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RESEARCH ARTICLE

Transient Effects of Exenatide on Intraocular Pressure in a Rat Bone Defect Model

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Abstract

This study aimed to evaluate whether the glucagon-like peptide-1 (GLP-1) receptor agonist exenatide influences intraocular pressure (IOP) in Sprague–Dawley rats subjected to a bone defect model, and whether the timing and duration of administration modify this effect. A total of 36 male rats (8–10 weeks old, 200–250 g) were randomly allocated into six groups, including two control groups and four treatment groups receiving exenatide either preoperatively or postoperatively for different durations. Baseline IOP was measured in all animals prior to surgical creation of a bone defect. Exenatide or saline was administered intraperitoneally, and IOP was re-evaluated on postoperative day 7 using a rebound tonometer. IOP measurements were included as an exploratory secondary outcome within the experimental bone defect model rather than the primary endpoint of the study. The results demonstrated a statistically significant change in IOP only in the group receiving exenatide for three days postoperatively (P=0.027), whereas no significant changes were observed in the other treatment groups. In contrast, both control groups exhibited significant postoperative reductions in IOP (placebo group: P=0.023; sham group: P=0.026). These findings suggest that exenatide might transiently influence IOP under certain postoperative conditions, possibly counteracting decreases observed in control groups. However, due to potential confounding factors, the direction and magnitude of this effect remain uncertain and should be considered exploratory.

Key Words: Exenatide, glucagon-like peptide-1 agonists, intraocular pressure, ocular physiology, rat

Sıçan Kemik Defekti Modelinde Ekzenatidin Göz İçi Basıncı Üzerindeki Geçici Etkileri

Öz

Bu çalışma, glukagon benzeri peptid-1 (GLP-1) reseptör agonisti exenatidin, kemik defekti oluşturulan Sprague-Dawley sıçanlarda intraoküler basınç (IOB) üzerine etkisini ve uygulama zamanı ile süresinin bu etkiyi değiştirip değiştirmediğini değerlendirmeyi amaçladı. Sekiz-on haftalık, 200–250 g ağırlığında toplam 36 erkek sıçan, iki kontrol ve dört tedavi grubu olmak üzere altı gruba rastgele ayrıldı. Tedavi gruplarında exenatid, cerrahi öncesi veya sonrası dönemde farklı sürelerde intraperitoneal olarak uygulandı. Tüm hayvanlarda başlangıç IOB ölçümleri yapıldıktan sonra cerrahi olarak kemik defekti oluşturuldu ve yedinci postoperatif günde rebound tonometre ile tekrar IOB ölçümü gerçekleştirildi. IOB ölçümleri, çalışmanın birincil sonucu olmaktan ziyade, deneysel kemik defekti modelinde keşif amaçlı ikincil bir sonuç olarak dahil edilmiştir. Sonuçlara göre yalnızca postoperatif dönemde üç gün exenatid uygulanan grupta IOB'da istatistiksel olarak anlamlı bir değişiklik saptandı (P=0.027). Diğer exenatid uygulama protokollerinde anlamlı bir fark gözlenmedi. Buna karşılık, her iki kontrol grubunda da postoperatif dönemde IOB'da anlamlı düşüşler tespit edildi (plasebo grubu: P=0.023; yalnızca defekt grubu: P=0.026). Bu bulgular, ekzenatidin bazı postoperatif koşullar altında GİB'i geçici olarak etkileyebileceğini ve kontrol gruplarında gözlenen azalmayı kısmen dengeleyebileceğini düşündürmektedir. Ancak olası karıştırıcı faktörler nedeniyle etkinin yönü ve büyüklüğü belirsiz olup, sonuçlar keşifsel nitelikte değerlendirilmelidir.

Anahtar Kelimeler: Exenatid, glukagon benzeri peptid-1 agonistleri, intraoküler basınç, oküler fizyoloji, sıçan

INTRODUCTION

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist approved for the treatment of type 2 diabetes mellitus in 2005. By mimicking endogenous GLP-1, it enhances glucose-dependent insulin secretion, suppresses glucagon release, and promotes satiety (1-3). Beyond glycemic regulation, growing evidence suggests that GLP-1 receptor agonists may exert effects on ocular tissues, attracting attention in conditions such as diabetic retinopathy and glaucoma (4-6).

GLP-1 receptors are expressed in retinal tissues, including retinal pigment epithelial cells and retinal nerve layers. Experimental studies have demonstrated that exenatide may reduce retinal cell loss and preserve retinal structure in diabetic models, supporting a potential neuroprotective role (7). Moreover, epidemiological and experimental findings indicate that GLP-1 receptor agonists may be associated with a reduced risk of glaucoma, possibly through attenuation of retinal neuroinflammation and protection of retinal ganglion cells (8). In addition to diabetes-related complications, exenatide has shown neuroprotective potential in other optic neuropathies, such as Wolfram syndrome (9). Although direct evidence regarding the effects of exenatide on intraocular pressure (IOP) remains limited, its systemic metabolic and cardiovascular actions suggest a possible indirect influence on ocular physiology (10).

IOP is a dynamic parameter affected by anesthesia, positioning, environmental conditions, and systemic stress responses (11,12). Furthermore, surgical trauma and systemic inflammation may induce retinal changes even in the absence of direct ocular injury (13). These observations are particularly relevant in experimental models involving surgical interventions, where systemic physiological alterations may influence ocular parameters.

Although the primary aim of the experimental model was to investigate bone healing processes, IOP measurements were incorporated as an exploratory parameter to evaluate potential systemic physiological effects of exenatide. Therefore, this study aimed to investigate whether exenatide administration influences IOP in a rat bone defect model and whether the timing and duration of administration modify this effect.

MATERIAL AND METHODS

Animals

The animals used in this study had been previously utilized in the research entitled “Exenatide, a glucagon-like peptide-1 receptor agonist, may negatively impact bone healing in rats: histopathological, biochemical, and in silico findings.”. The study was conducted on young adult male Sprague-Dawley rats (250–300 g) housed at the Kastamonu University Experimental Animals Unit. In this study, IOP measurements were taken simultaneously while administering exenatide in groups created within the scope of the bone healing investigation, without disrupting the study's workflow. The animals were maintained under standardized conditions (22±2°C, 12-hour light/dark cycle; free access to food and water) in accordance with the Kastamonu University Local Ethics Committee for Experimental Animals (approval no: 2025/5), ensuring the welfare of the animals used in the research.

The sample size for this study was not determined based on a formal power analysis for IOP outcomes. The animals were originally enrolled in an experimental protocol designed to investigate the effects of GLP-1 receptor agonists on postoperative wound and bone healing. Accordingly, the number of animals per group was selected based on the statistical and methodological requirements of the primary bone healing study. IOP measurements were included as an additional, exploratory endpoint to assess potential ocular effects without altering the original study design.

Experimental Groups

IOP measurements were incorporated as an exploratory secondary outcome within the experimental bone defect model. The study was not primarily designed or powered to detect changes in IOP; rather, these measurements were performed to explore potential systemic physiological effects of exenatide under surgical conditions.

The timing of exenatide administration and IOP measurements was determined according to the primary objective of the study, which aimed to compare the effects of preoperative versus postoperative exenatide administration on bone healing. Therefore, treatment schedules and measurement time points were structured based on bone-healing endpoints rather than ophthalmic outcomes.

Before the experiment, the animals were acclimatized to laboratory conditions for 7 days. Following this period, the rats were randomly divided into six groups and six rats were assigned to each group (n=6). IOP measurements were taken in all groups before the administration of an intramuscular xylazine (10 mg/kg)-ketamine (80 mg/kg) combination in the same syringe. IOP measurements were performed by a single operator who was unaware of the group assignments.

Exenatide was administered to the Postop3, Postop7, Postop4/7, and Preop7 groups received an intraperitoneal injection of exenatide at a dose of 1 µg/kg body weight. The injection volume was calculated individually based on each animal’s weight, maintaining a standard volume of 0.1 mL per 100 g body weight to ensure consistent administration and minimize injection discomfort. Prepared exenatide solutions were discarded after each day to avoid loss of potency or contamination.

Sham group: The bone defect model was created under general anesthesia, with no further intervention or injection. IOP measurements were performed on postoperative day 7.

Placebo control group: The bone defect model was created under general anesthesia, and rats received daily intraperitoneal injections of saline for 7 days. IOP measurements were performed on postoperative day 7.

Postop3 group: The bone defect model was created under general anesthesia, and exenatide (1 µg/kg) was administered intraperitoneally once daily for 3 consecutive days immediately after surgery (postoperative days 1-3), followed by no treatment for the next 4 days. IOP measurements were taken on postoperative day 7.

Postop7 group: The bone defect model was created under general anesthesia, and exenatide (1 µg/kg) was administered intraperitoneally once daily for 7 consecutive days starting on the day of surgery. IOP measurements were taken on postoperative day 7.

Postop4/7 group: The bone defect model was created under general anesthesia. Exenatide (1 µg/kg, intraperitoneal) was administered once daily on postoperative days 4-7 (no injections on days 1-3). IOP measurements were taken on postoperative day 7.

Preop7 group: Exenatide (1 µg/kg) was administered intraperitoneally once daily for 7 consecutive days prior to surgery. The bone defect model was created under general anesthesia on the 7th day, and IOP measurements were taken just before anesthesia induction.

Surgical Procedure

Prior to surgery, each rat underwent a general clinical examination to confirm health status. The right forelimb was shaved and the surgical area disinfected first with a 50% diluted povidone-iodine solution and then sterilized using 70% ethanol. Sterile surgical drapes were applied to maintain asepsis throughout the procedure. Anesthesia was induced by intramuscular administration of a ketamine (80 mg/kg) and xylazine (10 mg/kg) combination. Once an adequate plane of anesthesia was achieved, the rat was positioned supine with the right forelimb extended and immobilized. A longitudinal skin incision approximately 2 cm in length was made over the mid-diaphyseal region of the right radius using a scalpel. The subcutaneous tissues and fascia were carefully dissected with blunt dissection techniques to expose the underlying extensor muscle group. The extensor muscles were gently retracted to expose the periosteum over the anterior surface of the radius. The periosteum was incised with a scalpel and carefully elevated from the bone using a periosteal elevator to expose the bone surface without damaging surrounding soft tissues. A standardized bone defect measuring 5 mm in diameter and 3 mm in depth was created on the exposed radial diaphysis using a low-speed dental bur (BT Marathon-3 SDE-M33Es) under continuous irrigation with sterile 0.9% saline to prevent thermal necrosis. Care was taken to maintain the integrity of the surrounding tissues and to avoid excessive trauma. After defect creation, the surgical site was thoroughly irrigated with sterile saline to remove bone debris. Hemostasis was achieved as necessary. The muscle and subcutaneous tissues were approximated, and the skin incision was closed with 4-0 absorbable suture material using interrupted sutures. Postoperative analgesia was administered as per institutional guidelines. Postoperative care included intramuscular administration of cefazolin sodium (20 mg/kg) once daily for three consecutive days as infection prophylaxis. Animals were monitored daily for signs of pain, infection, or complications.

Intraocular Pressure Measurement

All IOP measurements, including baseline and postoperative assessments, were performed prior to anesthesia induction to avoid the known effects of anesthetic agents on IOP. IOP was assessed using a rebound tonometer (iCare TONOLAB, Jorgensen Laboratories, Loveland, CO, USA), which is capable of self-calibration before each measurement. Prior to tonometric assessment, animals underwent a general clinical screening to exclude overt ocular pathology; however, a comprehensive ophthalmologic examination protocol (e.g., slit-lamp biomicroscopy or fundoscopic evaluation) was not performed. IOP measurements were performed by a single examiner, positioned at a 90° angle to the center of the cornea. All measurements were performed by the same experienced operator to reduce interobserver variability. IOP measurements were obtained exclusively from the right eye in all animals to ensure measurement consistency and minimize handling stress. The tonometer took six consecutive measurements and provided the average IOP in mmHg. All IOP measurements were performed between 10:00 and 12:00 during the light phase to reduce circadian variability. During measurements, rats were gently restrained by an experienced assistant in an upright position, ensuring that no pressure was applied to the eyelids or neck. Measurements were conducted in a quiet examination room under fluorescent room lighting (~300–350 lux), and animals were allowed a short acclimatization period before assessment.

Statistical Analysis

All statistical analyses were performed using SPSS software (version 22.0, IBM Corp., Armonk, NY, USA). The normality of data distribution was assessed using the Shapiro-Wilk test (Table 1). For comparisons between groups, one-way ANOVA was applied to normally distributed data, followed by post-hoc Tukey's test for pairwise comparisons. When data did not follow a normal distribution, the Kruskal-Wallis test was used, followed by Dunn's test for multiple comparisons.

For within-group comparisons of IOP at different time points, paired t-tests were used for normally distributed data, while the Wilcoxon signed-rank test was applied to non-parametric data. Statistical significance was set at $P<0.05$.

RESULTS

Descriptive statistics, including baseline (day 0) and postoperative day 7 IOP values and corresponding p values for all groups, are presented in Table 1. Baseline (day 0) and postoperative day 7 IOP values were recorded for all groups. In the Postop3 group, mean IOP changed from 22.0±2.52 mmHg at baseline to 25.0±3.57 mmHg on day 7 (P=0.027). In the Postop7 group, mean IOP changed from 18.50±7.14 mmHg to 12.30±3.82 mmHg (P=0.080). In the Postop4/7 group, values changed from 23.0±0.89 mmHg to 21.30±5.20 mmHg (P=0.244). In the Preop7 group, mean IOP changed from 24.50±3.56 mmHg to 22.40±3.82 mmHg (P=0.463). In the Placebo group, mean IOP changed from 23.40±0.51 mmHg to 19.40±1.36 mmHg (P=0.023), while in the sham group values changed from 23.0±2.36 mmHg at baseline to 18.8±0.40 mmHg on postoperative day 7 (P=0.026).

Table 1. Baseline (Day 0) and postoperative day 7 intraocular pressure (IOP) values (mmHg) expressed as mean±standard deviation (SD) for each experimental group, with corresponding within-group statistical comparisons (P values).

Grup	Day 0 IOP (Mean±SD)	Day 7 IOP Mean±SD	*P* values
Postop3	22.0±2.52	25.0±3.57	0.027
Postop7	18.5±7.14	12.3±3.82	0.080
Postop4/7	23.0±0.89	21.3±5.20	0.244
Preop7	24.5±3.56	22.4±3.82	0.463
Placebo	23.4±0.51	19.4±1.36	0.023
Sham	23.0±2.36	18.8±0.40	0.026

Abbreviations: **IOP**, intraocular pressure; **SD**, standard deviation; **Postop3**, exenatide administered for 3 days postoperatively; **Postop7**, exenatide administered for 7 days postoperatively; **Postop4/7**, exenatide administered on postoperative days 4–7; **Preop7**, exenatide administered for 7 days prior to surgery; **Placebo**, saline-treated control group; **Sham**, bone defect surgery without pharmacological intervention. *p* values represent within-group comparisons between baseline (Day 0) and postoperative Day 7 measurements.

Statistical analysis of baseline measurements revealed no significant differences among the groups (P>0.05). The temporal changes in IOP between Day 0 and Day 7 for each experimental group are shown in Figure 1.

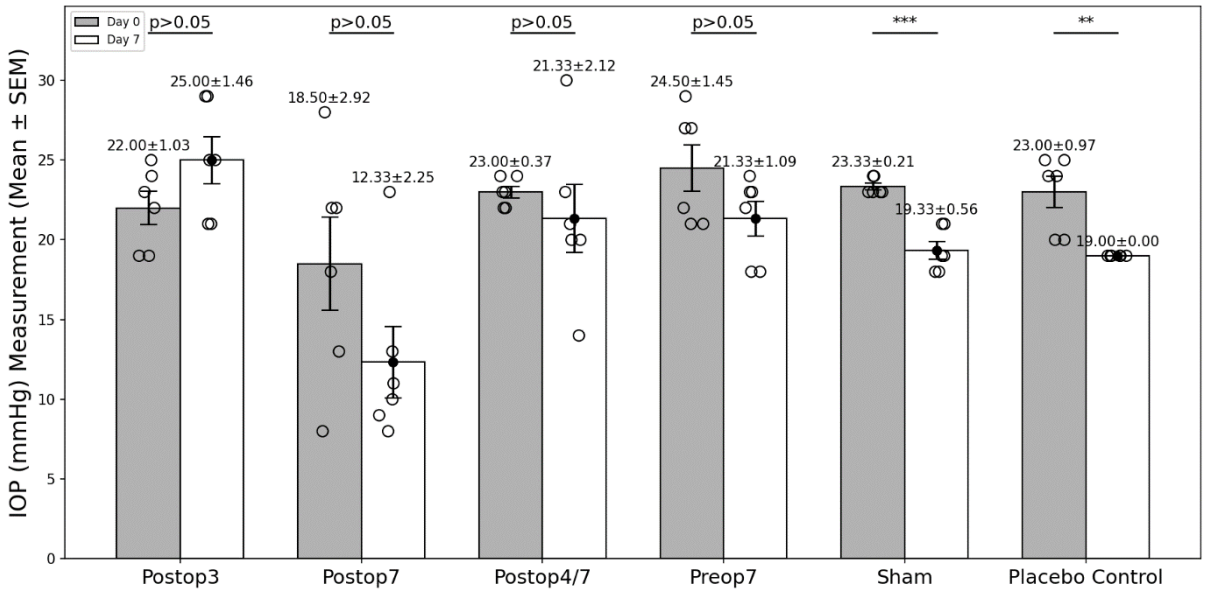

Figure 1. Comparison of intraocular pressure (IOP) measurements across experimental groups using bar plot visualization. Dark-colored bars represent baseline (day 0) IOP measurements, whereas light-colored bars represent postoperative day 7 IOP measurements. Data are presented as mean±standard error of the mean (SEM). Open circles indicate individual data points. Asterisks indicate levels of statistical significance for within-group comparisons between baseline and postoperative day 7 measurements (*P<0.05, **P<0.01, ***P<0.001).

DISCUSSION AND CONCLUSION

In this study, exenatide did not produce a consistent or statistically significant change in IOP across groups, except for a transient variation in the Postop3 group. The absolute magnitude of IOP changes observed across groups was modest and remained within a physiologically comparable range, suggesting limited biological impact under the present experimental conditions. These findings suggest that exenatide's influence on IOP may be context- and time-dependent rather than uniformly modulatory. Because all animals underwent bone defect surgery under the same anesthetic and analgesic regimen and received postoperative cefazolin, it is not possible to distinguish the specific contribution of each factor to the observed IOP changes. Therefore, the current findings should be interpreted as indicating that exenatide may have counteracted one or more of these postoperative influences rather than exerting a direct ocular effect. From a clinical perspective, the absence of marked IOP elevation in exenatide-treated groups may be relevant in terms of ocular safety, particularly in settings involving surgical stress or systemic inflammation.

Exenatide, a GLP-1 receptor agonist, has been investigated for potential physiological roles beyond glycemic control, including effects on neuropathy, retinal integrity, cardiovascular parameters, and ocular physiology (14-25). Recent studies have also explored Exenatide's impact on intraocular vascular structures and its potential neuroprotective effects, which are particularly relevant for managing glaucoma (26). Although these studies do not directly establish a causal relationship with IOP reduction, they provide biological plausibility for a modulatory effect on ocular microcirculation and tissue homeostasis.

In patients with type 2 diabetes who do not achieve adequate glycemic control with metformin, the administration of exenatide has been shown to significantly improve outcomes. The beneficial effects of GLP-1 and GLP-1 receptor agonists on cardiovascular risk factors, such as body weight

reduction, blood pressure regulation, and lowered blood lipid levels, warrant serious consideration (27,28). GLP-1 receptors are present in the retinal capillary endothelium, and GLP-1 agonists have been shown to regulate retinal capillary diameter through the GLP-1 receptor-PI3K/Akt-eNOS/NO-cGMP pathway (26). While these mechanisms have been demonstrated in retinal and vascular tissues, their direct relevance to IOP regulation remains to be clarified. Furthermore, GLP-1 receptor agonists inhibit the synthesis of C1q, IL-1α, and TNF-α from pro-inflammatory $CD11b^+$ cells, reducing A1 astrocytic transformation and preventing retinal ganglion cell loss (29). In patients treated with GLP-1 agonists, improvements in microvascular reactivity and reductions in systemic blood pressure have been reported (30,31), which could contribute to enhanced ocular perfusion and a reduced risk of optic nerve damage associated with elevated IOP. These systemic and microvascular effects suggest a potential indirect pathway through which exenatide could influence IOP stability, even if direct aqueous humor dynamics were not measured in the present study.

It is well-established that IOP is influenced by both the deep and superficial vascular plexus pressures within the eye (32). Elevated IOP can lead to changes in the blood flow dynamics of the central retinal artery. For example, artificially elevated IOP resulted in a progressive decrease in the peak velocities of blood flow within the central retinal arteries (33). Recent research suggests that GLP-1 receptor agonists have a vasoactive effect by modulating smooth muscle, thereby influencing the diameter of blood vessels, including mesenteric arteries, arterioles in adipose tissue, afferent arterioles, and regions involved in microvascular perfusion (34-36). These vasoactive properties suggest that GLP-1 receptor agonists may influence IOP by altering vascular resistance and ocular blood flow dynamics, which could have implications for ocular physiology. Our findings revealed no statistically significant differences between baseline and postoperative measurements in the Preop7, Postop7, and Postop4/7 groups. Notably, the relative preservation of IOP levels in these groups, compared with the decrease observed in control groups, may indicate a stabilizing rather than a pressure-lowering effect. While the lack of significant fluctuations could be partially influenced by confounding factors such as anesthesia and systemic stress responses, the relatively consistent IOP profiles in the exenatide-treated groups may indicate a possible modulatory effect of GLP-1 receptor agonists on ocular hemodynamics. These observations align with the hypothesis that GLP-1 receptor agonists might contribute to IOP regulation by influencing vascular stability or mitigating postoperative physiological fluctuations. Taken together, these findings suggest that exenatide may influence IOP regulation under certain postoperative or systemic stress conditions, although its precise effect and clinical relevance remain to be clarified.

However, when interpreting the observed IOP changes, it is also important to consider the potential contribution of systemic responses to surgery. Spesifically, the interpretation of IOP changes observed in this study should take into account potential systemic effects induced by the bone defect surgery itself. While our primary focus was to evaluate the effect of exenatide on IOP, it is possible that surgical stress, nociceptive stimulation, and postoperative inflammatory responses also played a role in modulating ocular pressure. Previous studies have demonstrated that systemic factors such as changes in posture during surgery, depth of anesthesia and acute stress and physiological conditions like pregnancy can significantly impact IOP even in the absence of direct ocular manipulation (3,11,15,37). Thus, it remains unclear to what extent the observed effects are attributable solely to the GLP-1 receptor agonist. Inclusion of systemic markers in future studies will be crucial for delineating the specific contribution of drug-related versus surgery-related influences on IOP regulation. Therefore, the present findings should be interpreted as hypothesis-generating, providing a framework for mechanistic and clinically oriented investigations rather than definitive evidence of a therapeutic IOP-modifying effect.

It is important to note that the Postop7 group appeared to have baseline IOP values that were somewhat distinct from other groups, potentially approaching outlier status. Such variation may be attributed to random chance fluctuations inherent in biological studies. This limitation might have been mitigated by alternative experimental designs, such as measuring baseline IOP prior to group assignment and balancing groups accordingly or utilizing inbred strains rather than outbred animals to reduce genetic variability. Given that IOP is known to be influenced by genetic background, these considerations are relevant and should be taken into account in future studies to minimize baseline differences and enhance data reliability. Future studies incorporating larger sample sizes and baseline-adjusted analytical approaches may further clarify whether the observed patterns represent true biological effects or random variation.

This study highlights the statistical difference observed between the baseline and postoperative IOP measurements in the Sham and Placebo groups. Combination of ketamine and xylazine reduces aqueous flow in mice more significantly than ketamine alone (38). This reduction in aqueous flow may be due to xylazine's depressant effect on sympathetic nerve function (39). Additionally, physiological responses to Xylazine-Ketamine anesthesia, such as changes in heart rate and blood pressure, can also affect ocular perfusion. Xylazine is known to cause bradycardia and hypotension, which can reduce ocular perfusion pressure (40). As detailed in our methods section, the Sham and Placebo groups received the xylazine-ketamine combination anesthesia. It is plausible that the suppression of sympathetic nerve function caused by xylazine, combined with the parasympathomimetic effects of ketamine, may have contributed to the observed differences in IOP. Furthermore, the lack of significant difference in IOP outcomes observed in the Postop3 group (despite receiving exenatide) compared to the groups that did not receive the drug, may suggest a diminished pharmacological effect. This may reflect a time-dependent decline in exenatide's short-term activity in ocular tissues. Given its short plasma half-life, the intraocular concentration of exenatide may not have been sustained until the time of measurement. Future studies including time-course pharmacodynamics would be valuable to determine the duration of action of GLP-1 receptor agonists on ocular physiology. Clarifying dose–response relationships and temporal dynamics will be essential before considering any potential translational or clinical implications.

This study has certain limitations. It is important to emphasize that the present study was not primarily designed to investigate IOP dynamics. IOP assessment was included as an exploratory secondary outcome within a bone healing model. Therefore, the experimental design, sample size, and measurement timing were optimized for the primary bone-related objectives rather than for ophthalmic endpoints. As a result, preoperative and postoperative IOP measurements were obtained under inherently different physiological conditions, which may have influenced the observed values. This should be considered when interpreting the findings. It was conducted exclusively on young adult male Sprague-Dawley rats, which may limit the ability to assess the impact of biological variables such as sex and age, as well as the generalizability of the findings to other animal species or female specimens. The use of a xylazine-ketamine combination anesthesia across all groups may have had an additive effect on IOP measurements due to the potential depressive effects of these anesthetics on ocular hemodynamics, such as bradycardia and hypotension. This presents a challenge in fully isolating the effects of exenatide on IOP modulation. Also, IOP were taken only at baseline and on the seventh postoperative day, which limits the ability to evaluate the long-term effects of exenatide and any potential adaptation mechanisms. As a result, the study focuses on short-term alterations. Furthermore, the lack of molecular or histopathological data to directly substantiate the mechanism by which exenatide influences IOP restricts a deeper understanding of the underlying processes. Likewise, we did not include physiological or endocrine markers such as blood pressure, plasma cortisol, or inflammatory cytokines that could help clarify whether the surgical bone defect procedure itself contributed to IOP fluctuations. Additionally, further investigation is warranted to determine whether GLP-1 receptors are expressed in ocular tissues directly involved in aqueous humor production and drainage, such as the ciliary body and trabecular meshwork. Publicly available single-cell RNA sequencing datasets may provide valuable insights into receptor localization in these tissues, which could clarify the mechanisms underlying the observed IOP changes. Future research should incorporate these analyses to better explore the mechanisms driving the observed effects. Taken together, these factors highlight that the present findings should be interpreted as exploratory and hypothesis-generating rather than confirmatory.

Our findings suggest that exenatide might transiently influence IOP under certain postoperative conditions, possibly counteracting the decreases observed in control groups. However, due to multiple confounding variables (including anesthesia, surgical stress, and timing of administration) the precise direction and magnitude of this effect remain uncertain. These results should be considered exploratory and hypothesis-generating. Future studies with extended time points, molecular analyses, and systemic markers are required to clarify the mechanisms and potential clinical relevance.

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There was no funding from any organization to conduct this research.

CONFLICT OF INTEREST

There is no conflict of interest to be declared by the authors.

AUTHOR CONTRIBUTIONS

CO: Conceptualization, Methodology, Investigation, Data curation, Writing – original draft. ABD: Methodology, Investigation, Formal analysis, Writing – review & editing. ED: Investigation, Resources, Data curation. FU: Formal analysis, Methodology, Visualization, Writing – review & editing. RT: Supervision, Project administration, Validation, Writing – review & editing.

ETHICAL STATEMENT

The study protocol was approved by Kastamonu University Local Ethics Committee for Experimental Animals (approval no: 2025/5).

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