finding is similar to that from an online survey in San Diego (2011), wherein most T2DM patients were aware of the symptoms of hypoglycaemia [21]. The finding in this study also agreed with a similar study done in India in 2013, where two-thirds of patients had good knowledge of the symptoms

Table 3. Association of occurrence of reported hypoglycaemia and sociodemographic and clinical characteristics among the study participants.

Variable	Odds Ratio	95% CI	p-value
Fasting blood sugar	1.090	0.944 - 1.258	0.240
Age	1.65	1.32 - 2.05	0.004
Duration of Diabetes	1.66	1.22 - 2.36	0.030
Possession of glucometer	1.09	1.09 - 1.72	0.041
Carriage of sugar around	0.129	0.014 - 1.213	0.073
Insulin use	4.50	3.42 - 5.32	0.001

of hypoglycaemia [12]. However, a study done in Kaduna, Nigeria, involving 347 patients attending two different outpatient clinics (117 of whom were diabetics) showed that a smaller number (34.2%) of patients were aware of the symptoms of hypoglycaemia [22]. Missed/delayed or inadequate meals were the most common precipitating factors responsible for hypoglycaemic episodes in this study; this agreed with findings in other studies [8] [23] [24].

In this study, most participants with hypoglycaemia had “mild/moderate” hypoglycaemia; the incidence of “severe” hypoglycaemia episodes was reported by 19.6% and hypoglycaemia requiring hospital admission by 16.1% of the patients. Similar study reported incidence of 19% among Indians [25] and 20% in a survey in America where 10% of them required assistance from another party and 6% were managed at Emergency Department [26]. The finding was also higher than 3% reported by Donnelly *et al.* [18] and 7% reported by UK Hypoglycaemia study [10]. The higher incidence in this study may be due to misclassification of mild/moderate symptoms as severe which probably led to unnecessary help from relatives or presentation for treatment in the emergency room, hence could have led to overestimation of severe hypoglycaemia in this study.

On the predictors/determinants of hypoglycaemia in our study, a number of factors were identified that influenced the risk of hypoglycaemia. We found an association between FBS, carriage of sugar around, older age, longer duration of diabetes, possession of a glucometer and use of insulin, respectively, and the risk of hypoglycaemia on bivariate analysis. However, this association disappeared on regression analysis for FBS, carriage of sugar around but remained for older age, longer duration of diabetes, possession of a glucometer and use of insulin. The increased risk with insulin use (OR-4.50, 95% CI-3.42 - 5.32) is in keeping with results of a number of observational studies such as UK Hypoglycaemia study [10], and a study by Donnelly *et al.* [18] which found increased incidence rates of hypoglycaemia in patients on insulin (25%) with longer usage. Self-monitoring of blood glucose (SMBG) was also predictive of hypoglycaemia episodes, most probably because of increased awareness in cases where episodes were asymptomatic. The unpleasant symptoms and consequent hypoglycaemia may result in fear of subsequent hypoglycaemia. Fear of future hypoglycaemic events may lead to corrective or counteractive action to prevent hypoglycaemia including repeated monitoring of blood glucose at the expense of undesirably high glucose levels [27]. This repeated significant hypoglycaemia blunts hormonal responses to hypoglycaemia leading to impaired awareness of hypoglycaemia (Hypoglycaemia Associated Autonomic Failure, HAAF) [28].

The practice of SMBG as a way to detect and prevent future occurrence of hypoglycaemic episodes in this study was low as only approximately half of participants (53.6%) has ever practiced SMBG to confirm their hypoglycaemia symptoms before managing it. It is well known that SMBG aids in better glucose control and prevention of hypoglycaemia among diabetics especially those on insulin, by allowing for adjustment in diet, physical activity and medications in response to test results [29] [30].

An interesting finding in this study was the fact that higher proportion of wives know of the diabetic status of their husbands compared to husbands knowing of the diabetic status of their wives. This may be related to perception of African women who sometimes believe that if their husbands know about their diabetic status it could make them marry other women as they might be considered not to be sexually appealing to them again. However, this is erroneous!

7. Strengths of the Study

With paucity of studies on hypoglycaemia in this environment, this study which explored knowledge of symptoms, frequency of hypoglycaemic episodes and practices adopted by patients during hypoglycaemia will serve as a reference study for future studies.

8. Limitations

The limitations of this study include its relatively small sample size; hence higher-powered studies are suggested to further explore the associations seen. Also, its cross-sectional nature only enables us to detect associations but not causality, hence longitudinal studies is suggested to further this study. Estimation of hypoglycaemia incidence was based on symptoms as reported by patients rather than confirmed low blood glucose levels with glucometer. However, this was not done because of low number of patients that correlated their symptoms with objective blood glucose measurements. Hence, these reported symptoms might not necessarily be symptoms of hypoglycaemia, since most of these symptoms are non-specific, that is, they are not pathognomic of hypoglycaemia.

9. Conclusion

The burden of hypoglycaemia in patients with type 2 diabetes is significant. Hence, the most important goal is to identify the patients at a high risk of hypoglycaemia and modify their treatment regimens based upon individual patient characteristics. Achieving adequate glycaemic control without causing troublesome hypoglycaemia is the key to providing optimum care to individuals with diabetes. Education should be provided at a level appropriate to the understanding of each patient. Educating patients for early identification of hypoglycaemic symptoms, its causes, and the various preventive measures are all important to reduce the burden of hypoglycaemia. Regular SMBG as one of the effective ways to monitor blood glucose trends and identifying asymptomatic hypoglycaemia should be encouraged.

What Is Known about This Topic

- Hypoglycaemia is a major and serious complication of diabetes management.
- Hypoglycaemia limits achieving diabetes goals in management.
- Insulin and other insulin secretagogues are major anti-diabetic agents that

cause hypoglycaemia in diabetes patients.

What This Study Adds to the Topic

- Burden of hypoglycaemia even among type 2 diabetics is high although mainly mild to moderate in severity.
- Practice of self monitoring of blood sugar (SMBG) to confirm/detect hypoglycaemia is low, most patients depend on symptomatology to assume hypoglycaemia.
- Higher proportion of wives is aware of the diabetic status of their husbands compared to husbands knowing about the diabetic status of their wives.

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Ethical Approval

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Authors' Contributions

MAO conceptualized; designed, involved in data collection, analysis interpretation of analysis and drafting of the manuscript; AAO, ACE and ATA were all involved in the initial drafting of the manuscript. All authors critically reviewed, edited and approved the manuscript.

Conflicts of Interest

The authors declare no competing interest.

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