

Hypogonadism among obese type 2 diabetic men in South-Western Nigeria

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Abstract

Background: Studies have shown that hypogonadism is closely related to the development of Type 2 Diabetes. This study aimed to assess hypogonadism among type 2 diabetic and obese male patients in Southwest Nigeria.

Methods: One hundred and twenty men consisting of thirty obese diabetics, thirty non-obese diabetics, thirty obese non-diabetics and thirty non-obese non-diabetics, were included in the study. Participants were interviewed to obtain data on biodata, reproductive characteristics, and anthropometry. Venous Blood was collected for the determination of fasting plasma Glucose, glycated haemoglobin, and reproductive hormonal levels.

Results: The prevalence of hypogonadism in this study was 20.8%. The mean age of all the participants was 43.39 ± 5.21 , most men being in the 40-44 years age group. In this age group, over a third (40%) of the men had low testosterone. Out of the 60 participants who were diabetic, 18 (30%) had low testosterone, two-third of whom (66.7%) were obese. Mean testosterone was significantly lower in obese diabetics when compared with non-obese diabetics. The mean testosterone and FSH were significantly lower in obese non-diabetics as well. Both diabetic and non-diabetic groups had significantly higher estrogen in the obese participants, than in the non-obese.

Conclusion: In conclusion, hypogonadism is a common finding among diabetic men, and it occurs in higher frequency with coexisting obesity. Hence, a holistic approach in the treatment of male patients with hypogonadism, type 2 diabetics and obesity should be considered, in order to safeguard their reproductive health.

Key Words: Hypogonadism, obesity, FSH, LH, testosterone, Nigeria.

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Hypogonadisme chez les obèses diabétiques de type 2 hommes dans le Sud-Ouest du Nigéria

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Résumé

Objectif : Des études ont montré que l'hypogonadisme est étroitement lié au développement du diabète de type 2. Cette étude visait à évaluer l'hypogonadisme chez les hommes diabétiques et obèses de type 2 dans le sud-ouest du Nigéria.

Méthode: Cent vingt hommes comprenant trente diabétiques obèses, trente diabétiques non obèses, trente non diabétiques obèses et trente non diabétiques non obèses ont été inclus dans l'étude. Les participants ont été interrogés pour obtenir des données sur les bidonnées, les caractéristiques de reproduction et l'anthropométrie. V Enous sang a été prélevé pour la détermination du plasma à jeun de glucose, glycolyse de l'hémoglobine, et les niveaux hormonaux de reproduction.

Résultats: La prévalence de l'hypogonadisme dans cette étude était de 20,8%. L'âge moyen de tous les participants était de $43,39 \pm 5,21$, la plupart des hommes étant âgés de 40 à 44 ans. Dans ce groupe d'âge, plus d'un tiers (40%) des hommes avaient une faible testostérone. Sur les 60 participants diabétiques, 18 (30%) avaient une faible testostérone, dont les deux tiers (66,7%) étaient obèses. La testostérone moyenne était significativement plus faible chez les diabétiques obèses par rapport aux diabétiques non obèses. La testostérone moyenne et la FSH étaient également significativement plus faibles chez les non diabétiques obèses. Les groupes diabétiques et non diabétiques avaient des œstrogènes significativement plus élevés chez les participants obèses que chez les non obèses.

Conclusion: En conclusion, l'hypogonadisme est une constatation courante chez les hommes diabétiques, et il se produit en fréquence plus élevée avec une obésité coexistant. Par conséquent, une approche holistique dans le traitement des patients masculins souffrant d'hypogonadisme, de diabétiques de type 2 et d'obésité devrait être envisagée, afin de protéger leur santé reproductive.

Mots-clés: hypogonadisme, obésité, FSH, LH, testostérone, Nigéria.

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INTRODUCTION

Diabetes mellitus (DM) is one of the most prominent health threats in modern societies, affecting about 422 million people worldwide, particularly in low- and middle-income countries (1). It is a chronic condition characterized by hyperglycemia, which when uncontrolled leads to microvascular damage in the major body systems (2). Male Hypogonadism also known as testosterone deficiency is an endocrine disorder characterized by the inability of the testes to produce the male sex hormone testosterone, sperm or both (3). Hypogonadism may be primarily due to testicular failure or from secondary causes attributed to Hypothalamic-Pituitary-Gonadal axis dysfunction. Male Hypogonadism may occur in men at any age, an earlier study reported that more than 60% of men aged greater than 65 have free testosterone levels below the normal values for men aged 30 to 35 years (4).

A closer look into Fertility rates of modern societies reveals that the increased incidence of Diabetes mellitus has been closely associated with falling fertility rates in both males and females (5,6). Recent studies have shown that hypogonadism is closely related to the development of Type 2 Diabetes Mellitus (T2DM) (7,8), and obese men with T2DM are significantly more likely to develop hypogonadism, with reported proportions of over a third of affected individuals (9). Obesity is a proinflammatory state resulting in increased release and secretion of proinflammatory cytokines and adipokines, free fatty acids, and estrogens from adipose tissue. These increases are important risk factors that may contribute to the development of metabolic syndrome and T2DM as well as androgen deficiency (10). Epidemiological studies support a bidirectional relationship between serum testosterone and obesity as well as between testosterone and the metabolic syndrome. Low serum total testosterone predicts the development of central obesity and accumulation of intra-abdominal fat (11). Also, low total and free testosterone and Sex Hormone Binding Globulin (SHBG) levels are associated with an increased risk of developing the metabolic syndrome, independent of age and obesity (12). Conversely, high BMI, central adiposity, and the metabolic syndrome are associated with and predict low serum total testosterone and to a lesser extent free testosterone and SHBG levels (11).

Although there is no doubt that Diabetes Mellitus is responsible for several pathological

and biochemical alterations that reduce male fertility, the impact of the disease on male reproductive health is varied. Sexual disorders, such as erectile dysfunction and retrograde ejaculation are known to occur in diabetic individuals and usually end-up in a reduction of sexual appetite that is often attributed to lethargy and a certain degree of tiredness associated with the hyperglycemic state (13-15). Previous researchers have found that the prevalence of hypogonadism was not dependent on severity of hyperglycemia assessed as glycosylated hemoglobin (HbA1c) levels (16).

The aim of this study was to assess hypogonadism among T2DM obese and non-obese males in Nigeria. This will enable clinicians in our environment improve on quality of holistic treatment in patients with conditions of hypogonadism, T2DM and Obesity.

MATERIALS AND METHODS

Study Setting

The study was conducted at the Dame Adebutu Centre for Diabetes Care of the Endocrinology, Diabetes and Metabolism division, Olabisi Onabanjo University Teaching Hospital (OOUTH), Sagamu, Ogun State, Southwest Nigeria. The Endocrinology, Diabetes and Metabolism division provides services to the patients of Sagamu and other satellite towns in Ogun state, as well as the neighboring states of Lagos, Oyo and Ondo.

Study Design

This was a cross-sectional, comparative, hospital-based study.

Recruitment of Participants

One hundred and twenty male participants were recruited into the study consisting of thirty diabetic obese males, thirty diabetic non-obese males, thirty non-diabetic obese males and thirty non-diabetic non-obese. Research participants were drawn from patients of the Dame Adebutu Centre for Diabetes Care of the Olabisi Onabanjo University Teaching Hospital (OOUTH). Diabetics who are hypertensive, smokers and individuals on narcotics and steroids were excluded.

Sampling Design

The sample size was calculated using the Cochran formula $N = Z^2 pq/d^2$ (17). With a prevalence of 1.85% based on male prevalence rate of T2DM in Abeokuta, Ogun state, Nigeria (18). This resulted in a sample size of 27.9

approximated to 30 for each study group.

Data collection

Personal interviews were conducted for each participant using a structured questionnaire that contained items on reproductive characteristics, anthropometric indices and biodata.

Ten (10) mls of blood sample was collected from each participant. Five (5) mls, 3mls and 2mls were dispensed into plain bottle (for assay of biochemical assay), EDTA bottle (for Haematological Assay) and Fluoride oxalate bottle (for Fasting Plasma Glucose) respectively.

Laboratory procedures

The blood collected was centrifuged at 4000 rev/min for 10 minutes. The serum from the plain bottle was separated into labelled plain bottles and stored at -20°C until analysis while the plasma from fluoride bottle and blood in EDTA bottle were analysed within 8hrs of collection.

Assays of blood HbA1c was done by the method of ion exchange resin. Serum FSH, LH, oestrogen and testosterone assays were performed using the Enzyme Immunoassay (EIA) kits from Bio-Inteco (UK) Ltd, England. Fasting plasma glucose was determined by the glucose oxidase method using kits from Randox Laboratories Ltd, United Kingdom.

Definition of terms

Hypogonadism was defined as:

BMI (Obesity) – 30-34kg/m²

HBA1c – 5.2-5.6 (Normal), 5.7-6.4 (Prediabetes), 6.5-7.0 (Diabetes), 7.1-8.4 (Harmful), 8.5-15 (Dangerous)

FPG – 70-110 mg/dl (normal)

FSH - <1.0 (low), 1.0-2.0(border), 2.1-14(normal)

LH – <0.1(low), 0.1-1.9(border), 2.0-7.4(normal)

Testosterone - <3(low), 3-10(normal)

Oestrogen - <10(low), 10-82(normal) (19).

Obese participants were defined as participants with BMI 30 to 34 kg/m² (20) (WHO, 2008).

Statistical analysis

Statistical Package for Social Sciences (SPSS), version 20 was used for data input and analyses. Chi-square test was used to test for significant association between categorical variables, while Student's t-test was used to test the difference between the means of two groups of continuous variables. Statistical significance was set at $P < 0.05$.

Ethical considerations

Approval for the study was obtained from the Health Research and Ethics Committee of OOUTH, with registration number OOUTH/HREC/08/10/2012. Written informed consents were obtained from all study participants. All relevant standards of the Revised Declaration of Helsinki were followed.

RESULTS

Sociodemographics

The mean age of all the (120) participants that were recruited into the study was 43.39 ± 5.21 with a range of 35 to 55 years. Most participants (38.3%) were between the age of 40 and 44 years. Other sociodemographic data can be found in Table 1. All the diabetic participants were on medications, with over half (51.7%) of them on metformin and another 35% on both metformin and insulin. Majority of the diabetic participants (86.7%) had history of Erectile Dysfunction. The few non-diabetic participants who used medication routinely (6.7%) only used multivitamin supplements. Only a small percentage of the non-diabetic participants (6.7%) had history of erectile dysfunction. Of all the participants, 11 (9.2%) had borderline Follicle Stimulating Hormone (FSH), 5 (4.2%) had borderline Luteinizing Hormone (LH), 25 (20.8%) had low testosterone and 2 (1.7%) had low oestrogen. All others had normal FSH, LH, testosterone and oestrogen (see Figure 1). 84.0% and 92.0% of the participants who had low testosterone, had inappropriately normal FSH and LH respectively, while the remaining 16% and 8% had borderline FSH and LH respectively. The age group with the highest frequency of borderline FSH was 45-49 years (36.4%), while the age group with the highest frequency of borderline LH was 40-44 years and 50-55 years. About 40% of those aged 40-44 years had low testosterone. Oestrogen was normal in all but 2 participants who had low oestrogen, 1 in the 40-44 years range, and the other in the 44-49 age range. Out of the 60 participants who were diabetic (30 – obese; 30 – non-obese), 18 individuals (30%) had low testosterone, while the others had normal testosterone. Two-third of them (66.7%) who were diabetic and had low testosterone, were obese.

Comparing Means

Details of the means of the Body Mass Index (BMI), glycated hemoglobin (HBA1c), Fasting Plasma Glucose (FPG), FSH, LH,

testosterone and oestrogen can be found in Table 2.

Diabetic groups (Obese Vs Non-obese)

The mean BMI, FSH, LH and oestrogen of the non-obese diabetics were within normal limits. However the mean HBA1c in this group was within harmful limits, while the FPG and testosterone were in the diabetic and low ranges respectively. On the other hand, the mean FSH, LH and oestrogen of the obese diabetics were within normal limits, while the mean BMI was in the obese range, and the HBA1c, FPG, and testosterone were in the harmful, pre-diabetic and low ranges respectively (see Table 2).

The BMI was significantly higher in the obese diabetics than in the non-obese diabetics ($P < 0.05$) (Table 3). Mean testosterone level was noted to be significantly lower in the obese diabetics than in the non-obese diabetics ($P < 0.05$) (Table 3). Conversely, the mean oestrogen level was significantly higher in the obese diabetics than in the non-obese group. There was no significant difference in the mean levels of the HBA1c, FPG, FSH and LH between the obese diabetics and the non-obese diabetics.

Non-diabetic groups

All means of the anthropometric and biochemical parameters (BMI, HBA1c, FPG, FSH, LH, Testosterone and Oestrogen) were within normal limits in the non-obese non-diabetic groups. Only the mean BMI was significantly elevated in the obese non-diabetic group ($p < 0.05$), whereas all other parameters were normal. However, the mean FSH and testosterone were significantly lower in the obese non-diabetics than in the non-obese non-diabetics ($p < 0.05$). Conversely, the mean oestrogen level was significantly higher in the obese non-diabetics than in the non-obese non-diabetics ($p < 0.05$) (see Table 2, Table 3).

Obese Groups (Diabetics Vs Non-Diabetics)

The mean FSH, LH and oestrogen levels of the obese diabetics were within normal limits, while the HBA1c was harmfully high, the FPG was in the pre-diabetic range, the testosterone was low and the oestrogen was within normal limits. Conversely, the obese non-diabetics had normal mean HBA1c, FPG, FSH, LH, testosterone and oestrogen. The BMI in both groups were in the obese range. The lower FSH, LH and testosterone observed in the obese diabetics were statistically significant. Similarly, the higher mean HBA1c, FPG and oestrogen

were statistically significant ($p < 0.05$) (see Table 2, Table 3).

Non-obese groups (Diabetics Vs Non-Diabetics)

The non-obese diabetic group had normal mean BMI, FSH, LH and oestrogen, while the HBA1c was harmfully high, the FPG was in the diabetic range and the testosterone was low. On the other hand, the means of all the anthropometric and biochemical parameters for the non-obese non-diabetics (BMI, HBA1c, FPG, FSH, LH, testosterone and oestrogen) were all within normal limits. The higher HBA1c, FPG and oestrogen in the non-obese diabetics was statistically significant, as were the lower FSH, LH and testosterone ($p < 0.05$). There was no significant difference in the BMI of both groups (see Table 2, Table 3).

Sex hormones and Erectile Dysfunction

Our findings show a significant relationship between low testosterone and erectile dysfunction ($p < 0.05$) (see Table 4).

DISCUSSION

Studies have shown that hypogonadism can occur at any age, though much more common amongst older males (21). One particular study reported hypogonadism in over a third of the men 45 years, with diabetes being the third commonest association, after hypertension and hyperlipidemia (22). In our study however, most of our participants who had low testosterone were slightly younger (in the 40-44 years range). The most prevailing pattern of hypogonadism from our study is the hypogonadotropic hypogonadism, which is characterized by low levels of testosterone accompanied by inappropriately normal to low FSH and LH. This is the same pattern obtainable in similar studies amongst diabetics, more so in obese diabetics (23).

The mechanism behind this finding is complex and likely multifactorial. The suppression of the gonadotropins in diabetes is postulated to be due to the excessive activity of aromatase in the obese which converts the androgens in estrogen which can potentially inhibit Gonadotropin Releasing Hormone (GnRH). Other researchers have however disproved this theory (24).

A study showed that one-third of men with obesity or type 2 diabetes have subnormal free testosterone concentrations. The lower free testosterone concentrations are observed in obese

men at all ages, including adolescents at completion of puberty (25). Aromatase, the enzyme that converts testosterone to estradiol, is mainly located in adipose tissue, and Obesity is associated with elevated estrogen in men activating hypothalamic estrogen receptors triggering inhibition of the Hypothalamic-Pituitary-Gonadal axis. Treatment with aromatase inhibitors reverses the Hypogonadotropic Hypogonadism associated with Obesity (26). The leptin theory also seems to be a viable explanation, as leptin resistance at the level of the hypothalamus, which is common in obesity, can reduce the stimulatory effect of leptin on the hypothalamo-pituitary-gonadal axis, resulting in hypogonadism (23).

The observation of elevated serum oestrogen levels in obese men (diabetic and non-diabetic) is probably due to the activity of aromatase, the enzyme that converts testosterone to oestrogen (25).

Our study also found that even in the non-diabetic groups, the obese participants had significantly lower FSH and testosterone. This goes to show the pivotal role that obesity plays in hypogonadism, with or without diabetes present. In the presence of diabetes, the testosterone and gonadotropins are further reduced, as obviated by our study.

Some researchers have reported that BMI, central adiposity, and metabolic syndrome are associated with and predict low serum testosterone (11). Visceral fat is an active secretory tissue producing inflammatory factors including interleukin (IL)-6, IL-1 β , plasminogen activator inhibitor-1, Tumor Necrosis Factor (TNF)- α , Angiotensinogen, vascular endothelial growth factor, and Serum amyloid A which contribute to systemic and peripheral vascular inflammation and dysfunction (26). However, in this study, the presence of low serum testosterone was not entirely dependent upon obesity but also on diabetes. This study showed that low serum testosterone is associated with men with T2DM while obesity as a cofounding factor resulted in further decrease in serum testosterone level.

CONCLUSION

Hypogonadism is a common finding among diabetic men and it occurs in higher frequency with coexisting obesity. Hence a holistic approach in the treatment of male patients with hypogonadism, type 2 diabetics and obesity should be considered, in order to safeguard their reproductive health.

Conflict of interests: Authors have declared no competing interests exists

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Table 1: Socio-demographic characteristics of Total Participants

Variable	Frequency (n = 120)	Percentage
Age group (in years)		
35-39	31	25.8
40-44	46	38.3
45-49	24	20.0
50-55	19	15.8
Marital Status		
Married	120	100.0
Not Married	0	0.0
Number of Children		
1	3	2.5
2	30	25.0
3	36	30.0
4	29	24.2
5	15	12.5
6	7	5.8
Total	120	100

Table 2 Anthropometry and plasma analytes of diabetic and non-diabetic participants

Variables	Non-Obese Diabetic (Mean ± SD)	Obese Diabetic (Mean ± SD)	Non-Obese Non-Diabetic (Mean ± SD)	Obese Non-Diabetic (Mean ± SD)
BMI (kg/m ²)	22.83 ± 2.57	32.52 ± 1.60	23.11 ± 2.67	32.67 ± 2.37
HBA1c (%)	7.72 ± 1.43	7.23 ± 1.12	5.17 ± 0.46	5.14 ± 0.42
FPG	128.87 ± 54.33	113.53 ± 22.29	86.47 ± 6.13	90.63 ± 10.26
FSH	3.92 ± 1.35	3.77 ± 1.31	7.72 ± 1.20	6.08 ± 2.02
LH	3.06 ± 0.99	3.17 ± 1.19	5.34 ± 0.93	5.02 ± 1.35
Testosterone	2.83 ± 0.45	2.57 ± 0.48	5.12 ± 0.74	3.64 ± 1.45
Oestrogen	20.43 ± 3.31	51.05 ± 8.81	12.08 ± 1.78	41.40 ± 13.20

Reference ranges**BMI (Obesity)** – 30-34kg/m²**HBA1c** – 5.2-5.6(Normal), 5.7-6.4 (Prediabetes), 6.5-7.0(Diabetes), 7.1-8.4(Harmful), 8.5-15(Dangerous)**FPG** – 70-110 mg/dl (normal)**FSH** - <1.0 (low), 1.0-2.0(border), 2.1-14(normal)**LH** – <0.1(low), 0.1-1.9(border), 2.0-7.4(normal)**Testosterone** - <3(low), 3-10(normal)**Oestrogen** - <10(low), 10-82(normal)

Table 3 Comparison of Means Using T-test

Comparison of Means	Non-obese Diabetic x Obese Diabetic T-test (p-value)	Obese Diabetic x Obese Non-Diabetic T-test (p-value)	Non-obese Diabetic x Non-obese Non-Diabetic T-test (p-value)	Non-obese Non-Diabetic x Obese Non-Diabetic T-test (p-value)
BMI (kg/m ²)	-17.25 (0.00*)	-0.29 (0.78)	-0.41 (0.68)	14.53 (0.00*)
HBA1c (%)	1.47 (0.15)	9.40 (0.00*)	9.15 (0.00*)	-0.25 (0.79)
FPG	1.41 (0.17)	5.03 (0.00*)	4.18 (0.00*)	1.88 (0.06)
FSH	0.43 (0.67)	-5.16 (0.00*)	-11.34 (0.00*)	-3.76 (0.00*)
LH	-0.41 (0.69)	-5.51 (0.00*)	-9.07 (0.00*)	-1.06 (0.29)
Testosterone	2.10 (0.04*)	-3.78 (0.00*)	-14.16 (0.00*)	-4.87 (0.00*)
Oestrogen	-17.51 (0.00*)	-3.27 (0.00*)	11.95 (0.00*)	11.85 (0.00*)

*Statistically significant at p < 0.05

Table 4 Association between Biochemical Parameters and Erectile Dysfunction

Variable	Erectile Dysfunction Frequency (%)		χ^2	P-value
	Yes (n = 52)	No (n = 8)		
HBA1c (%)				
Normal (5.2-5.6)	5(55.6)	4(44.4)	7.76	0.05
Pre-diabetes (5.7-6.4)	5(81.8)	2(18.2)		
Diabetes (6.5-7.0)	9(100.0)	0(0)		
Harmful (7.1-8.4)	20(95.2)	1(4.8)		
Dangerous (8.5-15)	13(92.9)	1(7.1)		
FSH (mIU/L)				
Borderline (1.0-2.0)	5(100.0)	0(0)	1.50	0.48
Normal (2.1-14)	47(85.5)	8(14.5)		
LH (mIU/L)				
Borderline (0.1-1.9)	11(91.7)	1(8.3)	0.36	0.49
Normal (2.0-7.4)	41(85.4)	7(14.6)		
Testosterone (ng/ml)				
Low (<3)	34(94.4)	2(5.6)	4.68	0.04*
Normal (3-10)	18(75.0)	6(25.0)		

*Statistically significant
 χ^2 -Chi square

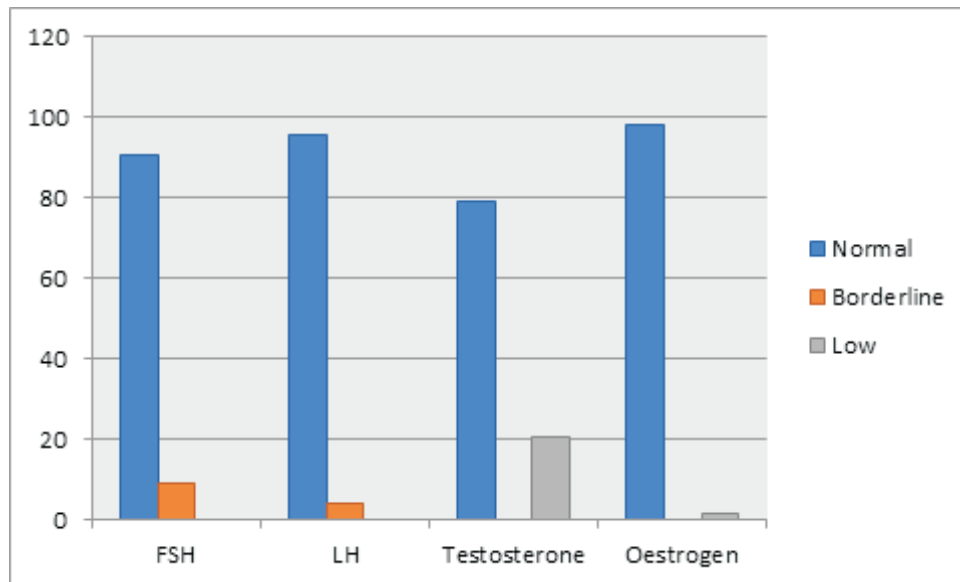


Figure 1 - Frequency distribution of Sex Hormone levels amongst Study Participants