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# Effect of Diabetes Mellitus on Male Reproductive Hormone of Diabetic Patients Attending Urology Unit of Federal University Teaching Hospital, Abakaliki, Ebonyi State, Nigeria

**Simon Uzor[1,2*], Mercy Chinedum Ajuka[3], Isaac Uzor[4], Ugonna Cassandra Aniokete[1,5], Favour Ebere Nwadum[1,2], Blessing Njideka Igwe[3], Onyebuchi Frederick Orinya[6], Ogwuegbu Alozie Okezie[7], Emmanuel Obasi[1,8], Ihuoma A. Obi[9], Oluchi Miracle Ehugbo[4], Joseph Daberechi Oshibe[3], Innocent Icha Imakwu[5,10], Gift Chinyere Onwe[3]**

[1]Department of Medical Laboratory Science, David Umahi Federal University of Health Sciences, Uburu, Nigeria
[2]International Institute for Oncology and Cancer Research, David Umahi Federal University of Health Sciences, Uburu, Nigeria
[3]Department of Medical Laboratory Science, Ebonyi State University, Ebonyi, Nigeria
[4]Department of Medical Laboratory Science, National Obstetrics and Fistula Center, Abakaliki, Nigeria
[5]International Institute for Infectious Diseases, Biosafety and Biosecurity Research of David Umahi Federal University of Health Sciences, Uburu, Nigeria
[6]Department of Medical Biochemistry, David Umahi Federal University of Health Sciences, Uburu, Nigeria
[7]Department of Medical Laboratory Science, Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Nigeria
[8]International Institute for Cardiovascular Diseases, David Umahi Federal University of Health Sciences, Uburu, Nigeria
[9]Department of Nursing Science, Ebonyi State University, Abakaliki, Nigeria
[10]Department of Pharmacology and Therapeutics, David Umahi Federal University of Health Sciences, Uburu, Nigeria
Email: *usomls@yahoo.co.uk

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## Abstract

**Background:** Diabetes is a set of metabolic abnormalities typified by hyperglycemia believed to be associated with aberrant insulin secretion, insulin action, or both. Erectile dysfunction and infertility are globally prevalent complications among male diabetic patients. There is a need to understand the role of a male reproductive hormone in the etiology of infertility in diabetic patients. **Objective:** This study aims to determine the effect of diabetes mellitus on the Male reproductive hormone (testosterone) on diabetic patients attending the Urology unit of Federal University Teaching Hospital, Abakaliki, Ebonyi State, Nigeria and the effect of industrial sugar consumption in rats model. **Materials and Methods:** 30 samples (including repeats, n = 3) were collected from known diabetic patients and 30 (including repeats, n = 3) control-non diabetic healthy individuals. Five millilitres (5 ml) of blood was collected from the antecubital vein of each participant and placed into a plain

container for serum testosterone measurement using the enzyme-linked immunoassay technique. Blood was also collected from the same subjects in a fluoride oxalate container for plasma enzymatic glucose estimation using a Randox Glucose oxidase kit. For *in vivo* rat model, the albino rats were grouped into 2 of five (5) rats. The control group (1) was only given normal rat food and water while the test group (2) was treated with 0.4 g of industrial sugar/mL/body weight in addition to rat food and water via oral intubation for 21 days. Blood samples were collected via ocular puncture into plain tubes for testosterone measurement as described above. **Results**: There is a significant ($p < 0.05$) increase in the glucose level of diabetic subjects compared to the control non-diabetic groups. Interestingly, the diabetic individuals have decreased levels of testosterone compared to the control ($p < 0.05$). The same was observed in rats treated with industrial sugar. **Conclusion**: In conclusion, data available from this study suggests that increased plasma glucose levels and excessive industrial sugar consumption are associated with decreased testosterone levels in both human and animal models respectively. The mechanism is yet unclear but it could be that DM alters conventional sperm parameters, spermatogenesis, and biosynthesis of testosterone and induces degenerative changes in the testis and epididymis and ejaculatory dysfunction. These mechanisms need to be investigated.

## Keywords

Diabetes, Mellitus, Reproductive Hormone, Testosterone, Industrial Sugar

## 1. Introduction

Diabetes mellitus (DM) is one of the biggest global health issues, associated with a number of microvascular complications including retinopathy, neuropathy, nephropathy, cardiovascular illnesses, and male infertility [1]. To further comprehend its function in male infertility, it is imperative to thoroughly examine how DM affects male reproductive hormones, especially testosterone. In light of these relationships, gaining knowledge about how diabetes affects male hormone balance will help manage infertility caused by diabetes and enhance treatment plans for those who are impacted.

By definition, diabetes is a set of metabolic abnormalities typified by hyperglycemia believed to be associated with aberrant insulin secretion, insulin action, or both [2]. In Africa and the Western World, diabetes is rampant and swiftly growing rapidly as a major public health issue that requires special attention. According to the International Diabetic Federation's diabetic atlas, 366 million people worldwide were affected by diabetes in 2011, and diabetes prevalence is anticipated to rise to 552 million by 2030 [3].

Industrial sugar use has increased significantly over the past century, mostly as a result of its widespread use in processed foods and beverages. Research shows that eating too much sugar is strongly linked to a number of health issues, including

hormonal imbalances and metabolic diseases [4]. But little is known about the specific effects of industrial sugar on testosterone levels, especially in animal models.

Significant microvascular consequences linked to diabetes mellitus include male infertility, diabetic retinopathy, neuropathy, nephropathy, and cardiovascular disease [5] [6]. According to reports, type 1 and type 2 diabetes are becoming more common in young people [7]-[9]. This rise is concerning and has to be addressed right now since it could cause severe infertility problems in men who are fertile. Furthermore, research indicates that the decrease in birth and fertility rates in contemporary civilizations is closely linked to the rise in diabetes rates [10]. For this reason, researchers should not only focus on COVID therapy and vaccines, but also gross attention and grants should be given to research focused on providing remedies to cob the ugly trend of diabetes mellitus which has subtly pushed Homo sapiens into gradual extinction.

Diabetes can cause male infertility by interfering with spermatogenesis, causing degenerative and apoptotic changes in the testes, and changing glucose metabolism at the Sertoli/blood-testes barrier [1]. These changes can lead to decreased testosterone production and secretion, ejaculatory dysfunction, and decreased libido, according to a growing body of research conducted on diabetic men and animal models [11]. Numerous *in vitro* and preclinical investigations have focused on the biochemical pathways impacted by diabetes mellitus, which are thought to be the source of these consequences [12]. Hormonal abnormalities in the hypothalamic-pituitary-gonadal axis or direct interactions between insulin and the testes or sperm cells may be the cause of diabetes's adverse effects on male reproductive capacity [13] [14]. It has been demonstrated that insulin replacement therapy can return sperm motility and count to normal in diabetic rat models [15]. However, insulin restores the function of the hypothalamo-hypophyseal-gonadal axis rather than directly affecting the tests to restore fertility [16]. In diabetic rats, the response to insulin treatment varies; some researchers have shown a quick recovery of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) [12], while other studies have reported no discernible recovery of these hormones [17] [18].

Oxidative stress may play a role in the pathogenesis of male reproductive problems associated with diabetes [19]-[21]. The Nrf2 gene is essential for the testes' oxidative defense, and its expression decreases in diabetics [22] [23]. In addition to changes in testicular metabolite levels and spermatogenesis, men with diabetes typically have sperm with higher levels of DNA fragmentation, advanced glycation end products (AGEs), and their receptors. These factors all contribute to a decline in sperm quality and performance [19]. According to recent research, antioxidant therapy can lower associated comorbidities, enhance glycaemic management, and guard against oxidative stress brought on by free radicals [24].

Men with diabetes frequently suffer from erectile dysfunction (ED), which is defined as the ongoing inability to obtain or sustain an erection strong enough for intercourse [25]. Compared to men without diabetes, men with type 1 or type 2 diabetes are three times more likely to experience erectile dysfunction (ED), which frequently manifests earlier in life and gets worse as the condition worsens. Since

ED is primarily regarded as a vascular condition, neuropathy, vascular damage, and endothelial dysfunction are thought to be important factors, even though the precise processes behind ED in diabetes are not well understood [25]. Between 50% and 75% of men with diabetes are thought to have some form of erectile dysfunction. Endothelial dysfunction, impaired nitric oxide (NO) pathways (including downregulation of NO synthase and degeneration of nitrergic nerves), aberrant signal transduction pathways, degeneration of smooth muscle in the corpora cavernosa, and tissue remodeling are the mechanisms underlying erectile dysfunction (ED) in men with diabetes [26]. The neural NO synthase/cGMP pathway is started when sexual stimulation activates the non-adrenergic, non-cholinergic neurons. Vasodilation and increased blood flow to the corpus cavernosum result from the release of NO, which encourages the relaxation of resistant arterioles and penile cavernosal arteries. The endothelium lining of the lacunar spaces of the corpus cavernosum is stimulated by this increased blood flow, which further causes endothelial NO to be released through endothelial NO synthase [27] [28]. Penile engorgement results from these physiological and biochemical mechanisms that relax trabecular smooth muscle and cause the sinusoids in the corpora cavernosa to expand [29]. The "venoocclusive" process is the result of the expanding corpora cavernosa pressing against the tunica albuginea, which causes veno-occlusion and traps blood under pressure. Androgens control both endothelium and neural NO synthases, which are essential for this process [30].

Furthermore, the penis's tissue architecture depends on androgen [31], thus, any changes or disturbances in the circulatory system, neuronal pathways, or fibroelastic characteristics of erectile tissue might affect the veno-occlusion process and lead to erectile dysfunction. Additionally, it has been demonstrated that diabetes impairs endothelium-dependent smooth muscle relaxation, which results in ED through smooth muscle failure in the penis' microvasculature tree [32] [33].

Therefore, examining how DM affects male reproductive hormones, especially testosterone, is crucial to comprehending its role in male infertility. Better treatment plans for individuals with diabetes and more efficient management of diabetes-induced infertility can result from an understanding of how diabetes affects men's hormonal balance.

## 2. Materials and Methods

### 2.1. Study Area

This cross-sectional study was carried out at Alex Ekwueme Federal University Teaching Hospital Abakaliki, (AE-FUTHA). Alex Ekwueme Federal University Teaching Hospital Abakaliki, (AE-FUTHA) is the only teaching hospital in Abakaliki metropolis. It is the major tertiary health facility for accessing healthcare and services in the state.

### 2.2. Ethical Approval

The protocol for this study was approved by the Ethics and Research Committee

of Alex-Ekwueme Federal Teaching Hospital, Abakaliki (AE-FUTHA) Nigeria with Health Research Ethics committee approval number NHREC/16/05/22/148 in accordance with the ethical standards. A written informed consent was obtained from all participants of the study. The whole Study was carried out at no cost to the participants. Furthermore, all animal experiments adhered to the guidelines set by Ebonyi State University Research Ethics Committee (approval number EBSU/DRIC/UREC/VOL.07/058.

### 2.3. Study Participants

The study population includes patients attending Urology unit of Federal University Teaching Hospital, Abakaliki, Ebonyi State Nigeria. About 10 samples with 3 repeats (30 samples in all) were collected from known diabetic patients and 10 control healthy individuals (with 3 repeats, resulting to 30 control samples in all). All subjects acknowledged the protocol and consented to participate in the study.

### 2.4. Research Design

This research is a cross sectional analytical study aimed to comparatively study the effects of diabetes mellitus on male reproductive hormone (testosterone) of diabetic patients attending urology unit of Alex-Ekwueme Federal University Teaching Hospital Abakaliki, Nigeria using non diabetic adult males as controls. To study the effect of industrial sugar on serum testosterone levels in rat model, we purchased adult male albino rats from the University of Nigeria's Veterinary Department in Nsukka, Enugu State. Before the experiment, the animals were kept in steel laboratory cages and given a week to get acquainted to the laboratory environment. They were given unlimited access to water and regular rat feed throughout the experimental period. Every animal was given the proper care in compliance with the Investigations and Ethics Committee's recommendations and community laws governing the use of experimental animals. The albino rats were split into two groups, each with five (5) rats: a control group (Group 1) and a test group (Group 2), which received only standard rat food and water and industrial sugar in addition, administered via oral intubation for 21 days.

### 2.5. Sample Collection

Blood samples were taken from each rat via ocular puncture into plain tubes for testosterone measurement at the end of the treatment period whilefive millilitre (5 ml) of blood was collected from antecubital vein of each human participant into a plain container. It was spun at 1500 gravity (g) for 5 minutes to obtain serum for testosterone estimation. From same subjests blood were collected in fluoride oxalate container for plasma glucose estimation after 12 hours fasting.

### 2.6. Glucose Estimation

Glucose estimation for determination of plasma glucose levels in subjects were performed using Glucose randox kit bought from Randox Laboratories ltd, United

Kingdom. The procedures were as per the manufacturer's protocols.

### 2.7. Enzyme Immunoassay Techniques for Testosterone Estimation

#### 2.7.1. Assay Procedure

Desired number of coated wells in the holder were secured and 25 µl of standards, specimens and controls were dispensed into appropriate wells, followed by 50 µl of rabbit anti-Testosterone reagent to each well and thoroughly and completely mixed for 30 seconds. Then 100 µl of Testosterone- Horseradish Peroxidase (HRP) conjugate reagent was dispensed into each well and were incubated at 37˚C for 60 minutes. The micro wells were rinsed and flicked 5 times with washing Buffer (1X) and 100 µl of 3,3',5,5'-Tetramethylbenzidine (TMB) substrate was dispensed into each well with gentle mix for 10 seconds, and incubated at room temperature (18˚C - 22˚C) for 20 minutes. The reaction was stopped by adding 100 µl of stop solution to each well and were gently mixed for 30 seconds. We ensured that all the blue colour changed to yellow colour completely. The absorbance was read at 450 nm with a micro titer well reader made from Germany; HEPOBIO (model number of HP-ELISA3000B).

#### 2.7.2. Statistical Analysis

Data were expressed as the mean ± standard error of the mean (SEM). Once the data were checked for normal distribution, GraphPad Prism version 8.0 was used for statistical analysis, and a one-way analysis of variance (ANOVA) was carried out to compare the means of the independent groups, with statistical significance taken at $p < 0.05$.

## 3. Results

This research is a cross sectional analytical study aimed to comparatively study the effects of diabetes mellitus on male reproductive hormone of diabetic patients attending urology unit of Alex-Ekwueme Federal University Teaching Hospital Abakaliki. Results are presented in Figure 1 and Figure 2 and Table 1.

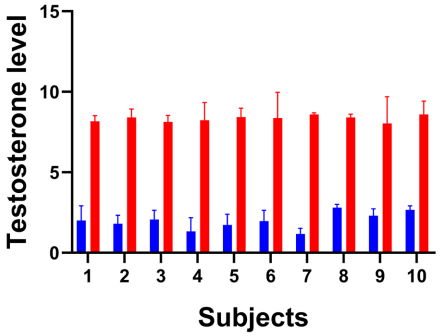


Figure 1. Graph of testosterone of male diabetic patients against healthy controls. As indicated, the blue colors represent the testosterone levels of male diabetic subjects while the red colors indicate the respective healthy non diabetic controls. The error bars are also indicated. When the testosterone levels of diabetics were compared with the testosterone levels of the control, $p < 0.05$, $n = 3$.

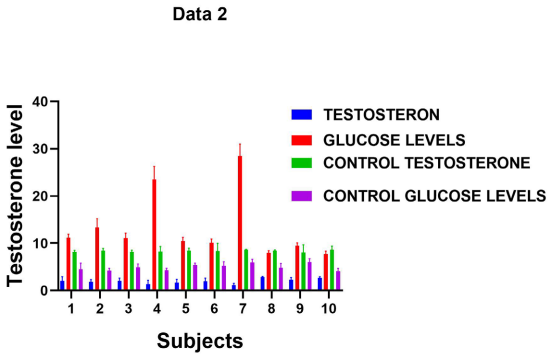


**Figure 2.** A graph comparing the testosterone with glucose levels of diabetic subjects. As indicated, the blue colors represent the testosterone levels of male diabetic subjects while the red colors indicate the glucose levels of the diabetic patients. The Green colors indicates the testosterone levels of the control group of non- diabetic male patients, n = 3. When the testosterone levels of diabetics were compared with the testosterone levels of the control, $p < 0.05$. When the glucose levels of diabetics were compared with the glucose levels of the control, $p < 0.05$.

The effects of industrial sugar on testosterone level of male albino rats were also studied. In this study, albino rats were grouped into 2 (control and test) of five (5) rats in each group. The test group was treated with industrial sugar via oral intubation for 21 days after which the rats were starved for 12 hours, and blood samples collected for testosterone measurement using ELISA technique. The result of this research is presented in **Table 1**.

**Table 1.** Comparison of the effects of industrial sugar on testosterone level of male albino rats.

| | Testosterone (ng/mL) | P-value |
|---|---|---|
| **Group 1 (Control)** | 4.09 ± 0.23 | 0.218 |
| **Group 2 (test)** | 2.67 ± 0.89 | 0.059 |

The effects of industrial sugar on weight of the albino rats were also measured and the result depicted in **Figure 3**.

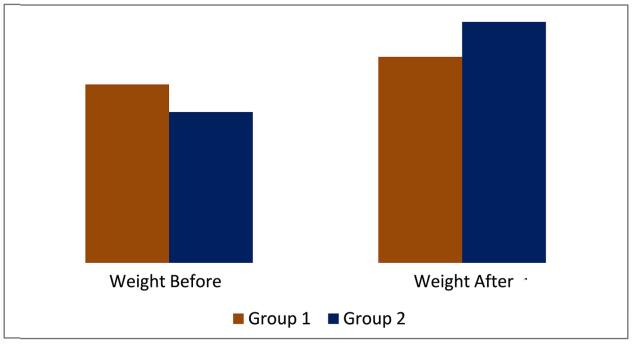


**Figure 3.** Effects of industrial sugar on weight of male albino rats. The brown coloured bars indicate the average weight of the control known to be group 1, while the blue coloured bars represent the average weight of the test group treated with industrial sugar. The bars at the left side show the initial weight of the rats before treatment, while the weight after treatment is indicated at the right hand side.

## 4. Discussion

Male fertility is critically dependent upon normal intratesticular concentrations of testosterone to support qualitative and quantitative normal spermatogenesis. Diabetes mellitus, whether primary or unexplained, is a long-term disorder of carbohydrate, lipid, and protein metabolism characterized by glucose intolerance, hyperglycemia, and glycosuria. Great number of infertility cases have been linked to diabetes mellitus in both male and female. Neuropathy, vascular insufficiency, and hyperglycemia are believed to play a role in the pathogenesis of impotence, ejaculation disorders, and decreased libido, along with decreased vaginal lubrication and orgasm dysfunctions [34]. There has been a rise in the frequency of diabetes and use of industrial sugar among teenagers, which calls for concern since it might compromise men's fertility during their reproductive years (foetal origin of adult disease), leading to a fall in birth rate, fertility and gradual human extinction. [35]. As a consequence, it is crucial to investigate the impact of diabetes and industrial sugar consumption on male reproductive hormone (testosterone) in male diabetic patients at the Federal University Teaching Hospital in Abakaliki, Ebonyi State, Nigeria, and in rat model.

From our studies, in **Figure 1**, result showed an increased significant level of testosterone among the healthy controls and a decreased testosterone level among the diabetic groups ($p < 0.05$) which is consistent with the previous work by Gluud and associates [36]. They studied testosterone and androstenedione before and after 1 year of treatment in patients with newly diagnosed DM who presented with ketosis. They found significantly decreased testosterone levels prior to insulin therapy, with subsequent increase in testosterone levels 1 year later after improved control of carbohydrate metabolism. However, even with strict control of blood glucose, contradictory reports regarding the hormone levels of adult diabetics still exist.

**Figure 2** shows significant $p < 0.05$ effect of glucose on the testosterone. Subjects with higher levels of glucose level had a very significant decrease in their testosterone levels. For instance, group one had 11 mmol/l of glucose and the testosterone is 4 ng/mL. This is in conformity with group 7 with the highest glucose but lowest testosterone level of 1 ng/mL. However, studies with conflicting results, have been performed to assess the effect of diabetes upon the hypothalamic-pituitary gonadal axis. A potential cause for these discrepant results is the mixture of age and type of diabetes in the patient populations being studied. Another factor that may be responsible for variation in study results is the degree of control of serum glucose levels. The anterior pituitary gland is less responsive to gonadotropin stimulation in the presence of hyperglycemia (Li *et al.,* 2023). Furthermore, **Figure 2** compares the test testosterone with the control testosterone and their glucose levels. There is indeed a general decrease in the testosterone level of the diabetic individuals in contrast to the testsosterone level of individuals without diabetics. In **Table 1**, we investigated the effect of industrial sugar consumption on testosterone level in rat model. Our results indicated a significant reduction in

the testosterone levels of the test group. The control group exhibited an average testosterone level of 4.09 ± 0.23 ng/mL. In contrast, the test group's average testosterone level was lower, at 2.67 ± 0.89 ng/mL. This substantial reduction in testosterone levels suggests that high consumption of industrial sugar adversely affects endocrine function in males. Elevated weight gain was also observed in the rats treated with industrial sugar compared to the control.

## 5. Conclusion

Data available from this study suggest that diabetes mellitus and industrial sugar consumption significantly decreased the testosterone level of the volunteered male diabetic patients and in rats model compared to the controls, probably due to the alteration of conventional sperm parameters, spermatogenesis, biosynthesis of testosterone and induction of degenerative changes in the testis and epididymis, ejaculatory dysfunction and impairment of fertility in male diabetic patients as well as in experimental diabetic animals. The above-mentioned mechanisms have been proposed to explain these effects.

## Limitations

The study does not include the seminalysis data of the subjects (both tests and controls), because participants while consented to blood sample collection, did not give consent for collection of semen samples. Semen microscopy, culture and sensitivity would have been necessary as high blood glucose could harbor bacterial growth which may distort testicular function.

## Acknowledgement

Not applicable.

## Conflicts of Interest

The authors have no conflict of interest to declare.

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