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COMPARATIVE EVALUATION OF HORMONAL, BIOCHEMICAL, AND HISTOPATHOLOGICAL CHANGES IN DIABETIC VERSUS NON-DIABETIC FEMALE RABBITS

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Abstract

Diabetes mellitus is associated with significant endocrine, metabolic, and histopathological alterations affecting multiple organs, including the pancreas, ovaries, liver, and kidneys. This study evaluated the impact of partial and complete diabetes on hormonal profiles, metabolic parameters, and organ histology. Female subjects were divided into three groups: control, partial diabetic, and complete diabetic. Serum estradiol and progesterone levels were significantly reduced in diabetic groups, with the complete diabetic group showing the lowest concentrations (estradiol: 22 ± 4 pg/mL; progesterone: 1.9 ± 0.5 ng/mL), while luteinizing hormone, follicle-stimulating hormone, and prolactin levels were markedly elevated in a diabetes-dependent manner ($p = 0.0001$ for all). Metabolic assessments revealed progressive hyperglycemia and impaired insulin secretion in diabetic groups. Fasting blood glucose increased from 5.1 ± 0.4 mmol/L in controls to 18.5 ± 1.7 mmol/L in complete diabetics, whereas serum insulin decreased from 18.0 ± 2.2 µIU/mL to 4.1 ± 0.7 µIU/mL. Glycated hemoglobin (HbA1c) levels also reflected poor glycemic control, rising to 9.8 ± 0.6% in the complete diabetic group. Lipid profile analysis showed significant dyslipidemia, with total cholesterol and triglycerides reaching 180 ± 18 mg/dL and 170 ± 20 mg/dL, respectively, in complete diabetics. Hepatic enzyme levels (ALT and AST) and renal markers (serum creatinine and blood urea nitrogen) were significantly elevated in diabetic groups, indicating hepatic and renal impairment. Histopathological evaluation demonstrated progressive tissue damage associated with diabetes. Pancreatic islets showed marked degeneration in complete diabetics (score: 3.3 ± 0.4), paralleled by ovarian follicular degeneration (3.1 ± 0.5) and stromal fibrosis (2.8 ± 0.6). Renal glomerular damage (score: 3.0 ± 0.5) and hepatic steatosis (2.9 ± 0.5) were also most pronounced in the complete diabetic group. These findings indicate a strong correlation between the severity of diabetes and structural organ damage.

INTRODUCTION

Diabetes mellitus (DM) is a persistent metabolic disorder characterized by chronic hyperglycemia, arising from either inadequate insulin production, impaired insulin action, or a combination of both [1]. As a major global health challenge, the prevalence of diabetes continues to rise, prompting extensive research into its systemic effects. These effects include disruptions

in hormonal balance, metabolic imbalances, and tissue-specific structural changes. According to the American Diabetes Association (ADA), DM affects carbohydrate, lipid, and protein metabolism [2]. The World Health Organization (WHO) attributes the increasing incidence of diabetes to lifestyle shifts, urbanization, and an aging population [3]. Research by Kharroubi and Darwish further links DM to a higher risk of cardiovascular disease, kidney impairment, and other organ-specific complications [4]. A significant focus of contemporary studies has been the molecular and cellular mechanisms driving the progression of diabetes and its long-term effects on multiple organs.

While rodent models, particularly rats and mice, are frequently employed in experimental diabetes research, rabbits have recently emerged as valuable intermediate models. Rabbits share several physiological features with humans, including lipid metabolism, reproductive physiology, and susceptibility to diabetes-related complications [5, 6]. These similarities make rabbits especially useful for investigating the pathophysiology of diabetes and for testing potential treatments. With growing recognition of rabbits as relevant models for human disease, their inclusion in long-term studies is crucial for understanding chronic diabetic complications [5, 6].

Alloxan monohydrate is a widely used diabetogenic compound that selectively destroys pancreatic β-cells, leading to insulin deficiency and hyperglycemia, thereby modeling type 1 diabetes in humans [7, 8]. Alloxan-induced models have been extensively utilized to examine both the immediate and long-term consequences of elevated blood glucose. Its ability to induce reproducible β-cell destruction allows researchers to study the metabolic and systemic impacts of diabetes. However, most studies using alloxan in rabbits have a relatively short duration, typically lasting only a few weeks, which restricts the assessment of long-term complications [9]. Short-term studies are insufficient for capturing the full spectrum of chronic diabetic changes, such as kidney disease, fatty liver, dyslipidemia, and reproductive impairments [10]. In humans, many diabetic complications, including damage to the kidneys, liver, pancreas, and reproductive organs, develop over years, underscoring the need for extended experimental models.

Female rabbits are particularly susceptible to diabetes-induced metabolic disturbances. Insulin and reproductive hormones, such as estrogen and progesterone, play critical roles in female reproductive physiology, and chronic hyperglycemia can disrupt this balance. Altered insulin levels and hormonal imbalances can impair follicular maturation, ovulation, and endometrial receptivity, potentially leading to infertility or other reproductive disorders [11, 12].

Beyond reproductive effects, diabetes markedly influences various biochemical markers, including blood glucose, serum proteins, cholesterol, triglycerides, liver enzymes, and renal function indicators [13]. Persistent hyperglycemia promotes oxidative stress, inflammation, and metabolic dysregulation, resulting in structural changes in the pancreas, liver, kidneys, and reproductive tissues, which contribute to long-term organ dysfunction. These disruptions not only compromise reproductive health but also elevate the risk of other diabetes-associated complications, including cardiovascular disease and renal failure [14].

Materials and methods

Experimental design

A total of 36 juvenile New Zealand White rabbits, aged 8–10 weeks and weighing 2–2.5 kg, were utilized in the study. The animals underwent a one-week acclimation period, which included routine deworming, grooming, and health assessments. Following acclimatization, the rabbits were randomly divided into three groups, each consisting of 12 animals (n = 12 per group).

Group	Treatment
A – Control Group	Healthy, non-diabetic males and females; maintained under standard conditions without diabetes induction.
B – Partial Diabetic Group	Female rabbits induced with diabetes; male rabbits remain healthy.
C – Complete Diabetic Group	Both male and female rabbits induced with diabetes.

Rabbits were kept in stainless steel cages (10 × 6 × 3 ft) under controlled conditions (16–22°C, 30–70% RH, 12:12 h light-dark cycle). They were fed commercial rabbit pellets (HF 5326, Lab Diet), timothy hay cubes (Bio-Serv, NJ, USA), and provided filtered water ad libitum, with weekly fresh vegetables and environmental enrichment.

Insulin dose optimization: Individual insulin responses were assessed using glucose tolerance curves, with blood glucose measured hourly for 10 hours post-insulin injection. Insulin doses were then adjusted for each rabbit to achieve optimal glycemic control, targeting a peak BGL above 350 mg/dL and a nadir above 50 mg/dL. Dosages were iteratively modified until this response was consistently achieved.

Pinna wound healing model: Standardized full-thickness 6 mm excisional wounds were created on the inner pinna of each rabbit. Post-operative analgesia included subcutaneous buprenorphine (0.05–0.3 mg/kg) and transdermal fentanyl patches (25 µg/hr). Wounds were regularly monitored for infection and healing, and high-resolution imaging with a Nikon Eclipse Ti microscope was used for quantitative analysis of closure and tissue regeneration via Nikon Elements software.

Biochemical analysis: Blood samples were collected and centrifuged at 2,500 × g for 20 minutes at 4°C to separate plasma, which was then aliquoted and stored at −20°C for analysis. A broad panel of biochemical markers, including LDH, CK, AST, ALT, total protein, cholesterol, triglycerides, BUN, creatinine, and β-hydroxybutyrate, was measured using the Roche Diagnostic System with reagents from CTACHEN [15].

Tissue sampling and histopathology: At the conclusion of the 4-month study, rabbits were humanely euthanized with intravenous pentobarbital sodium (100 mg/kg) following ethical guidelines. Major organs, including the pancreas, ovaries, and kidneys, were excised, blotted, and weighed. Tissues were fixed in 4% buffered formalin for 24–48 hours, then processed for paraffin embedding. Serial 5–7 µm sections were prepared and stained with hematoxylin and eosin (H&E). Histopathological evaluation was performed using light microscopy to assess diabetes-related structural changes and treatment effects.

4.9 Body weight and condition

At the end of the study, the rabbits had a mean body weight of 2,513 ± 524 g. Body condition and adiposity were assessed non-invasively using a 5.0 MHz linear probe. Perirenal fat thickness was measured as an indicator of overall fat reserves [29], allowing for consistent quantitative evaluation without causing animal distress.

Blood and cytological

Blood samples were collected weekly from the central auricular artery into EDTA-coated tubes, centrifuged, and plasma stored at −20°C for biochemical and hormonal analyses. Reproductive status was monitored via vaginal cytology using sterile saline-moistened swabs, with cells transferred to slides, air-dried, and stained. Estrous cycle stages and hormonal changes were determined based on cellular morphology, following the methods of [3, 32], enabling non-invasive tracking of reproductive function.

4.11 Ultrasonographic monitoring

Pregnancy and fetal development were monitored using a Honda HS-2000 ultrasound with a 5/10 MHz linear transducer, following protocols from previous studies [7, 26, 30, 34]. Ventrodorsal scanning was used to locate the uterus and assess gestational structures. Real-time imaging allowed evaluation of fetal number, viability, and growth parameters, including crown-rump length and heart activity, providing reliable, non-invasive monitoring throughout gestation.

Reproductive and developmental parameters

Reproductive and developmental parameters were systematically monitored during gestation and postpartum. Fetal growth was assessed by ultrasonography, and gestational length was recorded from confirmed mating to parturition. Mammary development, including teat enlargement, was evaluated as an indicator of late gestation. At birth, neonates were weighed and litter sizes recorded, with weekly monitoring of postnatal body weights to track growth and developmental health. These assessments were conducted across first and second parities to evaluate reproductive performance and offspring viability.

Statistical analysis

Data are presented as mean ± standard deviation (SD). Comparisons between two independent groups were analyzed using Student's t-test, while repeated-measures data were evaluated with one-way or two-way ANOVA, as appropriate. Post hoc tests were applied to identify specific group differences. Statistical analyses were conducted using GraphPad Prism (GraphPad Software Inc., San Diego, CA, USA), with $p < 0.05$ considered statistically significant.

Results

Serum estradiol (pg/mL)

The control group had the highest mean estradiol concentration at 55 ± 6 pg/mL. The partial diabetic group showed a reduced mean level of 38 ± 5 pg/mL, while the complete diabetic group exhibited the lowest mean estradiol concentration of 22 ± 4 pg/mL. The p-value of 0.0001 indicates that these differences are highly significant. This pattern demonstrates a clear progressive decline in estradiol levels from control to partial and complete diabetic states, reflecting the effect of diabetes on ovarian hormone production.

Table-1 Serum estradiol (pg/mL)

Groups	Mean ± SD	P-value
G_1 = Control	55 ± 6[a]	0.0001
G_2 = Partial Diabetic	38 ± 5[b]	
G_3 = Complete Diabetic	22 ± 4[c]	

Serumprogesterone (ng/mL)

The control group had the highest mean concentration at 6.4 ± 0.8 ng/mL. The partial diabetic group showed a reduced mean level of 3.6 ± 0.6 ng/mL, while the complete diabetic group exhibited the lowest mean progesterone concentration of 1.9 ± 0.5 ng/mL. The p-value of 0.0001 indicates that these differences are highly significant.

Table-2 Serumprogesterone (ng/mL)

Groups	Mean ± SD	P-value
G_1 = Control	6.4 ± 0.8[a]	0.0001
G_2 = Partial Diabetic	3.6 ± 0.6[b]	
G_3 = Complete Diabetic	1.9 ± 0.5[c]	

Luteinizing hormone (mIU/mL)

The complete diabetic group exhibited the highest mean luteinizing hormone level at 6.2 ± 0.8 mIU/mL. The partial diabetic group showed an intermediate mean of 4.5 ± 0.7 mIU/mL, while the control group had the lowest mean luteinizing hormone level of 2.8 ± 0.5 mIU/mL. The p-value of 0.0001 indicates that these differences are highly significant.

Table-3 Luteinizing hormone (mIU/mL)

Groups	Mean ± SD	P-value
G_1 = Control	2.8 ± 0.5^a	0.0001
G_2 = Partial Diabetic	4.5 ± 0.7^b	
G_3 = Complete Diabetic	6.2 ± 0.8^c	

Follicle-stimulating hormone (mIU/mL)

The complete diabetic group showed the highest mean follicle-stimulating hormone level at 7.0 ± 0.7 mIU/mL. The partial diabetic group had an intermediate mean of 5.2 ± 0.6 mIU/mL, while the control group exhibited the lowest mean follicle-stimulating hormone level of 3.0 ± 0.4 mIU/mL. The p-value of 0.0001 indicates that these differences are highly significant.

Table-4 Follicle-stimulating hormone (mIU/mL)

Groups	Mean ± SD	P-value
G_1 = Control	3.0 ± 0.4^a	0.0001
G_2 = Partial Diabetic	5.2 ± 0.6^b	
G_3 = Complete Diabetic	7.0 ± 0.7^c	

Prolactin (ng/mL)

The complete diabetic group exhibited the highest mean prolactin concentration at 14.5 ± 1.8 ng/mL. The partial diabetic group showed an intermediate mean of 11.0 ± 1.5 ng/mL, while the control group had the lowest mean level of 8.5 ± 1.0 ng/mL. The p-value of 0.0001 indicates these differences are highly significant.

Table-5 Prolactin (ng/mL)

Groups	Mean ± SD	P-value
G_1 = Control	8.5 ± 1.0^a	0.0001
G_2 = Partial Diabetic	11.0 ± 1.5^b	
G_3 = Complete Diabetic	14.5 ± 1.8^c	

Fasting blood glucose (mmol/L)

The complete diabetic group had the highest mean glucose level at 18.5 ± 1.7 mmol/L. The partial diabetic group showed an intermediate mean of 11.8 ± 1.2 mmol/L, while the control group exhibited the lowest mean glucose level of 5.1 ± 0.4 mmol/L. The p-value of 0.0001 indicates that these differences are highly significant.

Table-6 Fasting blood glucose (mmol/L)

Groups	Mean ± SD	P-value
G_1 = Control	5.1 ± 0.4^a	0.0001
G_2 = Partial Diabetic	11.8 ± 1.2^b	
G_3 = Complete Diabetic	18.5 ± 1.7^c	

Serum insulin (µIU/mL)

The control group exhibited the highest mean insulin concentration at 18.0 ± 2.2 µIU/mL, whereas the partial diabetic group showed a reduced mean level of 8.4 ± 1.4 µIU/mL. In contrast, the complete diabetic group recorded the lowest mean insulin concentration at 4.1 ± 0.7 µIU/mL. These results reveal marked differences among the groups, with a highly significant p-value of 0.0001 confirming the statistical reliability of these findings.

Table-7 Serum insulin (µIU/mL)

Groups	Mean ± SD	P-value
G_1 = Control	18.0 ± 2.2^a	0.0001
G_2 = Partial Diabetic	8.4 ± 1.4^b	
G_3 = Complete Diabetic	4.1 ± 0.7^c	

HbA1c (%)

The complete diabetic group exhibited the highest mean HbA1c value at 9.8 ± 0.6%, while the partial diabetic group showed an intermediate level of 7.2 ± 0.5%. In contrast, the control group demonstrated the lowest mean HbA1c of 4.8 ± 0.3%. These results highlight clear differences among the groups, and the highly significant p-value of 0.0001 further confirms the statistical strength of these findings.

Table-8 HbA1c (%)

Groups	Mean ± SD	P-value
G_1 = Control	4.8 ± 0.3^a	0.0001
G_2 = Partial Diabetic	7.2 ± 0.5^b	
G_3 = Complete Diabetic	9.8 ± 0.6^c	

Total cholesterol (mg/dL)

The complete diabetic group exhibited the highest mean cholesterol level at 180 ± 18 mg/dL. The partial diabetic group showed an intermediate mean of 145 ± 15 mg/dL, while the control group had the lowest mean level of 110 ± 10 mg/dL. The p-value of 0.0001 indicates that these differences are highly significant.

Table-9 Total cholesterol (mg/dL)

Groups	Mean ± SD	P-value
G_1 = Control	110 ± 10^a	0.0001
G_2 = Partial Diabetic	145 ± 15^b	
G_3 = Complete Diabetic	180 ± 18^c	

Triglycerides (mg/dL)

The complete diabetic group showed the highest mean level at 170 ± 20 mg/dL. The partial diabetic group had an intermediate mean of 120 ± 15 mg/dL, while the control group exhibited the lowest mean triglyceride level of 70 ± 8 mg/dL. The p-value of 0.0001 indicates that these differences are highly significant.

Table-10 Triglycerides (mg/dL)

Groups	Mean ± SD	P-value
G_1 = Control	70 ± 80^a	0.0001
G_2 = Partial Diabetic	120 ± 15^b	

G_3 = Complete Diabetic	170 ± 20[c]	

Alanine aminotransferase (U/L)

The complete diabetic group exhibited the highest mean ALT level at 85 ± 10 U/L. The partial diabetic group showed an intermediate mean of 55 ± 8 U/L, while the control group had the lowest mean level of 35 ± 5 U/L. The p-value of 0.0001 indicates that these differences are highly significant.

Table-11 Alanine aminotransferase (U/L)

Groups	Mean ± SD	P-value
G_1 = Control	35 ± 50[a]	0.0001
G_2 = Partial Diabetic	55 ± 80[b]	
G_3 = Complete Diabetic	85 ± 10[c]	

Aspartate aminotransferase (U/L)

The complete diabetic group had the highest aspartate aminotransferase level at 90 ± 12 U/L. The partial diabetic group showed an intermediate of 60 ± 7 U/L, while the control group exhibited the lowest mean level of 40 ± 6 U/L. The p-value of 0.0001 indicates that these differences are highly significant.

Table-12 Aspartate aminotransferase (U/L)

Groups	Mean ± SD	P-value
G_1 = Control	40 ± 6[a]	0.0001
G_2 = Partial Diabetic	60 ± 7[b]	
G_3 = Complete Diabetic	90 ± 12[c]	

Serum creatinine (mg/dL)

The complete diabetic group exhibited the highest mean creatinine level at 1.45 ± 0.15 mg/dL. The partial diabetic group had an intermediate mean of 0.95 ± 0.10 mg/dL, while the control group showed the lowest mean level of 0.70 ± 0.06 mg/dL. The p-value of 0.0001 indicates that these differences are highly significant.

Table-13 Serum creatinine (mg/dL)

Groups	Mean ± SD	P-value
G_1 = Control	0.70 ± 0.06[a]	0.0001
G_2 = Partial Diabetic	0.95 ± 0.10[b]	
G_3 = Complete Diabetic	1.45 ± 0.15[c]	

Blood urea nitrogen (mg/dL)

The complete diabetic group exhibited the highest mean blood urea nitrogen level at 34 ± 4 mg/dL. The partial diabetic group showed an intermediate mean of 22 ± 3 mg/dL, while the control group had the lowest mean level of 14 ± 2 mg/dL. The p-value of 0.0001 indicates that these differences are highly significant.

Table-14 Blood urea nitrogen (mg/dL)

Groups	Mean ± SD	P-value
G_1 = Control	14 ± 2[a]	0.0001
G_2 = Partial Diabetic	22 ± 3[b]	
G_3 = Complete Diabetic	34 ± 4[c]	

Serum amylase (U/L)

The complete diabetic group exhibited the highest mean amylase activity at 580 ± 50 U/L. The partial diabetic group showed an intermediate mean of 500 ± 48 U/L, while the control group had the lowest mean level of 420 ± 35 U/L. The p-value of 0.0001 indicates that these differences are highly significant.

Table-15 Serum amylase (U/L)

Groups	Mean ± SD	P-value
G_1 = Control	420 ± 35[a]	0.0001
G_2 = Partial Diabetic	500 ± 48[ab]	
G_3 = Complete Diabetic	580 ± 50[b]	

Pancreatic islet damage score

The complete diabetic group showed the highest mean score of 3.3 ± 0.4, indicating marked to severe islet damage. The partial diabetic group had an intermediate mean score of 2.1 ± 0.5, reflecting moderate damage, while the control group exhibited the lowest mean score of 0.2 ± 0.3, indicating near-normal pancreatic histology. The p-value of 0.0001 indicates that these differences are highly significant.

Table-16 Pancreatic islet damage score (1-4 score)

Groups	Mean ± SD	P-value
G_1 = Control	0.2 ± 0.3[a]	0.0001
G_2 = Partial Diabetic	2.1 ± 0.5[b]	
G_3 = Complete Diabetic	3.3 ± 0.4[c]	

Ovarian follicular degeneration score

The complete diabetic group exhibited the highest mean score of 3.1 ± 0.5, indicating marked follicular degeneration. The partial diabetic group showed an intermediate mean score of 1.9 ± 0.6, reflecting moderate degeneration, while the control group had the lowest mean score of 0.3 ± 0.4, indicating nearly normal ovarian follicles. The p-value of 0.0001 indicates that these differences are highly significant.

Table-17 Ovarian follicular degeneration score

Groups	Mean ± SD	P-value
G_1 = Control	0.3 ± 0.4[a]	0.0001
G_2 = Partial Diabetic	1.9 ± 0.6[b]	
G_3 = Complete Diabetic	3.1 ± 0.5[c]	

(0 = normal, 1 = mild, 2 = moderate, 3 = marked, 4 = severe)

Ovarian stromal fibrosis score (0-4)

The complete diabetic group exhibited the highest mean score of 2.8 ± 0.6, indicating marked fibrosis. The partial diabetic group showed an intermediate mean score of 1.6 ± 0.5, reflecting moderate fibrosis, while the control group had the lowest mean score of 0.2 ± 0.3, and indicating nearly normal ovarian stroma. The p-value of 0.0001 indicates that these differences are highly significant.

Table-18 Ovarian stromal fibrosis score

Groups	Mean ± SD	P-value
G_1 = Control	0.2 ± 0.3[a]	0.0001
G_2 = Partial Diabetic	1.6 ± 0.5[b]	
G_3 = Complete Diabetic	2.8 ± 0.6[c]	

Kidney: glomerular damage score

The complete diabetic group showed the highest mean score of 3.0 ± 0.5, indicating marked glomerular damage. The partial diabetic group had an intermediate mean score of 1.8 ± 0.6, reflecting moderate damage, while the control group exhibited the lowest mean score of 0.3 ± 0.4, indicating near-normal glomeruli. The p-value of 0.0001 indicates that these differences are highly significant.

Table-19 Kidney: glomerular damage score

Groups	Mean ± SD	P-value
G_1 = Control	0.3 ± 0.4[a]	0.0001
G_2 = Partial Diabetic	1.8 ± 0.6[b]	
G_3 = Complete Diabetic	3.0 ± 0.5[c]	

Liver: hepatic steatosis score

The complete diabetic group exhibited the highest mean score of 2.9 ± 0.5, indicating marked hepatic fat accumulation. The partial diabetic group showed an intermediate mean score of 1.7 ± 0.6, reflecting moderate steatosis, while the control group had the lowest mean score of 0.4 ± 0.5, and indicating nearly normal liver histology. The p-value of 0.0001 indicates that these differences are highly significant.

Table-20 Liver: hepatic steatosis score

Groups	Mean ± SD	P-value
G_1 = Control	0.4 ± 0.5[a]	0.0001
G_2 = Partial Diabetic	1.7 ± 0.6[b]	
G_3 = Complete Diabetic	2.9 ± 0.5[c]	

Discussion

In the control group, the rabbits demonstrated normal reproductive endocrine activity, with mean estradiol levels of 55 ± 6 pg/mL and progesterone of 6.4 ± 0.8 ng/mL, reflecting robust ovarian steroidogenesis, likely maintained by intact insulin signaling and metabolic homeostasis. By contrast, both partially and fully diabetic animals exhibited a progressive decline in these ovarian hormones. Such reductions underscore the damaging effects of hyperglycemia and insulin deficiency on ovarian function, consistent with earlier reports that experimental diabetes impairs granulosa and luteal cell steroid production [15,13]. Beyond ovarian suppression, diabetes disrupted the hypothalamic–pituitary axis: in fully diabetic rabbits, luteinizing hormone (LH) rose to 6.2 ± 0.8 ng/mL, follicle stimulating hormone (FSH) to 7.0 ± 0.7 ng/mL, and prolactin to 14.5 ± 1.8 ng/mL, significantly higher than in controls. This elevation is most plausibly a compensatory response to reduced negative feedback from declining estradiol and progesterone, mirroring earlier findings in diabetic models where the pituitary and hypothalamus increase gonadotropin secretion to counter ovarian insufficiency [40,42]. The endocrine profile thus reflects a breakdown of normal feedback regulation: diminished steroid hormone output fails to restrain pituitary activity [27,42]. These disturbances in the hypothalamic–pituitary–gonadal (HPG) axis have broader ramifications. Chronic hyperglycemia and low insulin levels impair follicular maturation, disrupt hormone biosynthesis, and reduce ovulation [35]. Importantly, partially diabetic rabbits exhibited intermediate hormone levels compared to control and fully diabetic groups, suggesting a dose-dependent relationship in which the severity of metabolic dysfunction correlates with the extent of reproductive endocrine disruption [28].

Metabolically, fully diabetic rabbits displayed profound hyperglycemia (18.5 ± 1.7 mmol/L), the lowest insulin concentrations (4.1 ± 0.7 µIU/mL), and elevated HbA_1c (9.8 ± 0.6 %), confirming

sustained glycemic dysregulation and extensive β cell damage, as seen in alloxan models [17,4,16]. These changes scaled with disease severity, since the partially diabetic group showed more moderate derangements. Moreover, dyslipidemia was evident in fully diabetic rabbits: cholesterol rose to 180 ± 18 mg/dL and triglycerides to 170 ± 20 mg/dL. These lipid abnormalities likely result from impaired insulin-mediated lipid uptake and utilization, causing increased free fatty acid mobilization and hepatic lipogenesis — a pattern consistent with previous studies in diabetic animal models [22,11]. Liver injury was also apparent: serum alanine aminotransferase (ALT) reached 85 ± 10 U/L and aspartate aminotransferase (AST) 90 ± 12 U/L in the fully diabetic group, indicative of hepatic stress [37,24]. Such increases are in line with accumulating evidence that diabetes precipitates liver dysfunction via lipid accumulation, oxidative stress, and mitochondrial impairment [37,24]. Renal impairment was likewise reflected in elevated creatinine (1.45 ± 0.15 mg/dL) and blood urea nitrogen (BUN: 34 ± 4 mg/dL), consistent with early diabetic nephropathy characterized by glomerular damage and reduced filtration [8,9].

The pancreas was not spared: fully diabetic rabbits exhibited increased amylase activity (580 ± 50 U/L), suggesting exocrine pancreatic stress, likely tied to β cell destruction, oxidative insult, and microvascular compromise — phenomena also observed in prior models of chronic hyperglycemia [19,20]. Histopathologically, the most severe lesions in fully diabetic rabbits appeared in pancreatic islets (score 3.3 ± 0.4), ovaries (follicular degeneration 3.1 ± 0.5, fibrosis 2.8 ± 0.6), glomeruli (3.0 ± 0.5), and liver (fat accumulation 2.9 ± 0.5). Partially diabetic animals showed moderate, but discernible, damage, while controls maintained near normal tissue architecture. These structural derangements parallel previous observations of islet atrophy, glomerulosclerosis, and hepatic steatosis in diabetic models [5,18,2]. Notably, ovarian fibrosis and follicular degeneration likely underpin the drop in sex steroid levels, as structural compromise directly impairs steroidogenic capacity [13,27].

The present study illustrates that experimental diabetes in rabbits produces a multi-organ pathology that worsens in proportion to glycemic burden. Fully diabetic animals exhibited the most profound endocrine dysregulation (including HPG axis disruption), metabolic disturbance (dysglycemia, dyslipidemia), and tissue injury (pancreatic, hepatic, renal, and ovarian). Partially diabetic rabbits manifested an intermediate phenotype, underscoring a dose-dependent effect of hyperglycemia. These findings echo earlier work [28,42,35,20] and highlight the critical importance of early and sustained glycemic control to mitigate systemic damage and preserve reproductive, metabolic, and organ health [1,43].

Conclusion

From the present study it could be concluded that the diabetes induces significant endocrine dysfunction, metabolic derangements, and multi-organ histopathological alterations. The progressive decline in ovarian hormones, elevation of gonadotropins and prolactin, along with impaired glucose and lipid metabolism, underscores the systemic impact of diabetes. Histological analysis corroborates these biochemical changes, highlighting severe pancreatic, ovarian, renal, and hepatic damage in complete diabetes. These results emphasize the importance of early detection and management of diabetes to prevent extensive organ dysfunction.

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