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Profile and Role of Serum Hypothalamic-Pituitary-Testicular-Axis Hormones on Sexual Function of Older Men with Type-2 Diabetes

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Abstract: Little information is available on the complex endocrinology of sexual dysfunction, which is frequently associated with ageing and diabetes. We wanted to examine the serum profile of hypothalamic-pituitary-testicular-axis (HPTA) hormones and how they relate to sexual function in older men with type-2 diabetes. This study included 74 participants (44 type-2 diabetics and 30 healthy controls). The enzyme-linked immunosorbent assay (ELISA) method was used to measure serum levels of total testosterone (Te), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and prolactin (PRL). Compared to controls, diabetic patients had significantly higher FSH and PRL levels but lower Te levels. Testosterone was found to be significantly correlated with sexual intercourse frequency ($p<0.01$), erectile function, and libido ($p< 0.001$). We discovered significant ($p < 0.001$) relationships between libido, penile erection, and FSH, as well as between PRL and libido ($p< 0.05$). When compared to the other hormones, testosterone had the strongest associations with the frequency of sexual intercourse ($p< 0.05$), libido ($p< 0.05$), and penile erection ($p< 0.01$). Our findings indicated that HPTA hormones might have a significant influence on sexual functions in type-2 diabetic patients, with Te being the most important HPTA hormone influencing sexual functions in diabetic patients. This study, therefore, helps to clarify the complex endocrinology and physiology of the sexual dysfunction frequently observed in older men with type-2 diabetes and also supports the use of testosterone replacement therapy in older diabetic adults.
Keywords: Follicle-stimulating hormone, luteinizing hormone, prolactin, testosterone, sexual dysfunction.

INTRODUCTION

Diabetes mellitus, a metabolic disorder marked by chronic hyperglycemia and impaired carbohydrate, lipid, and protein metabolism, is one of the most prevalent chronic diseases affecting millions worldwide (Deshpande, 2008), (American Diabetes Association, 2013). It is typically accompanied by increased morbidity and mortality. Diabetes affects many end organs and causes psychological stress,

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increasing the risk of sexual problems in people with diabetes (Lue, 2000). For instance, diabetic hyperglycemia in patients damages the arterial blood vessels' normal anatomical structure and reduces their elasticity, weakening the arterial blood supply and delaying the cavernous sinus' filling (Ewing, 2011). The system-wide micro and macrovascular complications ultimately make it difficult for the person to become sexually aroused, which makes it difficult for him to enjoy and perform a sexual activity to the fullest extent possible and eventually results in sexual dysfunction (Gandhi et al., 2016). According to reports, sexual dysfunction is a common issue, especially for men and women with diabetes (Lue, 2000). Any issue that prevents a person or a couple from feeling sexually satisfied during any stage of the sexual response cycle, such as desire, arousal, physical pleasure, plateau, orgasm, and preference, is called sexual dysfunction (Clevand, 2015). Male sexual dysfunction in diabetic patients is primarily characterized by libido loss, erectile dysfunction, ejaculatory issues, and infrequent sex (Penson, 2004). For diabetic patients, all of these types of male sexual dysfunction can result in significant psychological stress, which can impact their quality of life.

The coordination of several human systems, including the nervous, cardiovascular, reproductive, and endocrine systems, is necessary to maintain normal sexual function (Trajanovska et al., 2013; Gerra et al., 2016; Ujah et al., 2017). The hypothalamic-pituitary-testicular axis (HPTA), which is perfectly coordinated by the endocrine regulation of the male reproductive system, maintains normal sexual function (Corradi PF et al., 2016). Pulsatile gonadotrophin-releasing hormone (GnRH) secretion from the hypothalamus triggers the anterior pituitary gland to release several hormones necessary for reproduction, including adrenocorticotropin, growth hormone, prolactin, and thyroid-stimulating hormone (TSH) (Sussman et al., 2008). To produce testosterone, inhibin B, an androgen-binding protein, luteinizing hormone, and FSH act on cells in the testes, including Leydig, Sertoli, and germ cells (Corradi PF et al., 2016). Males with physiological levels of prolactin (PRL) have also been shown to have improved luteinizing hormone receptors in Leydig cells, which causes the release of testosterone and, ultimately, spermatogenesis (Hair et al., 2002).

The HPTA hormone profile of older men with type-2 diabetes is poorly understood. To the best of our knowledge, there is a lack of information on the relationship between the HPTA hormones and the sexual functions of older men with type-2 diabetes. We are confident that the current study will contribute to a better understanding the intricate endocrinology and physiology underlying the sexual dysfunction frequently observed in older men with type-2 diabetes. Therefore, this study aims to assess the relationship between the serum profile of the HPTA hormones and the sexual functions of older men (40–68 years old) with type-2 diabetes.

MATERIALS AND METHODS

Subjects are a total of seventy-four people signed up for this study. Between January and November 2019, the Endocrinology Clinic at Central Hospital in Benin City, Edo State, Nigeria, recruited 44 older adult males with type-2 diabetes mellitus (mean age (SD), 53.0 (7.99) years) and 30 controls (mean age (SD), 46.9 (12.5) years) who appeared to be in good sexual health. From their case notes, the diabetic patients' medical histories and types of treatments were learned.

Based on the participant's self-report, medical history, clinical assessment, and glycated haemoglobin values greater than 6.5%, type-2 diabetes was identified.

A history of unstable cardiovascular and peripheral diseases, chronic illnesses, recent blood loss, age less than 40, and use of drugs known to interfere with glucose metabolism were among the exclusion criteria. Other exclusion criteria included the following: history of endocrine diseases, chronic consumption of alcohol or other drugs that may interfere with the serum hormone levels, use of hormone replacement therapy, or hormonal manipulation in the past or present.

Men who met the requirements for inclusion underwent structured questionnaire interviews. Information about a person's demographics and clinical characteristics, particularly chronic systemic diseases, smoking and drinking habits, type-2 diabetes in the family, current medications, mood/emotional rating, and frequency of sexual activity. All participants provided feedback on their level of libido and erection ability. The Zung Self-Rating Depression Scale, a 20-item self-report questionnaire that is frequently used as a screening tool and covers affective, psychological, and somatic symptoms associated with depression, was used to structure the participants' ratings of mood and emotional state. The individual item scores are added to create a total score of 80, then divided into four ranges: 25–49 for the normal range; 50–59 for mildly depressed; 60–69 for moderately depressed; and 70 and above for severely depressed. The categories were rated from 1 to 4 on a Likert scale. The participants were asked to record the frequency of their sexual activity for 30 days before completing the questionnaire interviews on sexual activity. For example, responses to questions such as 'how frequently do you have partial or full erections when sexually stimulated?'; 'how frequent are your erections firm enough for sexual intercourse?'; and 'how much difficulty do you experience in getting an erection over the previous 30 days?', were used to assess penile erectile function.

Similarly, responses to the questions "How many days do you have sexual desire in a week?" and "How would you rate your level of sexual desire based on the frequency of sexual desire?" were used to assess sex drive. Based on the responses to the question, "How many times have you had sex in a month," the frequency of sexual intercourse was evaluated. The frequency of sexual activity was classified as "none" if the response was zero, "rarely" if it was one to two, "occasionally" if it was three to four, and "regular" if it was five or more in a month or week as required. Each response was graded on a Likert scale from 1 to 4, and domain scores were calculated as the total scores for each question that made up the domain. After the interview, the patients were sent to the lab to have a blood sample taken for biochemical analysis to determine their HPTA hormone levels.

Ethical Considerations: Participants gave informed consent after being informed about the study's purpose, risks, potential benefits, and confidentiality. This work was approved by the Ministry of Health's ethics and research committee in Benin City, Edo State, under reference number HM.1208/7458.

Hormonal Assay

Blood samples were drawn via venipuncture between the hours of 8:00 and 11:00 am to test the serum levels of total Te (normal range: 3.0 - 10.0 ng/ml; Griffin et al., 1997), FSH (range: 1.4 - 18.1 mIU/ml), LH (range: 1.5 - 9.3 mIU/ml), and PRL (range: 2.1 - 17.7 ng/mL) (Chmitt et al., 2011). According to the manufacturer's instructions, serum levels of total Te, LH, FSH, and PRL were measured using the ELISA method and Calibiotech ELISA kits (Te, LH, FSH, and PRL), CA 92020, USA. The diabetic patients' primary hypogonadism was identified using a three ng/ml Te cut-off.

Data Analysis

For continuous data, the mean ± standard deviation, or median (percentile 25–75), was used, and for categorical variables, percentages were used. The non-parametric Mann-Whitney U test was used to compare the data from the control and diabetic groups. The Spearman Ranking test was used to conduct correlation tests involving two variables. The age, smoking, drinking, medication, and emotional state-adjusted correlations between the hormones of the hypothalamic pituitary-gonadotropic axis and the parameters of sexual function in diabetic patients were determined using Pearson's multivariate regression analysis. The cutoff for the significance test was $p<0.05$. IBM Software and SPSS were used for all statistical work (version 20).

RESULTS AND DISCUSSION

Table 1 presents the baseline demographics and characteristics of the study population. 44 type-2 diabetic patients with a mean age of 53 years (range: 40-68 years) and their healthy controls with a mean age of 46.9 years are included in the study (range: 35 – 85 years). According to the Mann-Whitney test, the type-2 diabetic patients were noticeably older than the control group. The majority of participants in the control (70%) and diabetic (47.7%) groups were under the age of 50. Most of the participants were: married (control, 76.7%; people with diabetes, 100%); employed as civil servants in both groups (control, 86.7%; diabetic group, 54.5%); Non-drinkers (control, 100%; people with diabetes, 90.9%) and non-smokers (93.2%) also had the lowest rates of diabetes. While every participant in the control group was classified as "not depressed," most participants in the diabetic group (52.3%) were depressed.

Table 2 compares the mean serum levels of LH, FSH, PRL, and Te in diabetic patients and their healthy controls. Compared to the control, the mean LH and PRL were significantly higher (Mann-Whitney test, $p = 0.048$ and $p < 0.001$, respectively). As opposed to the diabetic group, the control group showed a significantly higher ($p = 0.004$) mean Te. The mean PRL for the two groups (control, 5.56 ± 2.77 vs people with diabetes, 5.65 ± 4.42) did not differ significantly. The prevalence of primary hypogonadism among type-2 diabetic patients is shown in Figure 1. The majority of the patients (61.4%; n = 27) had primary hypogonadism (Te 3 ng/ml), while 38.6% (n = 17) had eugonadal (Te 3 ng/ml) conditions.

Table 3 lists the patients with type-2 diabetes sexual preferences. According to the data, 20.5% of diabetic patients reported "regular" sexual intercourse with their spouses, while 79.5% of diabetic patients reported "occasional sexual intercourse." Among the patients, 61% reported having "good" libido, while 38.6% had "poor" libido. The majority of patients (54.4%) reported "weak" and "strong" erections, respectively. According to the assessment of their sexual characteristics, type-2 diabetic patients' mean serum levels of HPTA hormones are expressed in Table 4. According to the Mann-Whitney test, patients with "poor" libido and "weak" erection were found to have significantly ($p < 0.001$) higher levels of FSH than those with "good" libido and "strong" erection. There was no discernible difference in FSH levels between patients who engaged in "occasional" and "regular" sex with their spouses ($p = 0.150$). Similarly, regarding the mean LH, there were no discernible differences in libido, penile erection, or frequency of sexual activity ($p = 0.621$, 0.507, and 0.190, respectively). Compared to patients with "good" libido, patients with "poor" libido had significantly higher mean PRL levels. However, there were no discernible differences in PRL between patients who engaged in "occasional" and "regular" sexual activity

(p = 0.110) or those who experienced "weak" and "strong" penile erections (p = 0.654). It's interesting to note that there were significant differences in Te for all patient sexual function domains. In comparison to patients with "occasional" sexual intercourse, "poor" libido, and "weak" erections, the mean Te was significantly higher in patients with "regular" sexual intercourse (p = 0.002), "good" libido (p < 0.001), and "strong" erection (p < 0.001, respectively).

The HPTA hormones and sexual functions in type-2 diabetic patients were correlated, as shown in Table 5. Significantly negative correlations between FSH and Te, libido, and erection were found using Pearson's bivariate correlation test (r = -0.712, p < 0.001), libido, and erection (r = -0.585, p < 0.001). LH and FSH had a significant positive correlation (r = 0.402; p < 0.01). There were no appreciable correlations between LH and Te, PRL, libido, penile erection, or FSI. The relationship between PRL and libido was significantly correlated (r = -0.353; p < 0.05). However, there was no correlation between PRL and FSI, LH, FSH, or penile erection. Te and libido (r = 0.636; p < 0.001), erection (r = 0.772; p < 0.001), and frequency of sexual activity (r = 0.484; p < 0.01) all showed significant positive correlations. A positive correlation between patients' penile erection and libido (r = 0.537; p < 0.001), as well as their frequency of sexual activity (r = 0.329; p < 0.05), was also found.

Table 1. Demographic and Baseline Characteristics of the Study Population

Characteristics	Control, n= 30 Mean ± SD or n (%)	Diabetic Patients, n = 44 Mean ± SD or n (%)	Size Effects Z or X^2	P-Value
Age (yrs)	46.9±12.5	53.0 ± 7.99	-2.93‡	0.003
≤ 50	21 (70.0)	21 (47.7)	9.45*	0.009
51 - 60	5 (16.7)	11 (25.0)		
>60	4 (13.3)	12 (27.3)		
Occupation				
Businessmen	2 (6.7)	4 (9.1)	9.82*	0.060
Civil Servants	26 (86.7)	24 (54.5)		
Unskilled Worker	1 (3.3)	4 (9.1)		
Farmers	0 (0)	1 (2.3)		
Retirees	0 (0)	5 (11.4)		
Unemployed	1 (3.3)	4 (9.1)		
Marital Status				
Married	23 (76.7)	44 (100)	11.34*	0.001
Single	7 (23.3)	0 (0)		
Smoking Habit				
Smokers	0 (0)	3 (6.8)	2.13*	0.267
Non-smokers	30 (100)	41 (93.2)		
Drinking Habit				
Current Drinkers	0 (0)	4 (9.1)	2.88*	0.118
Non-drinkers	30 (100)	40 (90.9)		
Emotional State				
Depressed	0 (0)	23 (52.3)	19.99*	<0.001
Not Depressed	30 (100)	21 (47.7)		

Abbreviations: SD, Standard Deviation; ‡, Z (Mann-Whitney correlation coefficient); *, X^2 (Chi-square coefficient).

Table 2. Serum Levels of the Hypothalamic-Pituitary-Testicular Axis Hormones in the Study Population

Variables	Control n = 30	Diabetic Patients n = 44	Man Whitney U Coefficient (Z)	P–Value
FSH (mIU/mL)				
Mean ± SD	16.66 ± 9.15	24.94 ± 22.75	-1.97	0.048
Range	3.50 – 44.50	4.40 – 142.70		
Median (percentile 25 – 75)	14.20 (9.9-20.0)	20.0 (13.65 - 29.7)		
Mean Ranking	31.52	41.58		
LH (mIU/mL)				
Mean ± SD	5.56 ± 2.77	5.65 ± 4.42	-0.63	0.527
Range	1.50 – 12.60	0.20 – 20.40		
Median (percentile 25 – 75)	5.90 (3.80-7.10)	5.0 (2.55 - 7.25)		
Mean Ranking	39.42	36.19		
PRL (ng/mL)				
Mean ± SD	0.26 ± 0.47	36.0 ± 25.01	-7.36	<0.001
Range	0 – 1.50	10.40 – 128.50		
Median (percentile 25 – 75)	0 (0 – 0.50)	28.35 (19.05 – 42.4)		
Mean Ranking	15.50	52.50		
Te (ng/mL)				
Mean ± SD	5.10 ± 3.92	3.01 ± 2.57	-2.89	0.004
Range	0.50 – 18.0	0.20 – 14.40		
Median (percentile 25 – 75)	4.45 (2.7 – 5.7)	2.40 (1.7 – 3.8)		
Mean Ranking	46.25	31.53		

Abbreviations: FSH, Follicle-Stimulating Hormone; LH, Luteinizing Hormone; PRL, Prolactin; Te, Testosterone; SD, Standard Deviation; Z, Mann-Whitney correlation coefficient

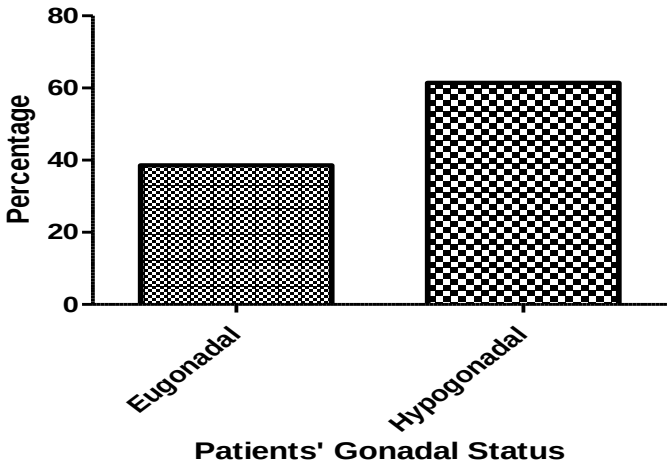

Figure 1. The Incidence Of Primary Hypogonadism Among Diabetic Patients (n = 44)

Table 3. Distribution of the Type-2 Diabetic Patients According to Their Sexual Characteristics

Patients' Characteristics	Number of Patients	Percentage
Frequency of Sexual Intercourse (per month)		
Zero (None)	0	0
1 – 2 times (Rarely)	0	0
3 -4 times (Occasionally)	35	79.5
≥5 times (Regular)	9	20.5
Libido		
Poor	17	38.6
Fair	0	0
Good	27	61.4
Penile Erection		
None	0	0
Weak	24	54.4
Strong	20	45.6

Table 4. Distribution of Mean Serum Levels of Hypothalamic-Pituitary-Testicular-Axis Hormones According to The Sexual Characteristics of Type 2 Diabetic Patients

Sexual Function	Number of Patients	FSH Mean ± SD	LH Mean ± SD	PRL Mean ± SD	Te Mean ± SD
Frequency of Sexual Intercourse	35	26.64 ± 24.51	5.90 ± 4.82	49.45 ± 35.32	2.43 ± 1.88
Occasionally	9	18.31 ± 12.88	4.67 ± 2.15	32.54 ± 20.92	5.25 ± 3.65
Regular		-1.44	-0.49	-1.60	-3.17
Z (p - value)		(0.150)	(0.621)	(0.110)	(0.002)
Libido					
Poor		38.20 ± 30.54	6.60 ± 5.77	39.30 ± 24.79	1.52 ± 0.67
Good	17	16.58 ± 9.71	5.06 ± 3.29	30.77 ± 25.21	3.94 ± 2.88
Z (p - value)	27	-3.83	-0.663	-2.31	-4.17
		(<0.001)	(0.507)	(0.021)	(<0.001)
Penile Erection					
Weak	24	32.47 ± 25.60	6.65 ± 5.39	35.89 ± 24.88	1.58 ± 0.79
Strong	20	15.90 ± 14.83	4.46 ± 2.51	36.14 ± 25.81	4.72 ± 2.92
Z (p - value)		-4.32	-1.29	-0.45	-5.06
		(<0.001)	(0.190)	(0.654)	(<0.001)

Abbreviations: FSH, Follicle-Stimulating Hormone; LH, Luteinizing Hormone; PRL, Prolactin; Te, Testosterone; N, Number of participants; SD, Standard Deviation; Z, Mann-Whitney correlation coefficient.

Table 5. Bivariate Correlation between the HPTA Hormones and Sexual Functions of the Type-2 Diabetic Patients

	FSH	LH	PRL	Te	Libido	Erection	FSI
FSH	1.00	0.402**	-0.232	-0.712***	-0.585***	-0.660***	-0.220
LH		1.00	-0.075	-0.159	-0.101	-0.198	-0.075
PRL			1.00	-0.224	-0.353*	0.068	0.244
Te				1.00	0.636***	0.772***	0.484**
Libido					1.00	0.537***	0.287
Erection						1.00	0.329*
FSI							1.00

Abbreviations: FSH, follicle-stimulating hormone; LH, Luteinizing hormone; PRL, prolactin; Te, testosterone; FSI, frequency of sexual intercourse. Rating of the self-reported frequency of sexual intercourse was scored on a Likert scale ranging from 1 to 4 (none =1; rarely = 2; occasionally = 3, regular = 4). Rating of Libido was based on a Likert scale of 1 – 3 (poor = 1, fair = 2, good = 3). The penile Erection score was based on a Likert scale of 1 – 3 (1 = none, weak = 2, strong = 3). Data are presented as Spearman's rank correlations; n = 20; *p < 0.05; **p < 0.01; ***p < 0.001.

After adjusting for age, smoking, drinking, medication use, and patient emotional states, Table 6 displays a multivariate regression analysis between the HPTA hormones and sexual functions in type-2 diabetic patients. After adjusting for the covariables, Pearson's multi-regression analysis showed that FSH was independently associated (r = -0.369; p = 0.005) with a penile erection but not sexual frequency or libido. LH or PRL did not significantly correlate with the frequency of sex, libido, or penile erections. The frequency of sexual activity (r = 0.382; p = 0.020), libido (r = 0.280; p = 0.048), and penile erection (r = 0.429; p = 0.002) were all independently and favourably correlated with testosterone.

Table 6. Multivariate Regression Analysis Between the Hypothalamic-Pituitary-Testicular-Axis Hormones and Sexual Functions of Type 2 Diabetic Patients

Hormones	Frequency of Sexual Intercourse			Libido			Penile Erection		
	Beta	T	P Value	Beta	T	P Value	Beta	T	P Value
FSH	-0.037	-0.22	0.823	-0.369	-2.96	0.005*	-0.219	-1.62	0.114
LH	-0.083	-0.54	0.592	-0.227	-1.79	0.081	-0.233	-1.82	0.077
PRL	0.298	1.90	0.064	0.165	1.20	0.235	-0.061	-0.43	0.666
Te	0.382	2.42	0.020*	0.280	2.04	0.048*	0.429	3.35	0.002*

Abbreviations: FSH, Follicle-Stimulating Hormone; LH, Luteinizing Hormone; PRL, Prolactin; Te, Testosterone.

The main findings of this study are as follows: Type-2 diabetic patients had low but normal mean levels of Te (3.01 ng/ml) and LH (5.65 mIU/ml), as well as elevated and above normal mean levels of FSH (24.94 mIU/ml) and PRL (36.0 ng/ml); significantly more type-2 diabetic patients had high levels of FSH and PRL than the control group; and significantly more type-2 diabetic men had poor erectile function and libido; significant correlations were observed between FSH, libido, and penile erection; and between PRL and libido; significant correlations were also seen between FSH and Te (negative) and LH (positive); after adjusting for co-factors, Te

appeared to be the strongest predictor of penile erection and frequency of sexual intercourse, while FSH was the strongest predictor of libido.

According to published normal ranges, serum Te concentrations in healthy men should be between 3.0 and 10.0 ng/ml (14). In contrast, serum LH, FSH, and PRL concentrations should typically be between 1.4 and 18.1 mIU/mL, 1.5 to 9.3 mIU/mL, and 2.1 to 17.7 ng/mL, respectively (Chmitt et al., 2011). The current findings are consistent with earlier research that found lower testosterone levels (Rosen, 2004; Dhindsa et al., 2005; Stanworth & Jones 2009a; Stanworth et al., 2009b), higher prolactin serum levels (Mooradian et al., 1985; Onah et al., 2013; Rasheed et al., 2019), higher FSH level, and no significant difference in LH level (Onah et al., 2013). Other studies have shown, in contrast to our results, that type-2 diabetic patients have significant decreases in LH and FSH compared with healthy controls (Almihy et al., 2015; Xiaoxia et al.,2017); type-2 people with diabetes have significantly higher LH levels than controls (Natah et al.,2013); and there are no significant differences between type-2 diabetics and non-diabetics in serum levels of FSH and Te (Baccetti et al., 2002), (Rezvani, 2012). Uncertainty surrounds the causes of the elevated FSH and PRL and low Te and LH levels. It is known that type-2 diabetic men are more likely to have low Te than men without the disease (George et al., 2013). The correlation between low Te levels and diabetes has been attributed to several factors, which are also linked to increased risk of type-2 diabetes. The factors include increased insulin resistance (Tsai et al., 2004; Yeap et al., 2009); decreased glucose transport and insulin responsiveness (Sato et al., 2008; Mitsuhashi et al., 2016); low expression of glucose transporter-4 (GLUT4), an important gene involved in insulin signalling and glucose uptake. Other factors include visceral obesity, which has been linked to increased insulin resistance (Tsai et al., 2000); abnormalities in lipid metabolism linked to decreased insulin sensitivity (Hairing et al., 2011; Senmaru et al., 2013); and elevated blood glucose levels themselves linked to hypotestosteronism in diabetic patients (Caronia et al., 2013). Increased production of the inflammatory cytokines IL-6 and TNF-, which block gonadotropin-releasing hormone secretion and lower Te production from Leydig cells (Hong et al., 2004), is linked to insulin resistance in type-2 diabetes. Furthermore, among factors associated with low Te levels and type-2 diabetes is the suppression of the HPTA, which lowers stimulation of the gonadotropin-releasing hormone and lowers gonadotropin secretion (Watanobe & Hayakawa, 2003); and reduced insulin resistance-defining SHBG (sex hormone-binding globulin) secretion (Gianatti & Grossmen, 2020). Additionally, the high prevalence of primary hypogonadism (61.4%) seen in people with diabetes (Figure 1) may help explain the lower mean Te values seen in diabetic patients compared with the controls and the low-normal mean levels observed in the same group.

As a pituitary compensatory mechanism for the low Te level seen in diabetic patients relative to controls, we had anticipated a significantly higher LH level in diabetic patients. The lower-than-expected level of LH found in the diabetic patients in this study could be explained by several factors, including secondary hypogonadism, which is caused by pituitary or hypothalamic dysfunction as a result of the high levels of oxidative stress in diabetic patients (Dhindsa et al., 2005; Onah et al., 2013). Additionally, earlier research using animal models suggested that diabetes mellitus can result in a notable drop in LH level (Seethalakshmi et al.,1987; Ballister et al.,2004). In secondary hypogonadism, defects in the hypothalamus or pituitary cause low or low-normal LH levels and low or low-normal testosterone levels as a result of insufficient stimulation of the Leydig cells (Hirsch, 2019). The

lack of a significant correlation between mean Te and LH in diabetic patients (Table 5) reflects the low-normal serum levels of both hormones found in these patients in our study.

It is believed that the high incidence of primary hypogonadism seen in this study may cause the above-normal level of FSH and the higher value in diabetic patients compared to controls (Figure 1). According to Tekaa et al. (2019), primary hypogonadism is brought on by testicular failure, which causes Te levels to drop and is characterized by high LH and FSH concentrations. FSH and LH levels rise when primary hypogonadism affects Te production because Te is insufficient to stop the production of FSH and LH (Ballister et al., 2004). This theory is supported by the fact that Te and FSH had a negative correlation in the diabetic patients in this study (Table 5).

Since the diet is known to affect serum PRL levels, one explanation for the elevated mean serum PRL level and observed hyperprolactinemia in type-2 diabetics may be dietary differences (Caticha et al., 1996; Mccrory et al., 1999), or (Moretto et al., 2011). It'sIt's interesting to note that chronically high blood sugar levels in diabetics have been proposed to increase serum PRL levels by reducing dopaminergic neuronal activity, a known PRL release inhibitor (Saller & Saller, 1980). In terms of physiology, elevated PRL levels may act as a barrier against the impairment of glucose homeostasis by causing normal adaptive increases in glucose-stimulated insulin secretion through cell mass expansion and increased hepatic insulin sensitivity. Additionally, elevated PRL levels may indirectly increase hypothalamic dopamine synthesis to improve energy and glucose homeostasis (Lapensee et al.,2006; Lyons et al, 2012). High levels of PRL, which exacerbate insulin resistance and reduce insulin secretory capacity, can result from pathological pituitary prolactinoma, which is frequently accompanied by hyperglycemia, obesity, and insulin resistance (Berinder et al., 2011). Another possibility for hyperprolactinemia is abnormalities resulting from microvascular infarcts of the pituitary stalk, which are linked to diabetes mellitus (Mooradian, 1985). It has been demonstrated that the microvascular infarct affects the PRL secretion inhibitory stimuli (Mooradian, 1985).

One of the most severe and significant complications of diabetes is deterioration in sexual function. Erectile dysfunction, ejaculatory dysfunction, and libido loss are the main complications in men (Kizilay, 2017). According to the current research, type-2 diabetic men had poor or decreased sexual function, including low frequency of sex (79.5%), weak penile erections (54.4%), and poor libido (38.6%) (Table 3). One of the HPTA's main roles is to control male reproductive hormone release and reproductive activity (Emmanuelle & Emmanuelle, 1987). Follicle-stimulating hormone, luteinizing hormone, and testosterone are the main hormones that affect how the male reproductive system works (United State Institutes of Health, 2019). Physiological amounts increase testosterone secretion, which results in spermatogenesis when PRL is administered to males (Hair et al., 2002). According to the results of this study, type-2 diabetic patients may experience significant changes in their sexual function due to their reproductive hormones. This is demonstrated by the statistically significant correlations between Te, frequency of sex, erectile function, and libido (sexual drive); between FSH, libido, and penile erection; and between PRL and libido in this study (Table 5). In addition, Te appeared to be the strongest predictor of penile erection and frequency of sexual activity among the four HPTA hormones examined. At the same time, FSH was the strongest predictor of libido (Table 6).

The relationship between the HPTA hormone serum levels and sexual functions in type-2 diabetic patients is poorly understood. The current finding, which showed a positive correlation between Te and sexual functions in diabetic men, is in line with earlier research (Gade et al., 2008; O'connor et al., 2011) that found that low testosterone causes low sex drive and erectile dysfunction in middle-aged and older men. The choice of testosterone replacement therapy in older type-2 diabetic patients with sexual dysfunction may be justified by the independent positive correlation between Te and sexual function domains, even after controlling for covariates. Given that it is known that LH and FSH play a role in promoting the production of androgens (testosterone) and androgen-binding proteins by the testes, it is surprising that there was a significant negative correlation between FSH, libido, and penile erection in the current study and that LH had no significant influence on either of the sexual functions. The negative correlation between FSH and Te can explain the negative correlation between FSH and the parameters relating to sexual function. Due to the non-inhibitory effect of insufficient Te levels (caused by an increase in the incidence of hypogonadism), which led to a decline in sexual functions in diabetic patients, FSH levels increased.

Additionally, there is no connection between LH and the various aspects of sexual function due to the absence of an association between Te and LH. The results showed a significant negative correlation between PRL and libido, which aligns with a previous study that found that low sex drive in men can be caused by high prolactin levels (Foster et al., 1990). Increased PRL interferes with gonadotropin-releasing hormone secretion in hyperprolactinemia, which causes hypogonadism and lowers Te levels (Zeitlin & Rajfer, 2000). It should be noted that after controlling for the patient's age, smoking, drinking, medication use, and emotional states, the correlation between PRL and libido vanished (Table 6). These findings suggest that the relationship between sex hormones and male sexual function is complex; however, there is no doubt that testosterone is a very important factor in the reproductive health of type-2 diabetic men. The present findings further suggest that when assessing the effects of sex hormones on people'speople's sexual performance, it's important to take co-factors affecting sexual function.

There is the possibility that some of our findings may be due to unmeasured confounding factors and influenced by subjective elements from self-reported lifestyle factors and sexual functions of subjects. Secondly, the sample size of diabetic patients was small. Regardless of these limitations, to our knowledge, this study may be the first one that studied the HPTA hormone profile of older men with type-2 diabetes about their sexual functions in Benin City, Nigeria.

CONCLUSIONS

According to the study results, type 2 diabetic patients' sexual functions may be significantly influenced by HPTA hormones. Hormone Te seemed to have the greatest influence on the sexual functions of diabetic patients out of the four HPTA hormones. The findings support the use of testosterone replacement therapy in these older diabetic adults. They may help to clarify the complex endocrinology and physiology of the sexual dysfunction frequently observed in older men with type-2 diabetes.

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CONFLICT OF INTEREST

None declared

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