# Obesity and Testosterone Levels in Ghanaian Men With Type 2 Diabetes

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## Introduction

The incidence of diabetes is increasing at an alarming rate. With the current rate of increase, it has been projected that 324 million people will have diabetes by 2025.[1,2] Uncontrolled diabetes leads to serious medical complications. Large blood vessel damage leads to stroke and cardiovascular complications, and damage to small vessels in the extremities, eyes, and kidneys leads to amputation, blindness, and kidney failure. As a result, the economic and human costs of this disease are devastating.

Obesity among adults in the developed world is defined as a BMI ≥ 30 kg/m$^2$.[3] Obesity in adults has become a major public health issue and is associated with increased risk of cardiovascular disease (CVD) and type 2 diabetes.[4]

Adipose tissue functions primarily to store energy. It also plays an important role in systemic glucose homeostasis. Recent epidemiological studies have shown that both serum total testosterone and free testosterone levels are decreased in obese men.[5,6]

Obesity—and especially abdominal adiposity—is a major risk factor for and the most common cause of insulin resistance and CVD.[7] In visceral obesity, there is increased deposition of abdominal adipose tissue in hypogonadal subjects, which in turn leads to a further decrease in testosterone concentrations through conversion to estradiol by aromatase.[8,9] In addition, insulin resistance, an essential component of the metabolic syndrome, is associated with decreased testosterone secretion in Leydig cells.[10] Low testosterone levels in men have been found to predict insulin resistance and the future development of type 2 diabetes.[11,12] Low testosterone levels have also been found to be associated with dyslipidemia and hypertension.[13]

The goal of this study was to gain a better understanding of the relationship among insulin resistance, BMI, and testosterone levels. There are no established data on Ghanaian men with type 2 diabetes who are hypogonadal, with or without a high BMI. This underscores the importance of investigating androgen levels in Ghanaian men with type 2 diabetes. Data in this area could eventually be useful as evidence for the treatment of hypogonadism in men with diabetes.

### IN BRIEF

Testosterone plays a vital role in obesity, glucose homeostasis, and lipid metabolism. The aim of this study was to investigate androgen levels and its association with obesity in Ghanaian men with type 2 diabetes. The study showed that serum total and free testosterone concentrations were lower in male patients with type 2 diabetes and that obesity was strongly associated with low levels of total and free testosterone in Ghanaian men with type 2 diabetes.

## Study Design and Methods

This was a hospital-based case-control study. Samples from men with diabetes between the ages of 30 and 60 years were compared to samples from nondiabetic men of the same age range. The study included 210 men (105 with and 105 without type 2 diabetes). Consecutive patients seen during 1 month at the diabetic clinic were asked to join the study. Of those asked, 10% participated. Questionnaires were administered to obtain information that would help identify androgen deprivation. The content of the questionnaire was explained in a language best understood by respondents to reduce measurement error.

### Laboratory testing

Blood samples were collected after subjects provided consent through a process reviewed and approved by the University of Ghana Medical School Ethical Committee. Fasting blood samples (10 ml) were drawn between 7:00 and 8:00 a.m. for all assays. Blood was collected from 10 subjects daily. Of the 9 ml of whole blood drawn, 2 ml were transferred into ethylene diamine tetra-acetic acid–containing tubes to estimate A1C; 2 ml were transferred into a sodium fluoride–containing tube and the plasma was separated to estimate glucose level; and the remaining 5 ml were put into serum separator tubes for processing. Serum samples were aliquoted in 1-ml portions into a sterile plain tube and stored at –20°C until needed.

**Biochemical analysis**

Serum total testosterone (TT), sex hormone binding globulin (SHBG) estradiol ($E_2$), luteinizing hormone (LH), and follicle-stimulating hormone (FSH) were determined by chemiluminescent immunoassay using the VITROS ECi immunodiagnostic system (Ortho Clinical Diagnostics, Rochester, N.J.). The system uses enhanced chemiluminescence detection technology to provide accurate and reliable results for heterogeneous assays. All reactions necessary took place in a coated well. Wells were included with assay reagent packs and are specific for one type of assay. Lipid profile, uric acid, albumin, and fasting blood glucose (FBG) were analyzed using the VITROS system autoanalyzer (version 950) (Ortho Clinical Diagnostics). Free and bioavailable testosterone levels were obtained

**Table 1. Clinical and Biochemical Parameters of the Study Population**

| Parameter | Men With Diabetes (*n* = 105) | Nondiabetic Men (*n* = 105) | 95% CI of Mean Difference | *P* |
|---|---|---|---|---|
| Age (years) | 48.9 ± 9.4 | 42.8 ± 5.6 | –8.193 to –4.007 | 0.0001* |
| Systolic blood pressure (mmHg) | 131.1 ± 17.5 | 122.9 ± 9.1 | –11.970 to –4.427 | 0.0001* |
| Diastolic blood pressure (mmHg) | 76.8 ± 10.4 | 74.7 ± 5.9 | –4.387 to 0.1871 | 0.0734 |
| BMI (kg/m$^2$) | 25.4 ± 3.7 | 24.0 ± 2.6 | –2.265 to –0.535 | 0.0017† |
| Testosterone (nmol/l) | 10.8 ± 5.0 | 15.6 ± 3.9 | 3.587–6.013 | 0.00018* |
| Free testosterone (nmol/l) | 0.20 ± 0.10 | 0.40 ± 0.10 | –0.24 to –0.16 | 0.0001* |
| Bioavailable testosterone (nmol/l) | 5.5 ± 2.8 | 8.3 ± 2.2 | –3.48 to –2.12 | 0.0001* |
| FSH (IU/l) | 5.8 ± 3.0 | 5.6 ± 2.3 | –0.9231 to 0.5231 | 0.5883 |
| LH (IU/l) | 5.4 ± 2.0 | 4.5 ± 1.5 | –1.374 to –0.225 | 0.0003† |
| Estradiol (pmol/l) | 76.4 ± 20.1 | 79.3 ± 15.8 | –1.990 to 7.790 | 0.2464 |
| SHBG (nmol/l) | 27.6 ± 2.0 | 27.9 ± 1.3 | –0.1563 to 0.7563 | 0.1989 |
| FBG (mmol/l) | 9.5 ± 4.5 | 4.5 ± 0.4 | –5.864 to –4.136 | 0.0001* |
| A1C (%) | 9.4 ± 2.4 | 6.1 ± 0.6 | –3.773 to –2.827 | 0.0001* |
| Total cholesterol (mmol/l) | 5.1 ± 1.2 | 4.8 ± 0.6 | –0.556 to –0.043 | 0.0229† |
| Triglycerides (mmol/l) | 1.2 ± 0.4 | 1.1 ± 0.2 | –0.221 to 0.021 | 0.0049† |
| HDL cholesterol (mmol/l) | 1.3 ± 0.2 | 1.3 ± 0.1 | –0.078 to 0.078 | 1.0000 |
| LDL cholesterol (mmol/l) | 3.2 ± 1.0 | 3.0 ± 0.5 | –0.413 to 0.013 | 0.0682 |
| VLDL cholesterol (mmol/l) | 0.6 ± 0.3 | 0.5 ± 0.1 | –0.161 to –0.039 | 0.0014† |
| Total cholesterol-to-HDL cholesterol ratio | 4.4 ± 1.4 | 3.5 ± 0.5 | –1.184 to –0.615 | 0.0001* |
| Albumin (g/l) | 45.3 ± 4.1 | 41.9 ± 4.2 | –4.523 to –2.277 | 0.0001* |
| Creatinine (µmol/l) | 103.1 ± 82.6 | 96.8 ± 14.5 | –22.340 to 9.741 | 0.4423 |
| Uric acid (µmol/l) | 343.8 ± 90.8 | 294.8 ± 63.3 | 29.830–72.170 | 0.0001* |
| Duration of diabetes (years) | 6.8 ± 5.7 | — | — | — |

*Values are given as mean ± SD.*
**Mean difference is highly significant (P < 0.0001).*
*†Mean difference is significant (P < 0.05).*

using a testosterone calculator.[14] A1C was measured using the Randox Daytona autoanalyzer (Randox Laboratories Ltd., Kearneysville, W.V.). The determination of A1C was based on a latex agglutination inhibition assay.

**Data analysis**

Data were entered into a spreadsheet and analyzed using Microsoft Office Excel 2007 (Microsoft Corp., Louisville, Ky.), and the values were expressed as mean plus or minus standard deviations (mean ± SD). The GraphPad Prism 3.02 (GraphPad Software, San Diego, Calif.) program was used to perform independent sample *t*-tests (Student's *t*-tests) with a level of statistical significance set at $P < 0.05$ for all tests and at 95% confidence interval (CI). Student's *t*-tests were used for comparison of means of variables between subjects with and without diabetes. One-way analysis of variance was performed to assess significant differences in mean testosterone levels across various age-groups. Variables with significant associations were assessed through stepwise linear and multiple regression to determine their independent contributions to the variance in total testosterone.

**Study Results**

Subjects included 105 men with type 2 diabetes who were not on insulin. These were matched for age with 105 apparently healthy nondiabetic men. The clinical and biochemical parameters of the study population are shown in Table 1. The mean ages of the diabetic men (study group) and the nondiabetic men (control group) were 48.9 and 42.8 years, respectively. The difference in mean between the two age-groups was highly significant ($P < 0.0001$). Systolic blood pressure was statistically significant ($P < 0.0001$) and elevated in the study group. No significant difference was observed in diastolic blood pressure between the groups ($P = 0.07$). In addition, the difference in mean BMI of the two study groups was significant ($P = 0.002$).

The between-group difference in mean total testosterone and mean free testosterone were highly significant ($P < 0.0001$). No significant between-group difference was observed for SHBG ($P = 0.1989$). A significant between-group difference ($P = 0.0003$) was also observed for mean concentrations of LH. However, no significant differences were observed for FSH ($P = 0.59$) or $E_2$ ($P = 0.25$).

Differences in FBG, A1C, cardiovascular risk, albumin, and uric acid between the two groups were highly significant ($P = 0.0001$). Significant differences ($P < 0.05$) were also observed for mean total cholesterol and mean triglyceride levels.

The percentage distributions of TT levels of the diabetic and nondiabetic subjects were investigated. Subjects were classified into three groups: hypogonadal (< 8 nmol/l), borderline (8–12 nmol/l), and eugonadal (> 12 nmol/l). A total of 37 of the men with diabetes (35.2%) and 7 control subjects (6.7%) were hypogonadal at < 8 nmol/l. Also, 21 men with diabetes (20%) and 10 nondiabetic men (9.5%) had TT levels between 8 and 12 nmol/l. In addition, 47 men with diabetes (44.8%) and 88 nondiabetic men (83.8%) were eugonadal (Figure 1).

Table 2 shows the association between BMI and TT in men with diabetes. Odds ratios (ORs) show that men with diabetes who are overweight (OR 2.29, $P = 0.01$) or obese (OR 5.95, $P = 0.004$) are more likely to have low TT levels than men with diabetes who are of normal weight or underweight.

Associations between several correlates (age, BMI, triglyceride level, A1C, FBG, and HDL cholesterol) and TT level were determined in the men with diabetes and are shown in Table 3. TT levels were inversely associated with BMI ($P = 0.04$), triglyceride level ($P = 0.025$), and FBG ($P < 0.001$). The study showed

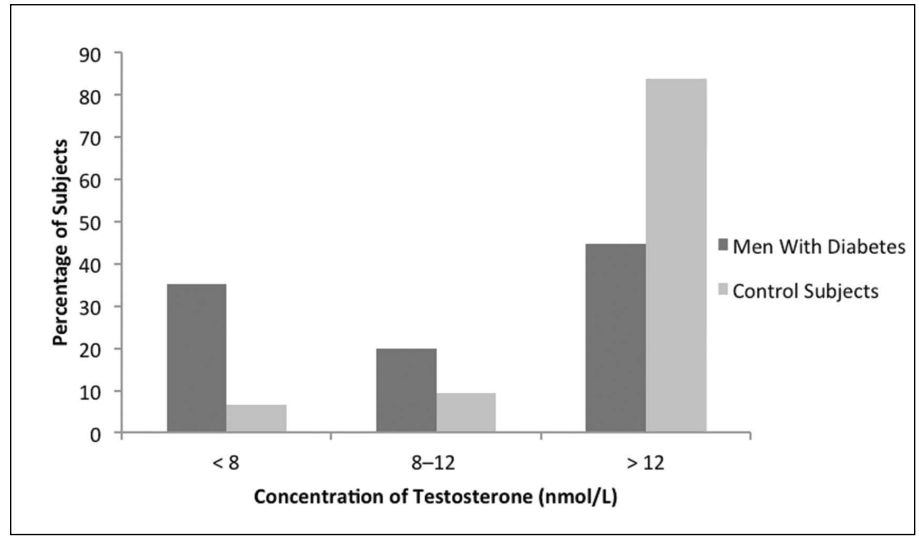


*Figure 1. Percentage distributions of categorized TT levels in the study. TT levels for each group are categorized into hypogonadal (< 8 nmol/l), borderline (8–12 nmol/l), and eugonadal (> 12 nmol/l). The percentage distribution of categorized TT levels for men with diabetes was 35.2 hypogonadal, 20.0 borderline, and 44.8 eugonadal. The percentage distribution of categorized TT levels for the control group was 6.7 hypogonadal, 9.5 borderline, and 83.8 eugonadal.*

| Table 2. BMI as a Risk Factor for Low Testosterone in Men With Diabetes | | | | |
|---|---|---|---|---|
| **Risk Factor** | **BMI Cut Point (kg/m²)** | **OR** | **95% CI** | ***P*** |
| Underweight | ≤ 18.5 | 3.0619 | 0.3130–29.9488 | 0.6212 |
| Normal weight | 18.5–24.9 | 0.2042 | 0.1101–0.3788 | < 0.0001 |
| Overweight | 25–29.9 | 2.2931 | 1.2498–4.2075 | 0.0102 |
| Obese | 30–24.5 | 5.9561 | 1.6517–21.478 | 0.0038 |

a steady but not statistically significant decline in TT with age in men with diabetes ($P = 0.063$). Also, no associations were observed for A1C ($P = 0.365$) or HDL cholesterol ($P = 0.511$). Thus, elevated FBG, higher BMI, and elevated triglyceride levels emerged as risk factors for low TT levels in men with diabetes.

## Discussion

Diabetes has been implicated in many complications, including hypogonadism.[9,15] The prevalence of hypogonadism in type 2 diabetes has been linked to adiposity and insulin resistance.[9,15] This study strongly linked low TT levels to the risk factors of type 2 diabetes (Table 1), including higher BMI, elevated FBG, elevated triglyceride levels, age, blood pressure, elevated total cholesterol, and higher A1C levels.

This study showed a higher average BMI in men with diabetes compared to their nondiabetic counterparts. Overweight and obese men with diabetes were found to be at two and six times higher risk, respectively, of being hypogonadal, whereas men with diabetes and BMIs in the normal or low ranges were not found to be at increased risk for hypogonadism (Table 2). The finding that testosterone levels are negatively correlated to BMI is in agreement with work done elsewhere.[16,17]

The underlying mechanism responsible for reduced testosterone levels in obese and overweight men with diabetes is not completely understood. However, it has been reported in these subjects that there is increased fat that leads to increased aromatase activity of testosterone to $E_2$, resulting in increased levels of $E_2$.[18,19] High circulating levels of $E_2$ downregulate the hypothalamic-pituitary axis and decrease the amount of circulating gonadotropin-releasing hormone and, hence, testosterone.[8,16] In addition, levels of leptin increase with obesity, and this hormone causes further reduction in androgen levels by inhibiting the hypothalamic-pituitary-gonadal axis.[8]

It is worth stating that, in this study, no association or relationship was found between $E_2$ concentrations and type 2 diabetes (Table 1). This finding is in agreement with some work done elsewhere[16] but disagrees with other published work.[8]

This study also showed an association between lipid profile (especially triglyceride levels) and testosterone levels in men with type 2 diabetes (Table 3). This finding is consistent with earlier research.[18,20] Increased abdominal fat leads to increased aromatase activity. The resulting low testosterone increases lipoprotein lipase activity, the main enzymatic regulator of triglyceride uptake in adipose tissue. This results in inhibition of triglyceride uptake, increased lipid mobilization leading to increased visceral adiposity, and insulin resistance. This, in turn, causes further hypogonadism and abdominal fat deposition.[20,21]

The prevalence of hypogonadism in men with type 2 diabetes in this study was 35.2%. Others have shown a prevalence of 30–80% in men with type 2 diabetes.[9,22] This study also revealed that FBG contributes to lowering TT levels in men with type

| Table 3. Multiple Regression Analysis of Correlates With Testosterone in Men With Diabetes | | | | |
|---|---|---|---|---|
| **Variables** | **Coefficients** | **Standard Error** | ***P*** | **95% CI** |
| Age (years) | 1.3928 | 0.7407 | 0.0630 | –0.0770 to 2.8627 |
| BMI (kg/m²) | –3.9429 | 1.9868 | 0.0400 | –7.8857 to –0.0002 |
| Triglycerides (mmol/l) | 31.4095 | 13.7968 | 0.0250 | 4.0302–58.7888 |
| A1C (%) | 2.9443 | 3.2353 | 0.3650 | –3.4760 to 9.3647 |
| FBG (mmol/l) | 6.4923 | 1.8674 | 0.0008 | 2.7865–10.1982 |
| HDL cholesterol (mmol/l) | 12.6551 | 19.2061 | 0.5115 | –25.4588 to 50.7689 |

2 diabetes. This finding is also supported by previous research.[9,16]

The association between glycemia and reduced TT concentrations may be an effect of glycemia on the testicular microvasculature. Thus, glycemia alters Ledig cell function, directly causing primary hypogonadism. This may account for the lack of an observed association between TT levels and gonadotropin hormones in men with type 2 diabetes. In addition, if glucose is not reaching the cells because of insulin insensitivity, there will not be enough energy generated for the various metabolic processes involved in maintaining testosterone levels.

**Conclusion**

Serum TT concentrations were found to be lower in a relatively large number of Ghanaian men with type 2 diabetes compared to healthy men. This study demonstrated that elevated FBG, triglyceride levels, and BMI are risk factors for hypogonadism in Ghanaian men with type 2 diabetes. In addition, it can be concluded that obesity (as indicated by elevated BMI) is an independent risk factor for hypogonadism in Ghanaian men with type 2 diabetes. This study also showed that these risk factors affected testicular microvasculature, accounting for primary hypogonadism. The implications of reduced serum TT concentrations in men with type 2 diabetes merit further investigation.

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