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Artigo original

Bone-protective effects of melatonin in ovariectomized rats: insights from histomorphometry

Efeitos protetores da melatonina no osso em ratas ovariectomizadas: insights a partir da histomorfometria

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ABSTRACT

Objective: To evaluate the effects of melatonin doses on structural and remodeling parameters in tibiae of ovariectomized (OVX) and sham-operated (SHAM) female rats. **Methods:** Sixty female Wistar rats underwent to OVX (n=30) or SHAM surgery (n=30) at 20 weeks of age. After surgery, each group was divided into three subgroups (n=10) receiving melatonin at 20 mg/kg, 50 mg/kg, or placebo via oral gavage for 8 weeks, starting 12 weeks post-surgery. At 40 weeks, tibiae were harvested for histomorphometric analysis. **Results:** In this study, both 20 mg/kg and 50 mg/kg doses maintained bone volume fraction (BV/TV); the 50 mg/kg dose preserved trabecular number (Tb.N), trabecular separation (Tb.Sp), and significantly decreased eroded surface (ES/BS),indicating improved bone microarchitecture and reduced resorption. In SHAM rats, melatonin at 50 mg/kg reduced ES/BS. Body weight with no correlation to bone parameters. HbA1c levels were significantly lower in melatonin-treated OVX groups in both melatonin doses. No significant changes were observed in other biochemical markers or CTX levels. **Conclusion:** Melatonin, particularly at 50 mg/kg, significantly enhances bone microarchitecture and mitigates osteoporotic deterioration in OVX rats. Its limited effect in SHAM rats underscores its efficacy in hypoestrogenism. These findings highlight melatonin's potential as a therapeutic agent for menopause-related bone loss and metabolic complications, warranting further translational research.

Keywords: Melatonin; Histomorphometry; Hypoestrogenism; Menopause; Wistar rats

RESUMO

Objetivo: Avaliar os efeitos da melatonina sobre parâmetros estruturais e de remodelação nas tíbias de ratas fêmeas *Wistar* ovariectomizadas (OVX) e submetidas à cirurgia SHAM. **Métodos:** Sessenta ratas *Wistar* foram submetidas à cirurgia de OVX (n=30) ou cirurgia SHAM (n=30) com 20 semanas de idade. Após a cirurgia, cada grupo foi dividido em três subgrupos (n=10) que receberam melatonina na dose 20 mg/kg, 50 mg/kg ou placebo por gavagem oral por 8 semanas, iniciadas 12 semanas após a cirurgia. Quando os animais atingiram 40 semanas de idade, as tíbias foram coletadas para análise histomorfométrica. **Resultados:** Ambas as doses (20 e 50 mg/kg) mantiveram a fração de volume ósseo (BV/TV). A dose de 50 mg/kg preservou o número de trabéculas (Tb.N), a separação entre as trabéculas (Tb.Sp) e reduziu significativamente a superfície erodida (ES/BS), evidenciando preservação da microarquitetura óssea e diminuição da reabsorção. Em ratas SHAM, a melatonina na dose de 50 mg/kg também reduziu ES/BS. Não foi observada correlação entre peso corporal e parâmetros ósseos. Os níveis de HbA1c foram significativamente menores nas ratas OVX tratadas com melatonina em ambas as doses. Não foram observadas alterações significativas em outros marcadores bioquímicos ou nos níveis de CTX. **Conclusão:** A melatonina, particularmente na dose de 50 mg/kg, preservou significativamente a microarquitetura óssea e atenuou a perda óssea em ratas OVX. Seu efeito limitado em ratas SHAM evidencia que a eficácia da melatonina é maior em condições de deficiência estrogênica. Esses achados destacam o potencial da melatonina como agente terapêutico para a perda óssea e as complicações metabólicas relacionadas à menopausa, apoiando a realização de pesquisas translacionais adicionais.

Palavras-chave: Melatonina; Histomorfometria; Hipoestrogenismo; Menopausa; Ratas *Wistar*

INTRODUCTION

Melatonin is a molecule present in several species. It is primarily produced by the pineal gland and plays a role as a hormone in vertebrates, especially in mammals. The melatonin secretion, by the pineal gland peaks at night and decreases in the morning, thereby regulating the 12h/12h light/dark cycle and circadian rhythm in response to daily and seasonal variations in light and darkness[1]. In sleep processes, melatonin synchronizes circadian rhythms and improves the onset, duration, and quality of sleep [2]. Its actions can occur through binding to receptors located on cell membranes and mitochondria, or independently through its antioxidant properties and free radical neutralization[3]. Melatonin is also involved in several other processes, including metabolic, immune, reproductive, and brain functions [3–5].

Hypoestrogenism, a condition characterized by reduced circulating estrogen levels, during menopause, leads to accelerated bone resorption, decreased bone mineral density, and increased risk OF fractures, representing a major contributor to osteoporosis in women [6]. Importantly, hypoestrogenism may alter melatonin secretion patterns, suggesting a complex interplay between these hormones in maintaining skeletal health[7]. Emerging evidence indicates that melatonin supplementation could partially counteract the detrimental effects of estrogen deficiency on bone, highlighting its potential therapeutic role in hypoestrogenic states, and several studies have shown beneficial effects of melatonin on bone metabolism[8]. *In vitro* studies have demonstrated that melatonin positively influences bone health by promoting osteoblastogenesis while inhibiting osteoclastic activity[9–11], whereas animal studies have shown the effects of melatonin on bone remodeling[12]. These findings indicate a potential role for melatonin in preventing osteoporosis in postmenopausal women[13].

Bone histomorphometry, the gold-standard method for assessing bone microarchitecture and remodeling[14], is widely used in research to evaluate the effect of drugs on bone tissue[15]. Previous studies using this technique have described changes in bone metabolism in animals administered with various doses of melatonin at different ages[16,17]. Due to differing methodologies in these studies, questions remain about the effects and optimal doses of melatonin on bone tissue in models of hypoestrogenism and high remodeling.

Based on these considerations, the aim of the present study was to evaluate the effect of two different doses of melatonin on structural and remodeling parameters, assessed by bone histomorphometry in adult female Wistar rats subjected to ovariectomy or sham surgery.

METHODS

This is a randomized, controlled, preclinical experimental study conducted in ovariectomized and SHAM-operated female Wistar rats to evaluate the effects of melatonin supplementation on bone microarchitecture, and metabolic parameters. The study protocol was approved by the Ethics Committee for Animal Use at Positivo University (CEUA-UP) under protocol number 550.

All experimental procedures were conducted in accordance with the guidelines for animal experimentation established by the Brazilian National Council for the Control of Animal Experimentation (CONCEA). Adult female Wistar rats were acquired from the Animal Vivarium and the animals were maintained in autoclaved cages with wood-shaving bedding, under standardized conditions (22°C, 12h/12h light/dark cycle) and without access to physical activity. They received *ad libitum* access to standard chow (Labina; ADM Presence, Santa Rosa, Brazil) and filtered water, which was renewed every 48 hours.

The animals were subjected to ovariectomy (OVX group; n=30) or sham surgery (SHAM group; n=30) at the age of 20 weeks. Both procedures were performed following a pre-anesthetic protocol that included the administration of morphine (2 mg/kg), ketamine (100 mg/kg), and xylazine (20 mg/kg), with anesthesia maintained with isoflurane inhalation supported by oxygen. After confirmation of anesthesia, trichotomy and asepsis with 70% alcohol and povidone-iodine were performed.

In dorsal recumbency, a midline incision was made, and the ovaries were identified, clamped, and removed. The abdominal wall was closed in two layers (muscle and skin) using 3.0 polyglactin sutures with a simple interrupted pattern and double ligature. In the SHAM group, the ovaries were left intact. Postoperative analgesia included a single subcutaneous dose of tramadol hydrochloride (5 mg/kg) and oral ibuprofen (15 mg/kg) every 12 hours for 3 days.

Each group was further categorized into three subgroups according to the allocated intervention. Two animals from the control group did not survive the surgery, and we were unable to use the tibiae of four other animals for histomorphometric analysis. The final distribution was as follows: melatonin 20 mg/kg – OVX 20 (n=9) and SHAM 20 (n=9); melatonin 50 mg/kg – OVX 50 (n=9) and SHAM 50 (n=9); and control group (CG) – OVX CG (n=10) and SHAM CG (n=8). Starting 12 weeks after surgery, the animals received their assigned daily dose of melatonin (liquid synthetic melatonin, Fragranza Compouding Pharmacy, Curitiba, Brazil) or placebo (1.5 ml of fluoridated water orally) via gavage, administered one to two hours prior to lights off, aligning with the beginning of the dark phase.

The intervention was conducted over 8 weeks, with melatonin doses adjusted based on body weight, which was recorded at the time of surgery, at treatment initiation (12 weeks after surgery), and at 15-day intervals throughout the experimental period. Euthanasia and biochemical analysis were performed at the end of the 8-week melatonin administration period.

The animals were placed in a CO_2 chamber until unconsciousness was achieved. Subsequently, a 5 mL blood sample was collected via intracardiac puncture, followed by euthanasia with a lethal dose of anesthetic. Biochemical analyses—including alanine aminotransferase (ALT), alkaline phosphatase (ALP), creatinine, total protein, total cholesterol, triglycerides, glycated hemoglobin (HbA1c), and C-terminal telopeptide of type I collagen (CTX) were conducted using a Mindray BS-230 analyzer with Labtest kits. These tests aimed to assess the effects of melatonin or placebo on bone resorption, lipid and glycemic profiles, and potential hepatic and renal toxicity.

CTX levels were measured at the Molecular Biology Laboratory using an immunoenzymatic assay kit (E-EL-R1456, Elabscience, Houston, TX, USA) based on the sandwich ELISA principle. Bone histomorphometry was performed on the right tibia, which was removed postmortem and fixed in 70% alcohol. The samples were embedded in polymethylmethacrylate (Polysciences, USA), sectioned longitudinally at 6 μm using a Leica RM2235 microtome, and stained with toluidine blue (Merck, Germany). Analyses were conducted using a Nikon Labophot II microscope equipped with an Olympus DP71 camera and OsteoMeasure software (OsteoMetrics, USA) by a single investigator (CAM) at the Bone Pathology Laboratory in Fundação Pró-Renal. The evaluated parameters followed the ASBMR guidelines[18] and included structural parameters such as bone volume fraction (BV/TV, %), trabecular thickness (Tb.Th, μm), trabecular separation (Tb.Sp, μm), and trabecular number (Tb.N, n/mm). Static formation parameters assessed were osteoid thickness (O.Th, μm), osteoid surface per bone surface (OS/BS, %), and osteoblast surface per bone surface (Ob.S/BS, %).

Additionally, static resorption was evaluated by measuring eroded surface per bone surface (ES/BS, %). Statistical analysis and graph generation were performed using IBM SPSS v.28.0 (IBM Corp., Armonk, NY, USA). Normality was assessed using the Shapiro-Wilk test. Quantitative variables are expressed as means ± standard deviations. Pearson or Spearman correlation coefficients were used to assess associations between quantitative variables. For comparisons among three groups, one-way ANOVA followed by Bonferroni's *post hoc* test was applied when assumptions of normality and homogeneity of variance were met. Non-normally distributed variables were analyzed using the Kruskal-Wallis test followed by Dunn's *post hoc* test with Bonferroni correction. Repeated measures ANOVA was used to analyze body weight over time, evaluating interactions between groups and time points. A significance level of $p < 0.05$ was adopted for all analyses.

RESULTS

Table 1 presents the results of the structural and static histomorphometric parameters for the OVX CG, OVX 20, and OVX 50 subgroups. Significant differences were observed among the groups for BV/TV ($p < 0.001$), Tb.Sp ($p = 0.005$), Tb.N ($p = 0.015$), and ES/BS ($p < 0.001$). *Post hoc* analysis showed that BV/TV was significantly higher in OVX 50 and OVX 20 compared to OVX CG ($p < 0.001$ and 0.042, respectively). For Tb.Sp and Tb.N, a significant increase was observed in the OVX 50 group compared to OVX CG ($p=0.040$ and $p=0.013$, respectively). Regarding ES/BS, significant differences were observed between OVX 50 and OVX 20 when compared to OVX CG ($p = 0.002$ and $p=0.029$, respectively).

Table 2 presents the results of the structural and static histomorphometric parameters in the SHAM CG, SHAM 20, and SHAM 50 subgroups. A significant difference was observed among the SHAM subgroups for ES/BS ($p = 0.027$). *Post hoc* analysis revealed that ES/BS was significantly higher in the SHAM CG subgroup compared to SHAM 50 ($p = 0.026$).

Table1 – Structural and static histomorphometric parameters in ovariectomized rat subgroups

Parameter	OVX CG	OVX 20	OVX 50	*p* value
BV/TV (%)	13.18 (± 3.63)	17.10 (± 3.38)*	20.91 (± 2.51)	<0.001*‡
Tb.Th (µm)	48.49 (± 8.98)	54.49 (± 7.36)	57.29 (± 8.88)	0.086
Tb.Sp (µm)	336.86 (± 102.46)	268.15 (± 57.85)	218.76 (± 30.28)	0.005*‡
Tb.N (n/mm)	2.76 (± 0.77)	3.09 (± 0.51)	3.65 (± 0.50)	0.015*‡
O.Th (µm)	2.55 (± 0.84)	3.04 (± 1.54)	2.31 (± 0.42)	0.330
OS/BS (%)	5.93 (± 5.61)	6.64 (± 4.21)	3.16 (± 1.25)	0.195
ES/BS (%)	6.64 (± 3.01)	3.93 (± 1.81)*	2.08 (± 0.82)	<0.001*‡
Ob.S/BS (%)	2.04 (± 1.59)	3.01 (± 1.94)	2.92 (± 1.33)	0.374

Abbreviations: BV/TV: bone volume/tissue volume; Tb.Th = trabecular thickness; Tb.Sp = trabecular separation; Tb.N = trabecular number; O.Th = osteoid thickness; OS/BS = osteoid surface/bone surface; ES/BS = eroded surface/bone surface; Ob.S/BS = osteoblastic surface/bone surface. Data are presented as mean ± standard deviation.* p<0.05 by one-way analysis of variance (ANOVA).‡ *post hoc* comparisons showed statistically significant differences between subgroups as follows: BV/TV: OVX 50 vs. OVX CG (p< 0.001), OVX 20 vs. OVX CG (p=0.042); Tb.Sp: OVX 50 vs. OVX CG (p=0.040); Tb.N: OVX 50 vs. OVX CG (p=0.013); ES/BS: OVX 50 vs. OVX CG (p=0.002); OVX 20 vs. OVX CG (p=0.029)

Table 2 – Structural and static histomorphometric parameters in SHAM-operated rat subgroups

Parameter	SHAM CG	SHAM 20	SHAM 50	*p* value
BV/TV (%)	21.14 (± 2.46)	25.11 (± 5.80)	22.79 (± 4.41)	0.211
Tb.Th (µm)	44.98 (± 5.99)	48.81 (± 8.02)	45.59 (± 4.67)	0.420
Tb.Sp (µm)	156.86 (± 21.18)	148.8 (± 28.55)	161.03 (± 45.62)	0.741
Tb.N (n/mm)	5.08 (± 0.74)	5.05 (± 0.76)	5.01 (± 0.93)	0.984
O.Th (µm)	2.72 (± 0.83)	2.89 (± 0.58)	2.31 (± 0.42)	0.162
OS/BS (%)	3.40 (± 2.50)	2.51 (± 2.01)	1.33 (± 2.50)	0.547
ES/BS (%)	4.36 (± 3.54)	2.34 (± 1.34)	1.33 (± 0.88)	0.027*‡
Ob.S/BS (%)	1.95 (± 2.60)	1.48 (± 1.51)	2.13 (± 1.11)	0.331

Abbreviations: BV/TV = bone volume/tissue volume; Tb.Th = trabecular thickness; Tb.Sp = trabecular separation; Tb.N = trabecular number; O. Th = osteoid thickness; OS/BS = osteoid surface/bone surface; ES/BS = eroded surface/bone surface; Ob.S/BS = osteoblastic surface/bone surface. Data are presented as mean ± standard deviation. * One-way analysis of variance (ANOVA), p<0.05. ‡ post hoc analysis, SHAM 50 vs. SHAM CG, p=0.026

We also compared BV/TV (%) between OVX and SHAM groups. OVX control rats showed a BV/TV of 13.18 ± 3.63%, significantly lower than SHAM rats (21.14 ± 2.46%; $p < 0.001$).

Treatment with melatonin increased BV/TV in OVX rats: the 20 mg/kg group reached 17.10 ± 3.38% ($p < 0.001$ vs. OVX control), and the 50 mg/kg group achieved 20.91 ± 2.51% ($p < 0.001$ vs. OVX control; $p = 0.04$ vs. 20 mg/kg). Comparisons among SHAM subgroups showed no significant differences (25.11 ± 5.80% vs. 22.79 ± 4.41%; $p = 0.211$). These results indicate that melatonin partially prevented trabecular bone loss induced by ovariectomy.

Table 3 presents the results of the biochemical analyses. HbA1c levels were significantly lower in the OVX 20 and OVX 50 subgroups compared to the OVX CG subgroup (p = 0.006). No other significant differences were found in the biochemical parameters within either the OVX or SHAM subgroups. Regarding HbA1c levels, *post hoc* analysis showed significant reduction in groups OVX 50 and OVX 20 compared to OVX CG (p=0.015 and p=0.019, respectively. Additionally, no significant correlations were observed between HbA1c levels and any of the evaluated histomorphometric parameters.

Table 3 – Serum biochemical markers across ovariectomized and SHAM-operated rats

Parameter	OVX CG	OVX 20	OVX 50	SHAM CG	SHAM 20	SHAM 50
Alkaline phosphatase (U/L)	115.30 (±43.27)	136.44 (±49.28)	131.00 (±49.57)	86.00 (±39.76)	94.78 (±28.13)	75.56 (±30.64)
Creatinine (mg/dL)	0.46 (± 0.11)	0.46 (± 0.05)	0.49 (± 0.08)	0.39 (± 0.11)	0.34 (± 0.13)	0.41 (± 0.10)
Alanine amino transferase (U/L)	113.90 (±122.60)	65.78 (±20.60)	89.89 (±51.87)	48.25 (±17.66)	65.22 (± 21.06)	49.00 (±32.26)
HbA1c (%)	0.73 (± 0.15)	0.37 *‡ (± 0.26)	0.36*‡ (± 0.24)	0.50 (± 0.11)	0.43 (± 0.22)	0.47 (± 0.10)
Cholesterol (mg/dL)	91.50 (± 14.56)	85.22 (±10.41)	91.78 (±15.21)	58.38 (±15.45)	70.89 (± 12.19)	70.67 (±14.78)
Triglycerides (mg/dL)	104.40 (± 39.57)	96.56 (±19.24)	101.56 (±50.66)	81.38 (±30.21)	104.56 (± 32.39)	99.22 (± 22.58)
Total protein (g/dL)	8.13 (± 0.50)	7.80 (± 0.86)	8.03 (± 0.79)	7.08 (± 1.59)	7.82 (± 1.28)	7.59 (± 1.18)
CTX (ng/mL)	12.07 (± 5.04)	12.07 (± 2.29)	11.99 (± 5.25)	7.75 (± 2.45)	10.15 (± 3.03)	10.68 (±2.49)

Abbreviations: Values are expressed as mean ± standard deviation (SD). *One-way ANOVA, p<0.05 showed (p=0.06). ‡ Kruskal-Wallis test (p< 0.05), followed by Dunn's *post hoc* analysis showed significant differences in HbA1c levels between OVX 50 and OVX CG (p=0.015), and between OVX 20 vs. OVX CG (p=0.019)

No significant interaction was observed between weight assessment time points during melatonin treatment within groups (p= 0.591) or between groups (p = 0.125). Similarly, no significant correlations were found between body weight and histomorphometric parameters at any time point in either the OVX or SHAM groups (data not shown).

DISCUSSION

This study provides valuable insights into melatonin's bone-protective effects in ovariectomized (OVX) rats, with the 50 mg/kg dose showing superior efficacy in mitigating osteoporotic bone loss. Key findings include significant improvements in bone volume fraction (BV/TV), trabecular number (Tb.N), reduced trabecular separation (Tb.Sp) and eroded surface (ES/BS) in OVX rats treated with 50 mg/kg melatonin, highlighting its targeted action in hypoestrogenic conditions. In sham-operated rats, only ES/BS was significant reduced at this dose, suggesting limited effects in non-estrogenic states.

Additionally, melatonin significantLY lowered HbA1c levels in OVX rats, indicating potential metabolic benefits alongside bone protection. The observed reduction in Hb A 1 c levels following melatonin supplementation in ovariectomized (OVX) rats, but not in sham-operated (SHAM) controls, can be attributeD to the interplay between estrogen deficiency and melatonin's effect on glucose metabolism. In OVX rats, the absence of estrogen leads to insulin resistance and impaired glucose homeostasis. Melatonin supplementation in this context has been shown to improve insulin sensitivity and reduce Hb A 1 c levels[19,20]. These results place melatonin, particularly at 50 mg/kg, as a promising therapeutic candidate for postmenopausal osteoporosis, with broader systemic implications. The significant reduction in Hb A 1 c levels in OVX rats suggests melatonin's role in glycemic regulation potentially through insulin modulation or antioxidant pathways.[10,21]

In OVX rats, melatonin's effects align with prior studies showing enhanced osteoblastogenesis and reduced osteoclastic activity[8,22–27]. The 50 mg/kg dose significant improved BV/TV, Tb.N, Tb.Sp and ES/BS, indicating better preservation of trabecular connectivity and reduced bone resorption compared to controls. In SHAM rats, the reduction in ES/BS at 50 mg/kg suggests a specific anti-resorptive effect, consistent with reports of melatonin's role in modulating bone remodeling [8,25,28]. The lack of significant changes in CTX, despite reduced ES/BS, may reflect variability in bone marker measurements influenced by factors like age or fasting.[29–32]. Limitations include the inability to assess dynamic bone formation due to unsuccessful calcein labeling, restricting the analysis to static histomorphometric parameters, and the testing of only two doses, limiting conclusions regarding dose dependency. Additionally the study did not evaluate endogenous estrogen levels or the expression of its receptors (ERα and ERβ)[33] . Differences in pharmacokinetics between rats and humans require cautious interpretation of clinical relevance [34]. Strengths include using adult OVX rats to mimic postmenopausal bone loss, oral melatonin administration with dose adjustments every 15 days, and comprehensive histomorphometric and biochemical analyses. These enhance the translational relevance and robustness of the findings.

FINAL CONSIDERATIONS

In conclusion, melatonin at 50 mg/kg significantly improves bone microarchitecture and reduces resorption in OVX rats, helped counteract hypoestrogenism-induced bone loss, as per the study's objectives. Its limited effect in SHAM rats confirms specificity to estrogen-deficient states, supporting its potential use in postmenopausal conditions and osteoporosis associated with menopause.

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