

Short communication

ASSOCIATION BETWEEN INTESTINAL ZONULIN EXPRESSION AND POLYCYSTIC OVARY SYNDROME IN RATS

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Abstract

Polycystic Ovary Syndrome (PCOS) is a complex endocrine disorder characterized by reproductive and metabolic disturbances, frequently associated with insulin resistance. Emerging evidence suggests that altered intestinal barrier function may be involved in the pathophysiology of PCOS, with zonulin recognized as a marker of increased intestinal permeability. This study aimed to investigate the association between PCOS and intestinal zonulin expression using an experimental animal model.

The research was done on female Wistar rats. Animals were randomly assigned to a control group or a PCOS-induced group. PCOS was induced through androgen

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administration, after which intestinal zonulin expression was measured and compared between groups. Statistical analyses were performed to evaluate intergroup differences and the association between PCOS induction and zonulin expression.

The results showed that PCOS-induced rats had significantly higher intestinal zonulin expression than controls (5.545 ± 1.163 vs. 3.775 ± 1.196 ; $p < 0.001$). Normality testing showed a non-normal distribution in the PCOS group (Shapiro–Wilk $p = 0.027$) and a normal distribution in controls ($p = 0.413$), supporting the use of non-parametric analysis. Mann–Whitney U test confirmed a significant difference between groups ($U = 58.0$, $Z = -3.849$), with a large effect size ($r = 0.61$). Structural modeling (SEM-PLS) demonstrated a significant direct effect of PCOS induction on zonulin expression ($T = 9.797$, $p < 0.001$), with substantial explanatory power (adjusted $R^2 = 0.511$) and predictive relevance ($Q^2 = 0.371$).

The results demonstrated that PCOS-induced rats exhibited significantly increased intestinal zonulin expression compared with healthy controls. Further analysis revealed a significant positive correlation between PCOS induction and elevated zonulin expression, suggesting altered intestinal barrier function, as inferred from the heightened zonulin levels in the PCOS model.

These findings suggest that PCOS is associated with increased intestinal permeability, supporting the involvement of gut barrier dysfunction in the metabolic features of the disorder. Intestinal zonulin expression may serve as a possible biomarker linked to metabolic disturbances, including insulin resistance, as indicated by previous studies and corroborative findings. This study provides experimental evidence highlighting the relevance of the gut–endocrine axis in PCOS pathophysiology and may contribute to the development of novel diagnostic or therapeutic strategies.

Keywords: Polycystic ovary syndrome, insulin resistance, rats, biomarkers, intestines

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a common endocrine disorder affecting 4–18% of reproductive-age women, characterized by oligo/anovulation, hyperandrogenism, and polycystic ovarian morphology (Brosens et al., 2015). It is frequently associated with insulin resistance, obesity, and long-term metabolic complications including type 2 diabetes mellitus and cardiovascular disease. Infertility remains the major clinical consequence, affecting up to 10% of patients and significantly impairing the quality of life (Joham et al., 2015). Despite extensive research, the exact mechanisms underlying PCOS pathogenesis remain incompletely understood.

Emerging evidence suggests that gut dysbiosis and impaired intestinal barrier integrity contribute to the metabolic and endocrine disturbances observed in PCOS (Sun et al., 2023). Zonulin, a physiological regulator of intestinal tight

junctions, plays a central role in modulating gut permeability. Elevated zonulin levels promote the translocation of bacterial lipopolysaccharides (LPS), triggering low-grade inflammation, insulin resistance, and subsequent disruption of ovarian function (Mkumbuzi et al., 2020; Serek and Oleksy-Wawrzyniak, 2021). Recent studies have reported increased zonulin levels in women with PCOS and other metabolic disorders, supporting its role as a potential biomarker linking intestinal permeability with endocrine dysfunction (He and Li, 2020; Veres-Székely et al., 2023).

However, most existing evidence in humans is observational, with limited exploration of direct causal pathways, restricting the ability to infer causal relationships between intestinal barrier dysfunction and PCOS. Experimental animal models provide an opportunity to elucidate mechanistic links between PCOS and the pathophysiology of zonulin expression. Alterations in gut permeability may impact metabolic and reproductive functioning via the gut–brain–gonad axis, in which microbial-derived inflammatory signals and metabolic mediators regulate hypothalamic–pituitary control and ovarian steroidogenesis. Experimental animal models provide a controlled approach to elucidate these mechanistic interactions. Therefore, the objective of this study was to explicitly evaluate the association between PCOS induction and zonulin expression using a PCOS animal model. Furthermore, this study introduces a novel analytical approach, applying Structural Equation Modeling - Partial Least Squares (SEM-PLS) to assess the direct effect of PCOS induction on zonulin expression, providing new experimental insight into the role of intestinal permeability in PCOS pathogenesis and its potential relevance as a therapeutic target. We hypothesized that PCOS induction would be associated with increased intestinal zonulin expression, reflecting impaired gut barrier integrity.

MATERIAL AND METHODS

Study design and animals

This research was an experimental study using a post-test control-only group design to evaluate the effect of polycystic ovary syndrome (PCOS) induction on zonulin expression as a marker of intestinal permeability. Forty female Wistar rats (*Rattus norvegicus*), aged 8–10 weeks and weighing 180–220 g, were used. The animals were randomly allocated into two groups (n = 20 per group): a control group and a PCOS-induced group. The sample size was determined based on previous experimental studies employing similar PCOS animal models, where comparable group sizes were sufficient to detect biologically meaningful differences (Wang et al., 2020). Randomization was done using a simple random allocation method. All histological and immunohistochemical evaluations were conducted by an investigator blinded to group allocation to avoid observer bias.

PCOS induction

PCOS was induced by oral administration of testosterone propionate for 21 consecutive days. Control animals received standard feed and water without hormonal treatment. Successful induction of PCOS was confirmed by estrous cycle monitoring using daily vaginal smear cytology and by ovarian histopathological examination at the end of the experimental period (Figure 1).

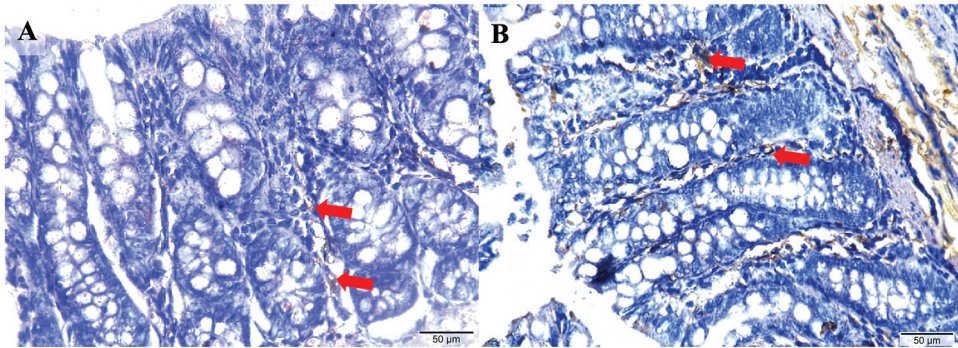


Figure 1. Zonulin expression in colonic epithelium (Immunohistochemistry, 400×). Representative micrographs show the colonic mucosal layer of Wistar rats evaluated via immunohistochemistry. Arrows indicate positive zonulin expression within the epithelial layer, highlighted by brown chromogen staining. (A) Control group showing baseline expression. (B) PCOS-induced group showing markedly increased, intense staining.

Tissue collection and histopathological evaluation

After the treatment period, the animals were sacrificed, and ovarian and colon tissues were collected. Ovarian tissues were fixed in 10% neutral-buffered formalin, embedded in paraffin, sectioned at 5 µm, and stained with hematoxylin and eosin. Microscopic examination demonstrated multiple cystic follicles, increased numbers of atretic follicles, and reduced corpora lutea in the PCOS group, consistent with polycystic ovarian morphology.

Immunohistochemical assessment of zonulin

Zonulin expression, an indirect indicator of intestinal permeability, was assessed using immunohistochemistry (IHC). Although serum-based assays were initially considered, only IHC-derived data were included in the final analysis to ensure methodological consistency.

Colon tissue samples were fixed in 10% neutral-buffered formalin, embedded in paraffin, and sectioned at 4 µm thickness. The sections were deparaffinized, rehydrated, and subjected to antigen retrieval using citrate buffer (pH 6.0).

Endogenous peroxidase activity was blocked with 3% hydrogen peroxide. The slides were incubated overnight at 4°C with a primary anti-zonulin antibody (rabbit polyclonal, Abcam, ab276405; dilution 1:200), followed by incubation with an HRP-conjugated secondary antibody. Visualization was achieved using 3,3'-diaminobenzidine, and the sections were counterstained with hematoxylin.

Zonulin expression was evaluated semi-quantitatively and expressed as the Immunoreactive Score (IRS). Staining intensity was graded as 0 (no staining), 1 (weak), 2 (moderate), or 3 (strong). The percentage of positively stained epithelial cells was scored as 0 (<10%), 1 (10–25%), 2 (26–50%), 3 (51–75%), or 4 (>75%). The IRS was calculated by multiplying intensity and percentage scores, yielding a total score ranging from 0 to 12. Ten randomly selected high-power fields were evaluated per sample.

Metabolic parameters, including fasting glucose, insulin levels, and HOMA-IR, were assessed as part of the same experimental protocol and animal population but will be reported separately.

Statistical analysis

Data were analyzed with SPSS version 26.0. Normality was assessed with the Shapiro–Wilk test. Normally distributed data were analyzed using independent t-tests, while non-normally distributed data were analyzed with the Mann–Whitney U test. To explore the association between PCOS induction and zonulin expression, SEM-PLS was done using SmartPLS version 4.0.8.6. Statistical significance was set at $p < 0.05$. SEM-PLS was applied to estimate the structural relationship between PCOS induction and zonulin expression, including path coefficients and predictive relevance indices (R^2 and Q^2). In this model, both PCOS induction and zonulin expression were treated as observed variables; therefore, outer model (measurement model) evaluation was not applicable. The use of SEM-PLS was intended to provide a scalable analytical framework for future studies incorporating multiple metabolic and inflammatory variables.

RESULTS AND DISCUSSION

Normality testing with the Shapiro–Wilk test revealed that zonulin expression scores in the control group were normally distributed ($p = 0.413$), but in the PCOS group were not ($p = 0.027$). Accordingly, between-group comparisons were done with the Mann–Whitney U test.

Immunohistochemical analysis revealed significantly higher zonulin expression in the PCOS-induced group compared with controls ($p < 0.05$) (Table 1, Figure 1). Descriptive analysis demonstrated an increased central tendency in the PCOS group, with a mean zonulin IRS of 5.545, when compared with 3.775 in the control group. The median IRS value was likewise higher in the PCOS group, and the

interquartile range was shifted upward, indicating a consistent increase in zonulin expression across samples. Although outliers were present in both groups, the overall distribution pattern clearly demonstrated higher zonulin expression in the PCOS model.

Table 1. Association between zonulin expression and PCOS

Variable	Group	Mean $\pm$ SD	Shapiro–Wilk Sig.	p-value ^a
Zonulin	Control (n=20)	3,775 $\pm$ 1,195	0.413	0.000
	Treatment (n=20)	5,545 $\pm$ 1,163	0.027	

^aMann-Whitney

The magnitude of the group difference was further supported by effect size analysis. The Mann–Whitney U test confirmed a significant difference ($U = 58.0$, $Z = -3.849$, $p < 0.001$), yielded a large effect size ($r = 0.61$), with a 95% confidence interval indicating a robust separation between control and PCOS groups, reinforcing the biological relevance of the observed difference.

All panels presented in Figure 2 (Panels A–I) depict zonulin staining across control and experimental groups, with Panels A–D showing normal folliculogenesis in healthy rats and Panels E–H showing disrupted folliculogenesis in PCOS-induced rats; Panel I shows an aberrant Graafian follicle showing follicular atresia. Representative images demonstrated stronger zonulin staining intensity and a higher proportion of positively stained epithelial cells in the colon tissue of PCOS-induced rats. Zonulin expression patterns were visualized using boxplots, which illustrated higher median values and a wider distribution in the PCOS group compared with controls (Figure 3).

To assess the strength of the association between PCOS induction and zonulin expression, SEM-PLS analysis was performed. The structural model demonstrated a strong explanatory capacity, with an adjusted $R^2 = 0.511$, indicating that 51.1% of the variance in zonulin expression was explained by PCOS induction. Predictive relevance testing yielded a positive Q^2 value of 0.371, confirming adequate predictive accuracy of the model.

Path analysis using SEM-PLS demonstrated a direct significant effect of PCOS induction on zonulin expression ($p < 0.05$; T -statistic > 1.96), reinforcing the strong association between PCOS and increased zonulin expression. The structural model revealed a significant direct effect of PCOS on zonulin expression (β = path coefficient, $T = 9.797$, $p < 0.001$), indicating that PCOS induction strongly and positively influences zonulin expression. The high t -statistic and low standard error further confirm the robustness of this relationship (Table 2).

This study demonstrated a significant increase in zonulin expression in the PCOS group, indicating enhanced intestinal permeability associated with PCOS. These experimental findings are consistent with clinical observations reporting elevated

zonulin in women with PCOS and its correlation with metabolic dysfunction (Zhang et al., 2015; Lindheim et al., 2017). Using an immunohistochemical approach, this study provides histological evidence of increased zonulin expression in the intestinal tissue.

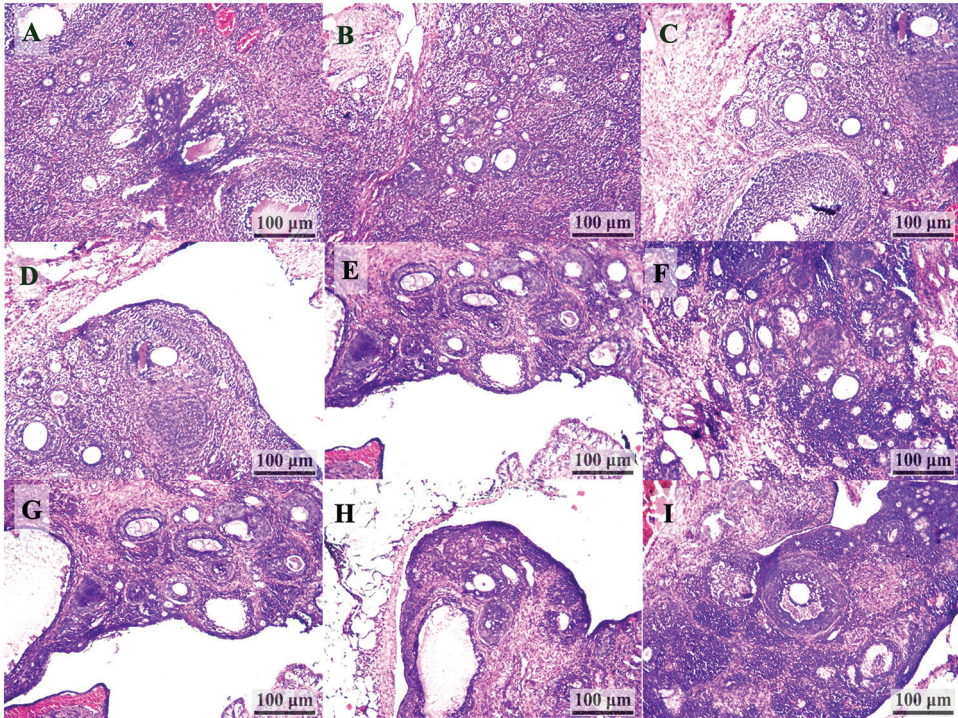


Figure 2. Comparative ovarian histopathology of healthy control and PCOS-induced Wistar rats (H&E, 100×). Panels A–D show normal folliculogenesis in healthy rats: (A) primordial follicles, (B) primary follicles, (C) secondary follicles, and (D) tertiary follicle with antral cavity formation. Panels E–H illustrate disrupted folliculogenesis in adrogen-induced PCOS rats: accumulation of primordial (E) and primary follicles (F), (G) numerous arrested secondary follicles in the cortical region, (H) tertiary follicles with cystic changes and thinning of granulosa cell layers, and (I) aberrant Graafian follicle showing follicular atresia. These findings highlight the contrast between balanced follicular development in healthy ovaries and follicular arrest with cystic degeneration in PCOS.

Zonulin is a physiological regulator of intestinal tight junctions; its upregulation increases epithelial permeability and facilitates the translocation of luminal antigens and endotoxins (e.g., LPS) into the circulation, which can trigger low-grade inflammation and impair insulin signalling—mechanisms that plausibly link zonulin elevation to insulin resistance observed in PCOS (Sturgeon and Fasano, 2016). Nevertheless, increased zonulin expression may also reflect alternative or complementary processes. Factors such as systemic inflammation, hormonal stress, dietary influences, or androgen-driven alterations in gut microbiota

composition may independently contribute to increased zonulin expression (He and Li, 2020). In this hyperandrogenic animal model, testosterone exposure itself may have influenced intestinal permeability either directly or indirectly through inflammatory pathways. Therefore, while zonulin elevation is strongly associated with PCOS induction, it should not be interpreted as a sole or exclusive driver of metabolic dysfunction.

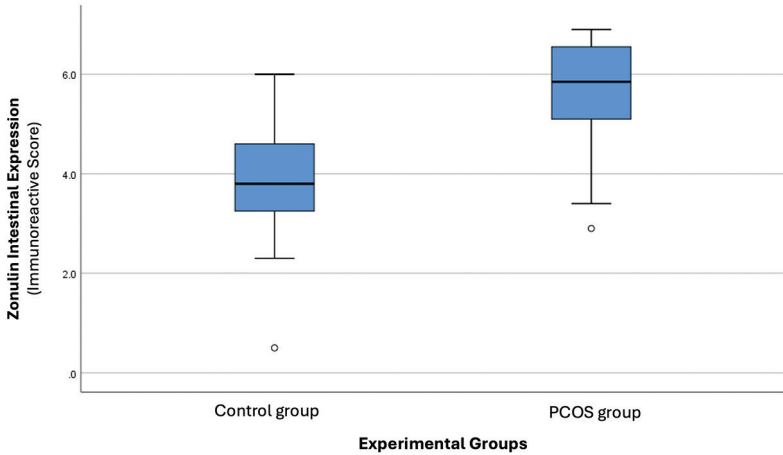


Figure 3. Comparison of intestinal zonulin expression in control and PCOS groups. Boxplots of intestinal zonulin immunoreactive scores in control rats ($n = 20$) and PCOS-induced rats ($n = 20$). The PCOS group demonstrated significantly higher zonulin expression than the control group (Mann–Whitney U test, $p < 0.001$).

Table 2. Direct Effect of PCOS on zonulin expression

Path	STDEV	T-Statistic	p-value	Significance
PCOS → Zonulin	0.073	9.797	0.000	Significant

From a translational perspective, targeting zonulin—either through interventions aimed at restoring gut microbiota composition or by directly modulating zonulin signalling—emerges as a potential strategy to reduce intestinal permeability and alleviate metabolic inflammation. Human intervention studies, including metformin therapy and lifestyle modification, have demonstrated improvements in metabolic status accompanied by reductions in zonulin, while recent reviews have also highlighted pharmacological agents targeting the zonulin pathway as potential therapeutic candidate (Karim et al., 2024). Nonetheless, interventional evidence remains limited and requires further clinical trials (Ibrahim and Ahmeid, 2021; Veres-Székely et al., 2023).

These findings position zonulin as a potential biomarker connecting intestinal barrier dysfunction with the metabolic phenotype of PCOS. However, it remains unresolved whether elevated zonulin causally drives ovarian dysfunction or primarily reflects accompanying metabolic disturbances; targeted interventional studies that specifically lower zonulin would provide stronger causal evidence (Osuka et al., 2019; Ryu et al., 2019). In this study, intestinal permeability was not directly measured in functional assays such as FITC-dextran or lactulose–mannitol tests. Therefore, the observed increase in zonulin expression should be interpreted as an indirect surrogate marker of barrier dysfunction rather than definitive evidence of increased permeability.

The strengths of this study include its controlled experimental design, which enables causal inference between PCOS induction and zonulin elevation, and the use of SEM-PLS to examine mechanistic relationships. Although the association between PCOS induction and zonulin expression could be evaluated with conventional statistical methods, SEM-PLS was employed to provide a model-based approach that allows future integration of additional variables. Nevertheless, the current findings should be interpreted within the context of a simple structural model. However, the study has several important limitations. First, a single PCOS animal model based on androgen induction was used, which reproduces key features such as hyperandrogenism and insulin resistance but does not fully reflect the clinical heterogeneity of PCOS. Second, intestinal permeability was inferred from zonulin expression rather than measured directly using functional permeability assays. Third, this study did not include interventions designed to modulate zonulin expression or intestinal permeability, limiting causal inference regarding its therapeutic potential.

Future studies should incorporate multiple PCOS models to capture phenotypic diversity and include direct permeability assessments to validate zonulin as a functional marker. Interventional approaches targeting the gut barrier, such as zonulin-modulating agents, dietary modifications, or probiotic and prebiotic supplementation, may help clarify whether reducing intestinal permeability improves metabolic and reproductive outcomes in PCOS. Such studies would strengthen the translational relevance of targeting the gut–endocrine axis in PCOS management.

CONCLUSION

This experimental study demonstrated that zonulin expression significantly increased in a PCOS animal model, suggesting a potential alteration in intestinal barrier function. These findings support the role of zonulin as a surrogate marker associated with metabolic features of PCOS; however, direct assessment of intestinal permeability is required to confirm functional impairment.

Authors' contributions

Conceptualization, FU, MIS, and BS; methodology, FU, MIS, KYE, PML, and WW; validation, WW and BS; formal analysis, WW and BS; investigation, FU, KYE, and PML; resources, MIS and EST; data curation, FU and BS; writing—original draft preparation, FU, EST, and BS; writing—review and editing, MIS, KYE, PML, WW, EST, and BS; visualization, BS; supervision, MIS, PML, and WW; project administration, FU. All authors have read and agreed to the published version of the manuscript.

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Data availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

Ethical statement

All experimental procedures were conducted in accordance with the institutional and international guidelines for the care and use of laboratory animals. The study protocol was reviewed and approved by the Institutional Ethics Committee (No: 3.KEH.150.10.2024). The study protocol was not registered in an external preclinical public registry prior to commencement

Competing interests

The authors declare no competing interests.

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POVEZANOST EKSPRESIJE INTESTINALNOG ZONULINA I SINDROMA POLICISTIČNIH JAJNIKA KOD PACOVA

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Kratak sadržaj

Sindrom policističnih jajnika (PCOS) je složen endokrini poremećaj kojeg karakterišu reproduktivni i metabolički poremećaji često povezani sa insulinskom rezistencijom. Novi dokazi ukazuju da izmenjena funkcija crevne barijere može imati ulogu u patofiziologiji PCOS-a, pri čemu se zonulin smatra markerom povećane crevne propustljivosti. Cilj ovog ispitivanja bio je istraživanje veze između PCOS-a i ekspresije zonulina u crevima, u eksperimentalnom animalnom modelu.

Eksperiment je urađen na ženjkama pacova rase Wistar. Životinje su nasumično raspoređene u kontrolnu grupu i grupu sa eksperimentalno izazvanim PCOS-om. PCOS je indukovao primenom androgena, nakon čega je merena ekspresija zonulina u crevima, i vrednosti upoređene između grupa. Statističkom analizom su procenjene razlike između grupa i veza između indukcije PCOS-a i ekspresije zonulina.

Rezultati su pokazali da je kod pacova sa indukovanim PCOS-om ekspresija zonulina u crevima bila značajno veća nego kod kontrolnih ($5,545 \pm 1,163$, odnosno $3,775 \pm 1,196$; $p < 0,001$). Testiranje je pokazalo da distribucija frekvencija nije bila normalna u grupi sa indukovanim PCOS-om (Shapiro-Wilk $p = 0,027$), dok u kontrolnoj grupi jeste bila ($p = 0,413$), te je primenjena neparametrijska analiza. Mann-Whitney U test potvrdio je značajnost razlika između grupa ($U = 58,0$; $Z = -3,849$), sa velikom veličinom efekta ($r = 0,61$). Strukturno modeliranje (SEM-PLS) pokazalo je značajan direktan efekat indukcije PCOS na ekspresiju zonulina ($T = 9,797$; $p < 0,001$), sa značajnom objašnjavajućom snagom (prilagođeni $R^2 = 0,511$) i prediktivnom relevantnošću ($Q^2 = 0,371$).

Rezultati su pokazali da su pacovi sa PCOS-om imali značajno povećanu ekspresiju zonulina u crevima u poređenju sa zdravom kontrolom. Dalja analiza je otkrila direktnu i značajnu

vezu između indukcije PCOS i povećane ekspresije zonulina, što ukazuje na izmenjenu funkciju crevne barijere, kao što se zaključuje iz povećane ekspresije zonulina u modelu PCOS.

Ovi nalazi ukazuju na to da je PCOS povezan sa povećanom crevnom propustljivošću, što podržava učešće disfunkcije crevne barijere u metaboličkim karakteristikama poremećaja. Ekspresija zonulina u crevima može poslužiti kao potencijalni biomarker koji je povezan sa metaboličkim poremećajima uključujući insulinsku rezistenciju, što impliciraju prethodne studije i komplementarni nalazi. Ovo ispitivanje pruža eksperimentalne dokaze koji ističu značaj crevno-endokrine ose u patofiziologiji PCOS i može doprineti razvoju novih dijagnostičkih ili terapijskih pristupa.

Ključne reči: Sindrom policističnih jajnika, insulinska rezistencija, pacovi, biomarkeri, creva