ISSN 2664-4169 (Print) & ISSN 2664-7923 (Online)
South Asian Research Journal of Biology and Applied Biosciences
Abbreviated Key Title: South Asian Res J Bio Appl Biosci

| Volume-8 | Issue-2 | Mar-Apr -2026 | **DOI: https://doi.org/10.36346/sarjbab.2026.v08i02.001**

Original Research Article

Serum Levels of Pituitary and Gonadal Hormones in Patients with Type 2 Diabetes Mellitus: A Sex-Based Comparative Study

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Article History
Received: 17.01.2026
Accepted: 24.02.2026
Published: 03.03.2026

Abstract: Type 2 diabetes mellitus (T2DM) is a multifaceted endocrine and metabolic disorder, which involves not only defects in insulin action and β-cell function. There is some evidence that the chronic hyperglycemia, increased visceral adipose tissue and low-grade inflammation seen in patients affected with T2DM may lead to derangement of hypothalamic–pituitary function and therefore gonadal steroidogenesis, however sex-specific hormonal profile has been poorly described in Middle Eastern individuals. The present case–control study addressed levels of pituitary and gonadal hormones in T2DM adults, and was conducted to assess their association with glycemic control. One hundred adults were recruited (50 patients with T2DM [25 men and 25 women] and 50 age- and sex-matched healthy controls). Anthropometric parameters, fasting plasma glucose (FPG), lipid profile and glycated haemoglobin (HbA1c) were estimated. Serum luteinizing hormone, follicle-stimulating hormone, prolactin, thyroid-stimulating hormone (TSH), testosterone (TT) in men and estradiol (E2) in women were measured with chemiluminescent immunoassays. Patients with T2DM showed higher body mass index, fasting plasma glucose, and HbA1c levels than controls ($p < 0.001$). Gonadotropin was significantly lower and prolactin, thyroid-stimulating hormone levels were higher in male as well as female patients. Men with T2DM had significantly lower testosterone and affected women had significantly lower estradiol concentration. Glycated hemoglobin significantly negatively correlated with gonadotropins and sex steroids, and positively correlated with prolactin and thyroid-stimulating hormone. These data showed that T2DM was associated with abnormalities in pituitary–gonadal and pituitary–thyroid function (represented by hypogonadism, hyperprolactinemia and thyroid axis alterations), regardless of gender; this finding highlights a need to carry out endocrinological evaluation in poorly controlled patients.

Keywords: Type 2 diabetes mellitus, Pituitary hormones, Gonadal steroids, Glycemic control, Hypogonadism, Middle East.

Introduction

Type 2 diabetes mellitus (T2DM) is among the fastest growing metabolic disorders globally and is a significant public health concern due to its high morbidity and mortality (Booth *et al*., 2016; Kirichenko *et al*., 2022). Although T2DM has traditionally been considered to be a disease primarily of glucose metabolism arising due to insulin resistance and progressive β-cell failure, emerging evidence suggests it is a multifaceted disorder with complex effects on endocrine, inflammatory, and neuro-metabolic axes (Mitrovic *et al*., 2022). Chronic hyperglycemia, visceral adiposity and subtle inflammation conspire together to disturb hormonal balance as well as metabolic control and reproductive function, in addition to thyroid function.

Hypothalamic signaling pathways, in particularly kisspeptin and gonadotropin-releasing hormone (GnRH) neurons, are known to be impaired by insulin resistance and obesity causing disturbed secretion of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) Pataky *et al*., 2021; Mongraw-Chaffin *et al*., 2021). In males, these central changes typically manifest in the form of functional hypogonadotropic hypogonadism, with reduced serum testosterone levels combined with normal or low gonadotropins, that is highly enriched for sarcopenia, visceral adiposity and endothelial dysfunction and predicts excess cardiovascular risk (Hayden, 2023; Kusters *et al.,* 2023). Androgen insufficiency could be a potential cause and/or consequence of metabolic derangement, which in turn would translate to a vicious cycle leading to the accelerated onset of T2DM (Saad *et al*., 1997).

In females, the reproductive axis also has been linked with insulin resistance and dysglycemia through an alteration in menstrual cycle followed by impaired ovulation and a decrease in estradiol (Luo & Liu, 2016; Hemat Jouy *et al*., 2024). Estrogen is important for proper glucose metabolism, lipid regulation, and vascular function [26], so changes in ovarian steroidogenesis may further contribute to worsening cardiometabolic risk in women with T2DM during perimenopause and postmenopause stage (Palomba *et al*., 2024). These findings underscore the need for sex-specific analyses in studies of endocrine function and metabolic disease.

Changes in pituitary hormone secretion are not confined to the gonadotropic axis in T2DM patients. Prolactin has also been linked to insulin resistance and inhibition of gonadotropins secretion, that could exacerbate the reproductive dysfunction in males or females (Zorena *et al*., 2020). The obesity-associated inflammation in hypothalamus and impaired dopaminergic inhibition have been proposed as contributing mechanisms for hyperprolactinemia noted in metabolic disorders (Deng & Scherer, 2010). In addition, hypothalamic–pituitary–thyroid axis dysfunctions such as high thyroid-stimulating hormone (TSH) and subclinical hypothyroidism are common in T2DM patients and have been correlated with dyslipidemia, decreased insulin sensitivity and increased cardiovascular risk (Datta *et al*., 2025).

While there is considerable evidence that T2DM is associated with perturbations in the endocrine functions, few studies have specifically addressed concomitant changes of pituitary and gonadal hormones with comparison between men and women in Middle East populations. Geographic, genetic, and lifestyle variations may affect the metabolic and hormonal profiles in FMF, emphasizing the necessity of country-based studies. Therefore, the objective of this research is to evaluate serum levels of certain pituitary and gonadal hormone among Iraqi type 2 diabetics compared with healthy group and to probe sex-based difference in their level as well as their relation with blood glucose control represented by glycated hemoglobin (HbA1c).

MATERIALS AND METHODS

Study Design and Participants

This case–control study was performed at a Tikrit Teaching Hospital in Salah Al-Din Governorate, Iraq, from September 2023 to March 2024. The study was performed according to the Declaration of Helsinki and it was approved by the local ethical institutional committee. Before enrolment written informed consent was obtained from all the patients.

One hundred adult individuals were enrolled in the study and divided into two groups. T2DM group The T2DM group included 50 patients (25 men and 25 women) who were diagnosed with type 2 diabetes mellitus. Fifty healthy matched aged and sex controls were served as a control group. The determination of T2DM was based on the American Diabetes Association criterion (American Diabetes Association [ADA], 2023).

Exclusion Criteria

Participants were excluded if they had a history of pituitary, thyroid, adrenal, or gonadal disorders, chronic hepatic or renal disease, malignancy, pregnancy or lactation, or if they were receiving hormone replacement therapy or any endocrine-active medications at the time of the study.

Clinical and Biochemical Assessment

Body weight and height were measured in standard conditions and body mass index (BMI) was calculated as the body weight into kilograms divided by the square of the body height into meters (kg/m^2). Overnight fasting for a minimum of 10 to 12 hours was observed prior to taking venous blood samples. Fasting plasma glucose and HbA1c (glycated hemoglobin) were measured by routine laboratory methods, using standardized enzymatic techniques.

Hormonal Measurements

Levels of serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), prolactin (PRL) and thyroid stimulating hormone (TSH) were determined in all participants. Serum testosterone was also determined in men and estradiol levels were measured for women. All hormone assays were conducted using commercial chemiluminescent immunoassay (CLIA) kits as per the manufacturers' instructions. Internal quality control of the assay was performed at every step of analysis to guarantee reliability and accuracy for the assays.

Statistical Analysis

Statistical analyses were conducted using standard statistical software. Values were presented as mean ± SD. Independent-sample t-tests were used to compare T2DM patients and control subjects. The correlation between HbA1c and hormonal variables was evaluated by the Pearson correlation coefficient. All of them were two-tailed and $p<0.05$ was considered to be statistically significant.

RESULTS

Demographic and Metabolic Characteristics

One hundred subjects (50 patients with T2DM [25 men and 25 women] and 50 age- and sex-matched healthy controls) were enrolled in the study. 0.05), indicated in Table 1 there was no significant difference in age between patients with T2DM and control subjects. On the other hand, BMI, fasting plasma glucose and glycated hemoglobin (HbA1c) were significantly higher in T2DM compared to control ($p < 0.001$ all), thus indicating poor glycemic control and greater adiposity of diabetic group.

Table 1: Demographic and Metabolic Parameters of Study Participants

Parameter	T2DM (n=50)	Control (n=50)	p value
Age (years)	48.6 ± 6.1	47.9 ± 5.8	0.61 ns
BMI (kg/m²)	29.5 ± 3.6	24.8 ± 2.9	<0.001
Fasting glucose (mg/dL)	170.8 ± 27.9	91.6 ± 10.8	<0.001
HbA1c (%)	8.5 ± 1.1	5.3 ± 0.5	<0.001

Pituitary Hormone Profiles

There were significant differences in the levels of serum pituitary hormones between the patients with T2DM and control subjects (Table 2). Both male and female T2DM patients showed remarkably lower levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), compared to their matched control groups. By contrast, (PRL and TSH were significantly higher in patients with T2DM of both genders. These 2 differences were statistically significant for all comparison ($p < 0.01$) and demonstrate the overall perturbation of pituitary hormone secretion in the T2DM subject group.

Table 2: Pituitary Hormones

Hormone	Male T2DM	Male Control	p	Female T2DM	Female Control	p
LH (IU/L)	3.2 ± 0.9	4.7 ± 1.1	0.002	4.1 ± 1.2	6.3 ± 1.4	<0.001
FSH (IU/L)	4.6 ± 1.0	6.1 ± 1.3	0.003	5.2 ± 1.5	7.4 ± 1.8	0.001
PRL (ng/mL)	15.0 ± 4.1	10.7 ± 3.0	0.009	19.4 ± 5.1	14.1 ± 3.9	0.007
TSH (µIU/mL)	3.3 ± 0.8	2.1 ± 0.6	0.003	3.5 ± 1.0	2.2 ± 0.7	0.002

Gonadal Hormone Profiles

Serum gonadal hormones between diabetes patients and controls showed statistically significant differences (Table 3). Serum testosterone level in the males with T2DM was significantly lower than that of the control group ($p < 0.001$). Similarly, women with T2DM had considerably lower estradiol levels than age-matched healthy unmedicated females ($p = 0.001$). These findings suggest the impairment of gonadal steroidogenesis in sex both with T2DM.

Table 3: Gonadal Hormones

Hormone	T2DM	Control	*p*
Testosterone (ng/mL) – males	3.3 ± 0.7	5.0 ± 0.9	<0.001
Estradiol (pg/mL) – females	53.1 ± 17.9	79.2 ± 20.8	0.001

Correlation between Glycemic Control and Hormonal Parameters

Correlations depicted that glycemic control was closely related with hormonal changes in T2DM. There was a negative association between HbA1c and LH, FSH, Testosterone (in males), and estradiol (females). On the other hand, HbA1c had a positive correlation with PRL and TSH levels. These links imply that worse glycemic control may be considered to cause more perturbation of pituitary and gonadal hormone regulation.

DISCUSSION

In this report, the findings show that men and women with T2DM have significant differences in pituitary and gonadal hormones when compared to healthy control subjects. The principal observations are diminished gonadotropin secretion, low sex steroids in blood and high levels of prolactin and thyroid-stimulating hormone. They found these hormonal imbalances were related significantly to poor glycaemic control represented by HbA1c, based on the fact that T2DM is a multi-system endocrine disorder not solely centered on glucose metabolism.

Decreases in luteinizing hormone (LH) and follicle-stimulating hormone (FSH) values seen in T2DM individuals would be in line with the aforementioned data showing that insulin resistance, visceral fat accumulation, and low-grade chronic inflammation hamper GnRH pulsatility of hypothalamic origin as well as pituitary drive at a gonadotropic level(Mongraw-Chaffin *et al.*, 2021; Pataky *et al.*, 2021). In rheumatological conditions, the combination of inflammatory cytokines, oxidative stress and impaired kisspeptin signaling has been shown to adversely affect the HPG axis, resulting in functional hypogonadotropic hypogonadism (Hayden, 2023).

In our male participants, the declines in testosterone levels were substantial (Table 1a) and are comparable to those observed in large epidemiological studies and meta-analyses that show a high prevalence of androgen deficiency in men with T2DM (Kusters *et al.,* 2023; Grossmann, 2022). Testosterone is an important regulator of lean body mass, insulin sensitivity and mitochondrial function. Its insufficiency results in more visceral fat, a higher systemic inflammation state and a further aggravation of insulin resistance which sets an oxidative path towards metabolic derailment (Grossmann, 2022; Kelly & Jones, 2015). The inverse association between HbA1c and testosterone found in this study adds to the evidence of a feedback between glycemic control and androgenicity.

Similarly, the levels of estradiol in female patients with T2DM were significantly lower than those in women withoutT2DM. This is in agreement with earlier studies that also related insulin resistance and dysglycemia to abnormal ovarian steroidogenesis, menstrual disturbance as well as diminished estradiol production (Luo & Liu, 2016; Palomba *et al*., 2024). Estradiol exerts protective effects on glucose metabolism, lipid homeostasis, and vascular function. Therefore, reduced estradiol levels, particularly in women approaching menopausal transition, may contribute to increased cardiometabolic risk in T2DM (Palomba *et al*., 2024; Mauvais-Jarvis, 2020). Although menopausal status was not stratified in the present study, the observed association between poor glycemic control and reduced estradiol levels underscores the importance of considering sex-specific endocrine factors in diabetic populations.

Elevated prolactin levels in patients with T2DM represent another important finding of this study. While physiological prolactin levels may support β-cell survival and glucose homeostasis, chronic hyperprolactinemia has been shown to suppress gonadotropin secretion and exacerbate reproductive dysfunction (Zorena *et al*., 2020). Obesity-related hypothalamic inflammation and impaired dopaminergic inhibition have been proposed as mechanisms underlying prolactin elevation in metabolic disorders (Deng & Scherer, 2010). The positive correlation between HbA1c and prolactin observed in this study suggests that prolactin dysregulation may reflect both metabolic stress and a contributing factor to pituitary–gonadal axis suppression in T2DM.

The pronounced elevation in TS H level observed in patients with T2DM reflects thyroid axis dysfunction, and may account for sub-clinical hypothyroidism. T2DM subjects also exhibited an increased prevalence of thyroid dysfunction, and abnormal TSH levels have been correlated with dyslipidemia, reduced insulin sensitivity and increased CVD risk (Datta *et al*., 2025; Han *et al*., 2021). Hormones secreted by the thyroid are essential modulators of basal metabolic rate and glucose metabolism, and even minor alterations in thyroid status can complicate metabolic control in patients with diabetes. The significant positive relation between HbA1c and TSH demonstrated in the present study indicates that thyroid axis derangements deteriorate as glycemic control decreases.

The significant correlations between HbA1c and pituitary–gonadal hormones reflect the intense interplay that exists in this bidirectional cross-talk between metabolic and endocrine homeostasis. Second, hypothalamic–pituitary signaling may be directly affected by poorly-controlled glycemia (via glucotoxicity, oxidative stress and microvascular damage), whereas hormonal deficiencies can similarly contribute to the insulin resistance and metabolic dysfunction state (Mauvais-Jarvis, 2020; Grossmann, 2022). Crucially, from interventional studies, it is known that the cheap weight loss as well as the better control of glycemia is able to ameliorate in part plasma levels of gonadal hormones proving therefore a partial reversibility of these endocrine disturbances (Kelly & Jones 2015).

Locally, there are few studies on the changes in pituitary and gonadal hormones of the T2DM patients from Middle East populations. The present report adds to our understanding by reporting sex-specific endocrinological profile in Iraqi adults with T2DM and significant links between hormonal abnormalities and glucose homeostasis. These results underscore the importance of endocrine assessment in patients with uncontrolled diabetes and provide support for further prospective clinical studies to elucidate causality and therapeutic benefits.

CONCLUSION

The results of the present investigation show that type 2 diabetes mellitus is accompanied by marked alterations in pituitary and gonadal hormone regulation in both sexes. Patients with T2DM showed downregulated gonadotropin and sex steroid release, upregulated prolactin and thyroid-stimulating hormone concentration consistent to impaired pituitary–gonadal and pituitary–thyroid axes operation. These hormone changes had a strong correlation with poor glycaemic control, thus indicative of the powerful interaction between metabolic dysfunction and endocrine homeostasis. The findings emphasize the need for including endocrine evaluation in the management of patients with T2DM. More longitudinally designed studies are needed to disentangle the burden of proof and understand if better glycemic control is able to reverse such hormonal alterations and lower associated metabolic risks.

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