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Prolactin as a Potential Biomarker of Glycemic Control in Women with Type 2 Diabetes Mellitus

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Abstract. *Prolactin, a hormone primarily known for its important role in lactation and reproductive function have recently been implicated in metabolic-processes including glucose regulation. This study aims to investigation the relationship between serum prolactin levels and markers of glucose metabolism—specifically HbA1c and fasting blood glucose (FBG)—in women with T2DM. A cross sectional study was conducted on 100 adult female patients with T2DM, aged 35–50 years. Participants were classified based on HbA1c into three groups: good (≤7.0%), moderate (7.1–8.5%), and poor (≥8.6%) glycemic control. They were also stratified into low, normal, and high prolactin level groups. Serum prolactin was measured by ELISA, HbA1c by HPLC, and FBG using an automated analyzer. Statistical analysis was performed with significance at $p \leq 0.05$. Although prolactin levels tended to increase with worsening HbA1c, the difference among HbA1c groups was not statistically significant. However, when stratified by prolactin levels, women in the high prolactin group had significantly higher HbA1c (7.38 ± 1.07%) and FBG (163.21 ± 25.23 mg/dL) compared to those in the low prolactin group (HbA1c: 6.82 ± 0.91%, FBG: 149.22 ± 22.24 mg/dL; $p = 0.041$ and $p = 0.040$, respectively). Elevated serum prolactin levels may be associated with poorer glycemic control in women with T2DM. These results showing the potential-role of prolactin hormone as a supplementary test in measuring glucose metabolism.*

Keywords: *Fasting Blood Glucose, Glycemic Control, HbA1c, Prolactin.*

1. INTRODUCTION

Type 2 diabetes-mellitus (T2DM) is a complex and chronic-metabolic disorder defined mainly by the combination of “insulin resistance” and an absolute impairment of insulin-secretion (Nolan & Prentki, 2019). Dissimilar to type 1 diabetes, which results from autoimmune damage of pancreatic β-cells, DM type 2 progresses over time as a consequence of reduced insulin sensitivity of body tissues combined with a progressive failure of β - cell function (Eizirik, Pasquali, & Cnop, 2020). It is the most prevalent types of diabetes diseases found in about 90–95% of all diagnosed cases worldwide. The global-prevalence of T2DM has escalated to alarming levels, primarily due to aging of the population, physical inactivity, and rising obesity (Rob et al., 2025). “International Diabetes Federation” statistics revealed that “there were more than 500 million adults living with diabetes in 2021 with a projected further increase in subsequent years” (Teo et al., 2021). The pathogenesis of type 2 diabetes diseases (T2DM) is brought about by a complex interaction of gene susceptibility, environment, and lifestyle (Kolb & Martin, 2017). At disease onset, there is insulin-resistance in the body's principal organs of muscle, fat, and liver. The pancreatic β - cells respond by secreting a larger quantity of insulin in order to maintain normal response blood glucose (Rutter, Pullen, Hodson, & Martinez-

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Sanchez, 2015). However, when the disease advances, these β - cells cannot keep pace with the rising demand, and there is recurrent hyperglycemia (Nair, Tzanakakis, & Hebrok, 2020). Recurrent hyperglycemia can lead to a wide range of complications, variable from damage to small-vessels causing in nephropathy, retinopathy and neuropathy and to large-vessels consequential in cardiovascular diseases like stroke, coronary artery disease and peripheral-arterial-disease (Ighodaro & Adeosun, 2018). Such obstacles not only reduce quality of life but also significantly add to diabetes morbidity and mortality. Optimal glycemic control remains one of the cornerstones in the controlling of type 2 diabetes disease (T2DM) (Khunti et al., 2025). Fasting-blood-glucose(FBG) and glycated-hemoglobin(HbA1c) are two biomarkers that are most commonly used to measure glucose homeostasis (Ketema & Kibret, 2015). FBG gives idea of short-term glycemic control whereas HbA1c is an accurate marker of mean blood sugar over two to four months (Lundholm, Emanuele, Ashraf, & Nadeem, 2020). Although these markers are important in the clinic, they do not necessarily reflect the complete magnitude of "the greater hormonal and metabolic disturbances characteristic of T2DM" (Ferrannini et al., 2013). This restriction exists to highlight the necessity to find and investigate additional-biomarkers that will contribute to disease process information and refine the strategy toward monitoring and upkeep of glycemic control.

Prolactin is a polypeptide-hormone largely formed by the anterior-pituitary-gland, usually recognized for its key functions in "lactation and reproductive physiology" and might have a function in metabolic control (Lopez-Vicchi et al., 2020). The occurrence of prolactin receptors in many tissues, including pancreatic islets, hepatocytes, adipose tissue and components of the immune-system suggests a broader physiological role beyond reproduction (Gorvin, 2015). Correlations between plasma prolactin levels and significant metabolic parameters such as insulin sensitivity, pancreatic β - cell function, and inflammation have been verified in studies (Manshaei et al., 2019; Yang et al., 2021). In contrast, both hypoprolactinemia and hyperprolactinemia were associated with negative metabolic profiles, and therefore prolactin has been postulated to have a dose-response, potentially U-shaped influence on glucose metabolism (Pirchio, Graziadio, Colao, Pivonello, & Auriemma, 2022).

The title role of prolactin in type 2 diabetes disease(T2DM) remains incompletely defined. Some studies have reported that elevated levels of prolactin are associated with "improved glycemic control" (Wang et al., 2013), others have reported an association with "poor metabolic control" (Macotela, Triebel, & Clapp, 2020). These conflicting results

may be due to heterogeneity of study populations, variations in study design, or variability in disease duration and severity. Interpretation of the interaction of prolactin with glucose metabolism could contribute to current understanding of T2DM pathophysiology and potentially reveal new biomarkers or therapeutic-targets for more effective treatment of the disease. This study aims to evaluation of serum-prolactin levels in adult women-patients with T2DM and investigate their relationship with fasting blood glucose and HbA1c to determine whether prolactin may serve as a potential biomarker for glycemic control.

2. MATERIALS AND METHODS

This (cross-sectional) study was directed at "Al Jawaden Special Lab" (Baghdad city, Iraq) between February 2024 and March 2025. This study was aimed to evaluate the association among blood prolactin hormone levels and glycemic-control tests including fasting-blood-glucose(FBG) and glycated-hemoglobin(HbA1c) in adult women patients with T2DM. Written-informed consent was gotten from all contributors-women prior to their enrollment in the study..

This study was conducted exclusively on female participants to minimize gender-related hormonal variation, particularly in prolactin levels, and to enhance the specificity of the findings. Eligible participants were adult women aged between 35 and 50 years who had been diagnosed with Type 2 Diabetes disease(T2DM) for at least (one year) in agreement with the diagnostic-criteria-established by the "American Diabetes Association" (ADA). All participants were required to have been on a stable anti-diabetic medication regimen for at least six months prior to enrollment. Additionally, only women with acceptable glycemic control, defined as having a glycated hemoglobin level of <10 were included. Participants also needed to be physically and mentally capable of providing informed written consent and complying with study procedures. These criteria were established to ensure a homogeneous study population and to reduce the influence of external variables on the metabolic and hormonal assessments.

Exclusion Criteria

Participant's women with any condition or factor that might influence prolactin levels or glucose metabolism and hence contaminate the study were excluded. Pregnancy and lactation women were also reasons for exclusion because prolactin levels would naturally be greater during these states. women with acute infection, chronic inflammatory

disorders or previous histories of thyroid, pituitary, liver, kidney, or heart disease were excluded. Besides, participants receiving drugs with known effects on prolactin release such as antipsychotics, antidepressants, estrogen replacement, or dopamine antagonists were excluded. Women with diabetes that was not under control, as indicated by an HbA1c level above or equal to 10%, were also excluded to minimize heterogeneity linked to end-stage disease. These exclusion criteria were applied to ensure that potential-confounders were controlled for and the results of the study made as accurate and reliable as possible.

Blood Sample Collection

Blood-samples from vein were collected from all members after an overnight fast of "at least 8 hours". Samples were processed immediately and aliquoted for biochemical and hormonal assays (HAYDER H Abed, Alwasiti, & Tawfeeq, 2020).

Fasting Blood Glucose (FBG)

FBG was measured using an automated glucose analyzer (Roche Cobas e411, Switzerland) based on the glucose oxidase-peroxidase method. Results were expressed in mg/dL (Hayder Hussein Abed, Ali, & Al-Ziaydi, 2023; Aamer M Ali, Abed, Al-Ziaydi, & Nayif, 2020).

HbA1c Measurement

HbA1c was measured using "high-performance-liquid-chromatography (HPLC)" a gold standard methods for assessing long-term glycemic control. Results were expressed as a percentage (%) (Aamer M Ali, Abed, Nayif, & Salman, 2024).

Serum Prolactin Measurement

Serum prolactin levels were determined using a commercial enzyme-linked immunosorbent assay (Roche, Cobas e411, Switzerland), following the manufacturer's instructions. Samples were run in duplicate to ensure accuracy. The assay's sensitivity, intra-assay, and inter-assay coefficients of variation were within acceptable limits (Gutiérrez, Gazzano, Torracca, Meucci, & Mariti, 2019).

Group Designed and Statistical Analysis

Participants were divided into subgroups based on two key variables: glycated hemoglobin (HbA1c) and serum prolactin levels.

Based on HbA1c values, which reflect long-term glycemic control, participants were categorized into three groups. The first group included women with good glycemic control, defined as an HbA1c level of 7.0% or lower. The second group consisted of participants with moderate glycemic control, having HbA1c values between 7.1% and 8.5%. The third group represented those with poor glycemic control, defined as having HbA1c values ranging from 8.6% to 10.0%.

In addition, the participants were also divided into three groups according to their serum prolactin level. The target population for the study was divided into low, medium, and high serum prolactin level groups. Stratification facilitated the assessment of potential associations between differential levels of prolactin and glucose metabolism. By grouping the participants by both HbA1c and prolactin levels to investigate fluctuations in prolactin were associated with differences in glycemia, and to determine the ability of prolactin as a biomarker for glucose regulation in women with Type 2 Diabetes Mellitus.

All statistical analyses were performed using GarphPad prism software (Version 8). Continuous variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. p value of less than 0.05 was considered statistically significant for all tests (Aamer Mousa Ali, Hussein, Jawad, Abed, & Mekkey, 2024).

3. RESULTS AND DISCUSSION

A total of 100 female participants with Type 2 Diabetes Mellitus were included in the analysis. When stratified by HbA1c levels, the mean prolactin level in the good glycemic control group (HbA1c ≤ 7.0%) was 23.03 ± 10.13 ng/mL, in the moderate group (HbA1c 7.1–8.5%) it was 25.37 ± 10.47 ng/mL, and in the poor control group (HbA1c ≥ 8.6%) it was 30.18 ± 4.01 ng/mL. Although a gradual increase in prolactin levels was observed with worsening glycemic control, this difference did not reach statistical significance (P = NS). The prolactin range varied widely in each group, with the highest individual level reaching 49 ng/mL in the moderate group as show in Table 1 and Figure 1.

Table 1. Results Prolactin in Glycemic control Groups, p value ≤ 0.05

HbA1c	N	Mean of prolactin ng/mL	Range	P value
Good (≤7)	52	23.03 ± 10.13	4.4 - 42	NS
Moderate (7.1 -8.5)	40	25.37 ± 10.47	4.3 - 49	
Poor (≥8.6)	8	30.18 ± 4.01	12 - 48	

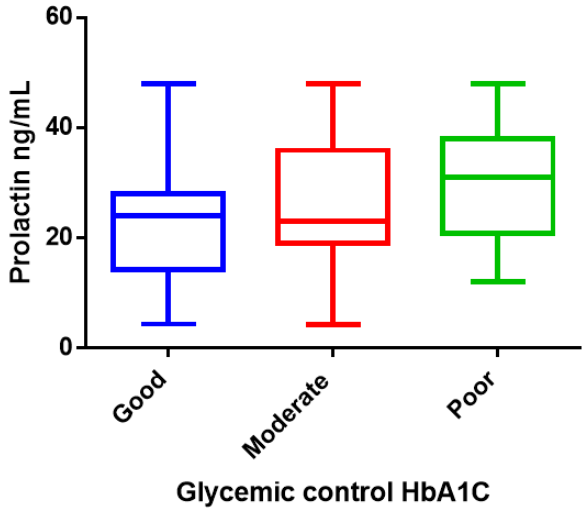

Figure 1. Statistical results of prolactin in glycemic control groups

The current study explored the relationship between serum prolactin levels and glucose metabolism in women with Type 2 Diabetes Mellitus (T2DM). Although prolactin is traditionally known for its role in lactation and reproductive physiology, accumulating evidence suggests it may also play a role in glucose regulation, insulin resistance, and metabolic homeostasis (Mastnak, Herman, Ferjan, Janež, & Jensterle, 2023).

Participants were also stratified by prolactin levels into three categories: low (<15 ng/mL), normal (15–25 ng/mL), and high (>25 ng/mL). The mean HbA1c was 6.82 ± 0.91% in the low prolactin group, 7.03 ± 0.95% in the normal group, and 7.38 ± 1.07% in the high prolactin group. A statistically significant increase in HbA1c was observed in the high prolactin group compared to the low group (P = 0.041, test a), while other comparisons were not significant (NSb). This suggests a modest but meaningful association between elevated prolactin levels and poorer long-term glycemic control as in Figure 2 and Table 2.

Table 2. Results of HbA1C in prolactin groups. P value ≤ 0.05

Prolactin ng/mL	N	Mean of HbA1C ± SD	range	P value
Low < 15	19	6.82 ± 0.91	6.1 -8.9	NS
Normal (15- 25)	36	7.03 ± 0.95	5.9 - 9	Ns
High > 25	45	7.38 ± 1.07	5.8. 9.9	S*[a] (0.041) NS[b]

* a: A statistically difference between Low and High groups

** b: Statistically difference between Normal and High groups

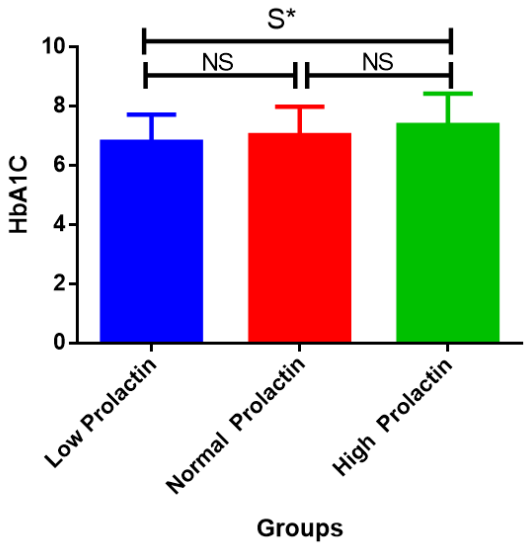

Figure 2. Statistically Results Of Hba1c In Prolactin Groups

In this study, a non-significant upward trend in prolactin levels was observed with increasing HbA1c, suggesting that higher prolactin levels may be associated with poorer glycemic control (Molina-Calle, De Medina, De La Torre, Priego-Capote, & De Castro, 2016). However, when participants were stratified by prolactin levels, a significant increase in HbA1c was noted in the high prolactin group compared to the low group. This supports the hypothesis that elevated prolactin may contribute to or reflect impaired glucose metabolism (Corona et al., 2022).

A similar stratification by prolactin levels revealed that the mean fasting blood glucose (FBG) was 149.22 ± 22.24 mg/dL in the low group, 160.7 ± 22.69 mg/dL in the normal group, and 163.21 ± 25.23 mg/dL in the high group. The difference between the high and low prolactin groups was statistically significant (P = 0.040, test a), whereas other comparisons were not (NSb). This indicates a potential trend toward higher fasting glucose levels in participants with elevated prolactin as in Figure 3 and table 3.

Table 3. Statistical analysis of prolactin groups according to fasting blood glucose.

P value ≤ 0.05

Prolactin ng/mL	N	Mean of FBG ± SD	range	P value
Low < 15	19	149.22 ± 22.24	93 - 188	NS
Normal (15- 25)	36	160.7 ± 22.69	99 - 194	Ns
High > 25	45	163.21 ± 25.23	102 - 199	S* [a] (0.040) NS[b]

* a: A statistically difference between Low and High groups

** b: Statistically difference between Normal and High groups

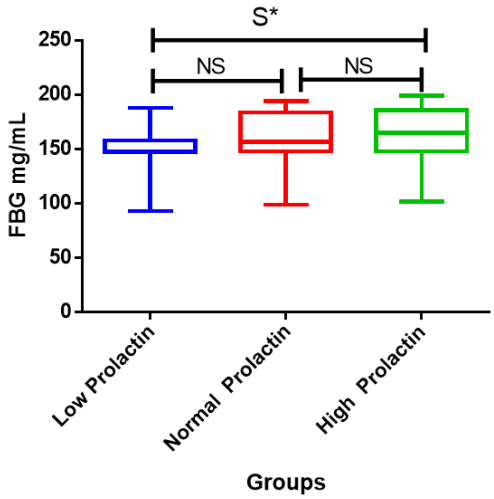

Figure 3. Statistical results of FBG according to prolactin groups

The significant rise in fasting blood glucose levels in participants with high prolactin levels reinforces this association. These findings align with some prior research that links hyperprolactinemia with insulin resistance, though the exact mechanisms remain unclear (Gierach, Bruska-Sikorska, Rojek, & Junik, 2022). Prolactin may affect glucose metabolism via modulation of insulin signaling pathways or by influencing hypothalamic-pituitary axis activity (Ni, Chen, Cai, Xiao, & Zhang, 2021).

It is important to note that while these associations were statistically significant in some comparisons, they were modest in magnitude, and the overall trends suggest a potential, but not definitive, role of prolactin in the pathophysiology of T2DM. The lack of significance in the primary HbA1c stratification may be due to the small sample size in the poor control group (n = 8), limiting statistical power.

These results highlight the potential utility of prolactin as a supplementary biomarker in assessing glycemic status in women with T2DM. However, further research with larger, more diverse populations and longitudinal designs is needed to confirm causality and understand underlying mechanisms.

4. CONCLUSION

This study investigated the association between serum prolactin levels and glucose metabolism in women with Type 2 Diabetes Mellitus. The findings suggest that higher prolactin levels may be modestly associated with poorer glycemic control, as reflected by elevated HbA1c and fasting blood glucose levels. Although the overall differences in prolactin levels across HbA1c groups were not statistically significant, significant associations were observed when participants were stratified by prolactin levels, particularly in relation to HbA1c and FBG. These results point to a potential role for prolactin as a supplementary biomarker in evaluating glucose regulation in women with T2DM.

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CONFLICT OF INTEREST

"Author declare that there is no conflict of interest regarding the publication of this manuscript".

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