Original Article

Clinicopathologic assessment of hypogonadism in men with type 2 diabetes mellitus

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ABSTRACT

Objective: To determine the prevalence of hypogonadism in men with type 2 diabetes mellitus and evaluate its clinical and pathologic correlates. **Subjects and Methods:** In a cross-sectional survey of 200 type 2 diabetic males aged 32–69 years, total testosterone (TT), follicle stimulating hormone, luteinizing hormone, waist circumference (WC), glycated hemoglobin, and lipids were measured. Clinical assessment of androgen deficiency was done using the androgen deficiency in aging male (ADAM) questionnaire. Overt hypogonadism was defined as a combination of positive ADAM score and TT < 8 nmol/L while possible hypogonadism was defined as positive ADAM score with TT 8–12 nmol/L. **Results:** Overt and possible hypogonadism occurred in 29.5% and 23% of the participants, respectively. Majority (76.3%) of the subjects who had overt hypogonadism had the hypogonadotrophic pattern. Hypogonadal subjects were significantly older ($P = 0.014$) and had higher mean WC ($P = 0.009$) than eugonadal ones. Erectile dysfunction was the most common symptom, occurring in 79.7% of overtly hypogonadal subjects. There was a significant negative correlation between WC and serum TT ($r = -0.41$, $P = 0.001$). **Conclusion:** There is a high frequency of symptomatic hypogonadism in men with type 2 diabetes and the frequency increases with advancing age and visceral adiposity.

Key words: Hypogonadism, Nigeria, prevalence, testosterone, type 2 diabetes

Introduction

Male hypogonadism is defined as a clinical condition characterized by both symptoms/signs and biochemical evidence of testosterone deficiency.[1] An association between type 2 diabetes mellitus (DM) and hypogonadism came to limelight over two decades ago when a high prevalence of low testosterone levels was observed in men with type 2 diabetes.[2] Subsequently, a meta-analysis confirmed that men with type 2 DM have significantly lower levels of testosterone than nondiabetic controls.[3] It has been demonstrated that up to one-third of men with type 2 DM have significantly subnormal levels of both free and total testosterone (TT).[4,5]

While the exact mechanism underlying the occurrence of hypogonadism in men with type 2 DM remains unclear, insulin resistance (IR), an important feature of type 2 DM, appears to be a common denominator. It has become increasingly evident that low testosterone in men is not only associated with reduced insulin sensitivity and hyperinsulinemia but also predicts IR and future development of type 2 DM.[6-8] Administration of testosterone to hypogonadal men with type 2 DM improved insulin sensitivity.[7,9]

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Access this article online	
Quick Response Code:	Website: www.ijem.in
	DOI: 10.4103/2230-8210.190554

Cite this article as: Ugwu TE, Ikem RT, Kolawole BA, Ezeani IU. Clinicopathologic assessment of hypogonadism in men with type 2 diabetes mellitus. Indian J Endocr Metab 2016;20:667-73.

Obesity appears to play an important synergistic role in this pathogenesis. Although hypogonadism also occurs in lean diabetic men, the prevalence rises with increasing body mass index.[4] Obesity is common in type 2 DM and is an important cause of IR.[10] Studies have shown that free testosterone (FT) levels are lower in obese men and inversely correlate with the severity of obesity.[11,12]

Testosterone deficiency in men is associated with negative consequences. For instance, there is a growing evidence that hypogonadism is a risk factor for coronary artery disease, the leading cause of mortality in patients with type 2 DM.[13] Other adverse effects reportedly associated with hypogonadism include poor quality of life, sexual dysfunction, increasing fat mass, increased fracture risk, cognitive decline, and mortality.[14,15]

There is a paucity of literature on diabetes-related hypogonadism in sub-Saharan Africa despite the continent having a high burden of DM. This study is aimed at determining the prevalence and pattern of hypogonadism and its clinical and pathologic correlates in Nigerian men with type 2 DM.

Subjects and Methods

This was a cross-sectional study of 200 males aged 30–70 years, diagnosed with type 2 DM according to the 1999 World Health Organization criteria.[16] Participants were purposely and conveniently recruited from the diabetes clinic of Obafemi Awolowo University Teaching Hospital Ile-Ife Nigeria. Approval was given by the hospital's Research and Ethics Committee while each patient gave written informed consent. Exclusion criteria were previous/present therapy with androgens or androgen antagonists, acute febrile illness in the last 1 week, known or suspected chronic debilitating illnesses including chronic heart failure, chronic liver disease, chronic renal failure, tuberculosis, chronic obstructive pulmonary diseases, acquired immunodeficiency syndrome, and malignancy.

Clinical assessment

With an interviewer-administered proforma, demographic information, and relevant medical history were documented. Central obesity was assessed by waist circumference (WC) measured at a point midway between the inferior border of the costal margin and the iliac crest in mid-axillary line to the nearest 0.5 cm. Subjects with WC ≥94 cm were regarded as obese, according to the international guideline.[17]

Two brachial blood pressure (BP) measurements were taken at least 10 min apart and their mean calculated. Subjects whose BP readings were ≥140/90 mmHg or currently on antihypertensive medication were regarded as hypertensive, according to expert recommendations.[18]

The androgen deficiency in aging male (ADAM) questionnaire was used for clinical evaluation of androgen deficiency. A positive response to ADAM's questionnaire consists of decreases in libido or strength of erections or any three nonspecific questions including fatigability, decreases in muscle strength, mood changes, and loss of height.[19]

Laboratory evaluation

Ten milliliters of venous blood were obtained from each patient via a sterile venipuncture between 8.00 and 10.00 am after an overnight fast and shared between two specimen bottles, one containing ethylenediamine tetra-acetic acid and the other plain. The former was used for analysis of glycated hemoglobin (HbA1c) (boronate affinity chromatography, in-2-it, Bio-Rad Laboratories, California, USA), and serum lipids. HbA1c <7% was regarded as good glycemic control while HbA1c ≥7% was regarded as poor glycemic control according to the expert guideline.[20] Dyslipidemia was diagnosed if any of the followings was present: Total cholesterol >4.5 mmol/L, low-density lipoprotein >2.6 mmol/L, triglycerides >1.7 mmol/L, and high-density lipoprotein <1.1 mmol/L).[17]

The latter blood sample was allowed to clot, centrifuged at 3000 revolutions per minute for 5 min to extract the serum and stored frozen. It was used for measurement of TT, follicle stimulating hormone (FSH) and luteinizing hormone (LH) by enzyme-linked immunosorbent assay technique, (Fortress Diagnostics, United Kingdom).

Serum TT <8 nmol/L, 8–12 nmol/L and >12 nmol/L were regarded as low, borderline and normal respectively according to expert recommendations.[14] Based on the Endocrine Society recommendations that a diagnosis of hypogonadism be made only in the presence of symptoms of testosterone deficiency and a subnormal testosterone level,[1] overt hypogonadism was defined as a combination of positive ADAM score with low TT concentration while possible hypogonadism was defined as a positive ADAM score with borderline TT concentration. Subjects who had serum TT >12 nmol/L irrespective of symptoms were regarded as eugonadal. Subjects who had hypogonadism with either low or normal FSH (≤14 mIU/ml), LH (≤7.8 mIU/ml) or both were diagnosed as hypogonadotropic hypogonadism while those with hypogonadism and elevated serum FSH (>14 mIU/ml), LH (>7.8 mIU/ml) or both were diagnosed as having hypogonadotropic hypogonadism.

Data analysis was done using the Statistical Package for Social Sciences version 17.0 (Chicago IL). Discrete variables were represented by frequencies and percentages while means and standard deviations (SDs) or medians and mean ranks were employed for continuous variables as appropriate. Associations between categorical variables were tested using the Chi-square statistics, whereas continuous variables were compared using the Student's *t*-test or Mann–Whitney U-test as appropriate. Nonparametric test of correlation (Spearman's test) was used to evaluate the strength of relationship between TT and WC. To determine predictors of hypogonadism, all the variables were entered into a multivariate logistic regression to compute their odds ratios (ORs). Statistical significance was established at $P < 0.05$.

Results

Baseline characteristics of the subjects

The mean age (±SD) of the study population was 57.99 ± 8.76 years (range 32–69 years). Over half of the participants (53.0%) were older than 60 years of age. The mean duration of DM was 6.62 ± 3.61 years (range 1–19 years), and 63.5% were on oral hypoglycemic agents. Central obesity was present in 56.0%. Mean TT was 14.37 ± 7.99 nmol/L (range 1.7–33.3) [Table 1].

Table 1: Sociodemographic, clinical and laboratory characteristics of the study population

Variable	Mean±SD	*n* (%)
Age (years)		
30-39	57.99±8.76	10 (5.0)
40-49		25 (12.5)
50-59		59 (29.5)
60-69		106 (53.0)
Waist circumference (cm)		
Obese (WC >94 cm)	94.22±4.54	112 (56.0)
Nonobese (WC <94 cm)		88 (44.0)
Duration of DM (years)		
≤5	6.62±3.61	108 (54.0)
6-10		57 (28.5)
11-15		28 (14.0)
>15		7 (3.5)
Treatment modality		
Lifestyle modification alone		5 (2.5)
Oral hypoglycemic agents		167 (63.5)
Insulin alone		7 (3.5)
Insulin + oral hypoglycemics		21 (10.5)
Hypertension		
Yes		122 (61.0)
No		78 (39.0)
HbA1c (%)		
Good DM control (<7)	7.65±1.72	90 (45.0)
Poor DM control (≥7)		110 (55.0)
Dyslipidemia		
Yes		69 (34.5)
No		131 (65.5)
Total testosterone (nmol/L)		
Low (<8)	14.37±7.99	59 (29.5)
Boderline (8-12)		47 (23.5)
Normal (>12)		94 (47.0)

Data are in numbers and percentages or means±SD. SD: Standard deviations, DM: Diabetes mellitus, HbA1c: Glycated hemoglobin, WC: Waist circumference

Prevalence and pattern of hypogonadism

Overt and possible hypogonadism occurred in 29.5% ($n = 59$) and 23% ($n = 46$) of the participants respectively. Of the 59 subjects who had overt hypogonadism, 45 (76.3%) had serum FSH and or LH that were either below or within the normal range, consistent with hypogonadotropic hypogonadism while 14 subjects (23.7%) had hypogonadotropic hypogonadism. Similarly, 42 (89.1%) of the 46 subjects who had possible hypogonadism were also hypogonadotrophic. Prevalence of hypogonadism by decades of age is shown in Figure 1.

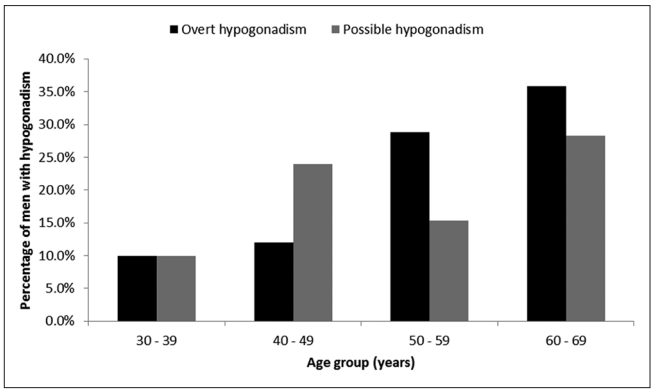

Figure 1: Prevalence of hypogonadism by age categories

Association between symptoms and serum testosterone levels

Erectile dysfunction (ED), reduced libido, fatigue, and mood changes were all significantly associated with TT levels, with the association being stronger for ED and low libido [Table 2]. Subjects who had low TT had a significantly higher frequency of ED than those with normal TT (OR = 5.287, $P = 0.001$).

Comparison of the clinical and biochemical parameters of subjects with and without hypogonadism

Subjects with overt hypogonadism were significantly older (mean age 59.68 ± 7.19 years) compared with eugonadal subjects (mean age 56.05 ± 9.72 years), ($P = 0.014$). Mean WC was also significantly higher in the hypogonadal than eugonadal subjects (96.98 ± 3.71 vs. 93.18 ± 4.20, $P = 0.009$). Following the exclusion of hypogonadotropic patients, subjects with overt hypogonadism had significantly lower levels of both FSH ($P = 0.002$) and LH ($P = 0.003$) than their eugonadal counterparts [Table 3].

Predictors of hypogonadism

Following a multivariate regression analysis, older age, and central obesity were the significant predictors of hypogonadism in the study population [Table 4]. Compared to those that were <60 years, subjects 60 years or older were more likely to be hypogonadal (OR = 2.175, 95% confidence interval [CI] = 1.016–4.657, $P = 0.046$). Subjects with WC 94 cm or more also had a higher probability of being hypogonadal (OR = 7.606, 95% CI = 3.143–18.407, $P = 0.001$).

Discussion

Prevalence of testosterone deficiency and hypogonadism

Our study has demonstrated that over a quarter of men with type 2 DM have symptomatic hypogonadism, and nearly another one-quarter are possibly hypogonadal. These findings lend support to those of many authors who had documented a high frequency of testosterone insufficiency in men with type 2 DM.[2-5] Our observed prevalence of 29.5% is somewhat lower than 33.5% reported by Ogbera *et al*. in a cross-sectional survey of 203 male type 2 diabetics in Lagos, Nigeria.[5] It is noteworthy that we used a more stringent operational definition of hypogonadism since the presence of symptom(s) was mandatory for the diagnosis of hypogonadism. In the above-cited study,[5] hypogonadism was diagnosed based on either low TT level <8 nmol/L alone or serum TT 8–12 nmol/L with symptoms. Dhindsa *et al*. had also reported a 33% prevalence, but it was based solely on testosterone measurements.[4] Using similar diagnostic criteria, Kapoor *et al*. however reported a much lower prevalence of 17%.[15] Differences in population sizes and demographics, duration and severity of diabetes and presence of other confounding co-morbidities may have led to these divergent prevalence rates. Nevertheless, most authors agree that hypogonadism is not only a frequent occurrence in men with type 2 DM, but it is also under-diagnosed.

IR, a common feature of type 2 DM, is known to be associated with low sex hormone binding globulin (SHBG) levels resulting in low TT levels.[6] This brings to fore the importance of FT measurement and the possibility that low SHBG levels may partly account for our finding. Unfortunately, owing to cost constraints, we could not measure SHBG to clarify this argument. However, an earlier study had reported even a higher prevalence of hypogonadism based on FT compared to TT, suggesting that the low SHBG associated with IR may not be blamed for this abnormality.[15]

The high prevalence of obesity (56%) in our study population is another possible confounder. Obesity is also an insulin resistant state and is associated with low SHBG.[10] However, studies have shown that FT levels are lower in obese men and inversely correlate with the degree of obesity.[11,12] Interestingly, 13.6% of nonobese subjects in this study had low TT levels. A greater number

Table 2: Association between symptoms and serum testosterone concentration

TT category	Erectile dysfunction		*P*	OR	95% CI
	Yes (*n*=120)	No (*n*=80)			
Low	47 (79.7)	12 (20.3)	0.001	5.287	2.487-11.242
Borderline	33 (70.2)	14 (29.8)	0.002	3.182	1.508-6.716
Normal	40 (42.6)	54 (57.4)			
	Low libido				
	Yes (*n*=79)	No (*n*=121)			
Low	39 (66.1)	20 (33.9)	<0.001	6.020	2.944-12.309
Borderline	17 (36.2)	30 (63.8)	0.148	1.749	0.819-3.734
Normal	23 (24.5)	71 (75.5)			
	Fatique				
	Yes (*n*=82)	No (*n*=118)			
Low	32 (54.2)	27 (45.8)	0.001	3.100	1.566-6.137
Borderline	24 (51.1)	23 (48.9)	0.007	2.729	1.317-5.657
Normal	26 (27.7)	68 (72.3)			
	Mood changes				
	Yes (*n*=43)	No (*n*=157)			
Low	21 (35.6)	38 (64.4)	0.001	3.776	1.685-8.462
Borderline	10 (21.3)	37 (78.7)	0.193	1.847	0.733-4.656
Normal	12 (12.8)	82 (87.2)			

Data are in numbers and percentages. TT: Total testosterone, OR: Odds ratio, CI: Confidence interval

Table 3: Clinical and biochemical profiles of subjects with and without hypogonadism

Variables	Hypogonadal	Eugonadal	*P*
Age (years)	59.68±7.19	56.05±9.72	0.014
Waist circumference (cm)	96.98±3.71	93.18±4.20	0.009
Duration of DM (years)	6.86±3.88	6.46±3.57	0.513
Hypertension	35 (59.3)	60 (63.2)	0.634
Dyslipidemia	22 (37.3)	31 (32.6)	0.554
HbA1C (%)	7.70±1.66	7.44±1.63	0.343
TC (mmol/L)	4.27±0.94	4.28±0.79	0.970
TG (mmol/L)	1.42±0.48	1.42±0.43	0.963
LDL (mmol/L)	2.13±0.71	2.11±0.53	0.866
HDL (mmol/L)	4.28±1.94	1.21±0.15	0.629
FSH (IU/ml)*	2.30 (63.45	3.80 (86.23)	0.002
LH (IU/ml)*	1.80 (63.89	2.30 (85.95)	0.003

Data are in means±SD or frequencies (%). *Data are in median (mean ranks). DM: Diabetes mellitus, HbA1C: Glycated hemoglobin, TC: Total cholesterol, TG: Triglycerides, LDL: Low-density lipoprotein, HDL: High density lipoprotein, FSH: Follicle stimulating hormone, LH: Luteinizing hormone, SD: Standard deviation

Table 4: Multiple logistic regression results of factors associated with hypogonadism

Variables	OR	95% CI for OR		*P*
		Lower	Upper	
Age ≥60 years	2.175	1.016	4.657	0.046*
WC ≥94 cm	7.606	3.143	18.407	<0.001*
Duration of DM <5 years	0.901	0.412	1.971	0.794
Hypertension	1.080	0.505	2.310	0.843
HbA1c <7%	0.819	0.387	1.736	0.603
Dyslipidemia	0.937	0.432	2.032	0.869

*statistically significant with *P* value < 0.05 WC: Waist circumference, DM: Diabetes mellitus, HbA1c: Glycated hemoglobin, OR: Odds ratio, CI: Confidence interval

of nonobese subjects (31%) in a previous study also had low TT levels.[4] It is, therefore, logical to conclude that even though obesity may have contributed to the high prevalence of hypogonadism in this study, it is likely that other factors associated with type 2 DM also play significant roles.

Gonadotrophin levels in subjects with hypogonadism

We observed that 76.3% of subjects with overt hypogonadism and 89.1% of patients with possible hypogonadism were hypogonadotrophic. Elevated gonadotrophins (hypergonadotrophic) were noted in 23.7% and 10.9% of subjects with overt and possible hypogonadism, respectively. Furthermore, both LH ($P = 0.003$) and FSH ($P = 0.002$) levels were significantly lower in the hypogonadal than eugonadal group. Findings are consistent with those of Dhindsa *et al.* and suggest that dysfunction of the anterior pituitary gland, the hypothalamus or both leading to low gonadotrophin secretion is primarily responsible for DM-associated hypogonadism.[4] Data from animal and human studies support hypothalamic rather than pituitary gland defect.[4,21,22] In one study, no difference in prolactin levels was observed between hypogonadal and eugonadal groups and no pituitary lesion was found in pituitary magnetic resonance imaging of a random selection of the subjects with hypogonadotrophic hypogonadism.[4] In another study of type 2 DM men with hypogonadotrophic hypogonadism, a normal LH and FSH rise following gonadotrophin releasing hormone (GnRH) administration was observed.[21] Brüning *et al.* had previously demonstrated that IR depresses hypothalamic secretion of GnRH leading to hypogonadotrophic hypogonadism.[22]

Relationship between symptoms and testosterone level

ED and low libido were the most frequent symptoms affecting 79.7% and 70.2% of participants with low and borderline TT, respectively. Our data showed that subjects with low TT were 5 times more likely to have ED than those with normal TT. Interestingly, subjects with ED had a significantly lower mean TT compared to those without ED (11.54 ± 6.82 nmol/L vs. 18.62 ± 7.76 nmol/L; $P = 0.001$). Literatures abound on the relationship between androgens and erectile function in both diabetic and nondiabetic populations. Kapoor *et al.* had previously reported 76% prevalence of ED in type 2 diabetic men with low TT.[15] Ogbera *et al.* similarly reported a significantly lower serum TT in diabetic men with ED compared to controls.[5] In nondiabetic population, meta-analysis has shown that approximately one-third of men with ED have androgen deficiency.[23] There are fewer data evaluating the relationship between reduced libido and low testosterone. However, in one study, poor morning erections, low libido, and ED had a syndromic relationship with low testosterone levels.[24] Furthermore, testosterone replacement in hypogonadal men improved both libido and erection.[25] The effects of testosterone treatment on libido were observed to be more consistent than on erectile function suggesting that androgens are probably more important in sexual drive than in penile erection.[23]

Age, hypertension, glycated hemoglobin, obesity, and testosterone levels in the diabetic population

We observed that the prevalence of overt hypogonadism increased progressively from 10% in the age group 30–39 years to 35.8% in the age group 60–69 years. Conversely, hypogonadal subjects were significantly older than eugonadal ones ($P = 0.014$). Age-related decline in testosterone levels in both diabetics and nondiabetics have been previously documented.[15,26] Normal ageing is associated with about 0.5–2% per year decrease in TT levels or about 0.110 nmol/L per year.[26] Although our study was not designed to compare testosterone levels in diabetics and nondiabetics, we compared the prevalence of hypogonadism in our study with that from the Baltimore Longitudinal Study of Ageing (BLSA),[26] one of the most studies describing the age-related decline in testosterone levels. In the BLSA involving 3661 participants of 40 years and above, 8, 12 and 19% of subjects in the age groups 40–49, 50–59, and 60–69 years respectively had hypogonadism defined as serum TT <11.3 nmol/L. Despite using a lower TT cut-off of <8 nmol/L, we observed a much higher prevalence of hypogonadism across all age groups (12, 28.8, and 35.8% in the age groups 40–49, 50–59, and 60–69 years, respectively). Other authors similarly reported a higher prevalence of hypogonadism in type 2 diabetics than age-matched subjects.[4,15] This suggests that factors other than ageing may contribute significantly to diabetes-related hypogonadism.

We did not observe any significant association between hypertension and hypogonadism. In contrast, some authors reported a significantly lower TT levels in hypertensive than normotensive subjects.[27] This is not surprising since IR which underlies hypertension and other components of the metabolic syndrome have been shown to be associated with low TT levels in men. However, other studies have failed to show any relationship between hypertension and testosterone deficiency just as testosterone replacement in hypogonadal men did not have any appreciable effect on BP in long-term.[9,15] Data on the association between testosterone deficiency and hypertension is presently at best, inconsistent.

No significant association was noted between glycemic control as assessed by HbA1c and testosterone levels ($P = 0.34$). Similar findings have been reported elsewhere.[8] In contrast, Kapoor *et al.* noted a significant

but weak correlation between serum TT and HbA1c ($r = -0.16$; $P = 0.04$).[15] However, when both HbA1c and WC were adjusted for in regression analysis, WC but not HbA1c remained a significant predictor of TT. Testosterone deficiency has been shown to reduce insulin sensitivity in type 2 diabetics, and this is expected to worsen glycemic control. Furthermore, testosterone replacement therapy has been shown to improve IR, glycemic control, cholesterol levels and WC in diabetic men with low testosterone.[9] Nevertheless, further research in this direction is needed.

A significant inverse correlation ($r = -0.41$, $P = 0.001$) was observed between WC and serum TT. Our data showed that subjects with central obesity were 7 times more likely to be hypogonadal than those with normal WC. This finding is consistent with that of Kapoor *et al.* and could be explained by the hypogonadal-obesity cycle described by Cohen.[15,28]

Conclusion

Symptomatic hypogonadism is a common occurrence in men with type 2 DM, particularly among the middle-aged and elderly. Symptoms of testosterone deficiency are however nonspecific and occur in a significant proportion of eugonadal subjects. ED is the most common symptom associated with low testosterone levels in diabetic men. There is an inverse relationship between WC and serum testosterone levels in men with type 2 diabetes.

We recommend routine screening of all high-risk type 2 diabetic men including those 60 years of age or older and those with central obesity.

The limitations of this study include its cross-sectional nature which does not permit inference on cause and effect relationship, a relatively small sample size and our inability to measure FT and SHBG due to unavailability of FT assays in our practice and cost respectively.

The major strength of our study is that to our knowledge; this is the first study of hypogonadism in men with type 2 DM in Nigeria that adopted the international diagnostic criteria for hypogonadism as recommended by the Endocrine Society, which is based on a combination of symptoms of androgen deficiency and low testosterone levels.

Acknowledgment

The authors are grateful to the management of the Obafemi Awolowo University Teaching Hospitals Complex Ile-Ife for providing a little financial support.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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