Bionatura
Latin American Journal of Biotechnology and Life Sciences

Bionatura Issue 4 Vol 8 No 1 2023

Article

Evaluation of differential effects of melatonin versus bromocriptine in protection fertility for rats with hyperprolactinemia

*Nidaa Abudallah Mizban[1], Hazar Shaker Saleh[2,]**
Biology Department, College of Education for Pure Sciences, University of Thi-Qar, Iraq
**Corresponding author: Email: hazarsaleh@utq.edu.iq*
Available from: http://dx.doi.org/10.21931/RB/CSS/2023.08.04.35

ABSTRACT
Hyperprolactinemia is a condition of elevated serum prolactin over the laboratory upper level of normal. It is considered a relatively common endocrine disorder. Melatonin is an indoleamine that is produced by various cells in the body. It organizes a variety of biological pathways, including circadian rhythms, hormone secretion, and reproduction. Our study aims to compare the effects of melatonin supplements versus bromocriptine on testicular protection in metoclopramide-induced hyperprolactinemic rats. A total of twenty-four male rats were divided into four groups: The first group(G1) was given only normal sa
line; the second group(G2) was given metoclopramide 5mg/Kg orally to induce hyperprolactinemic rats; the third group(G3), metoclopramide-induced hyperprolactinemic rats were given bromocriptine 2.5mg/Kg; and the fourth group (G4), metoclopramide-induced hyperprolactinemic rats were given melatonin 2.5 mg/Kg. After treatments, sperm parameters (sperm count, sperm viability, and sperm motility) were calculated, and the testis was isolated as well as routine paraffin-embedded section staining with hematoxylin and eosin. The results of our current study showed a significant increase ($P \leq 0.01$) in sperm parameters in the G3 and G4 compared with the G2. Histological changes showed tubular degeneration and shrinkage and an absence of germ cells in the G2. While there was mild hypo spermatogenesis in the third group, and in contrast to those in the fourth group, the spermatic tubes appeared with the germ cells in them gradually.
Keywords: hyperprolactinemia, testis, prolactin (PRL), melatonin (MT), bromocriptine (BRC)

INTRODUCTION

The term "hyperprolactinemia" is defined as a rise in serum prolactin levels as a result of the overproduction of prolactin by the pituitary gland [1]. It happens at any stage of life and its prevalence differs by around 1% in the adult population (0.2% in men and 1% in women) and 5% in cases of women with infertility [2, 3, 4]. It can result from physiological or pathological conditions [5]. Physiological causes such as gestation and lactation [6], stress and exercise [7], pharmacological causes (antipsychotic or antidepressant use), or pathological (prolactinomas, hypothalamic tumors) [6]. Hyperprolactinemia can be accompanied by reduced sexual desire, impotence, reduced sperm production, infertility, gynecomastia, and, rarely, galactorrhea. [8]. Hyperprolactinemia causes decreased testosterone synthesis, which manifests clinically as erectile dysfunction and loss of libido [9]. It

is also a hazard factor for fatness-associated metabolic syndrome [10], insulin resistance, and diabetes with a direct effect on pancreatic beta cells [4]. Bromocriptine (BRC) is an ergot derivative that decreases prolactin secretion from the anterior pituitary gland [11]. Melatonin MT (N-acetyl-5-methoxytryptamine) is extensively dispersed in nature and has numerous activities in single-celled organisms, plants, fungi, and animals [12]. MT is a hormone generated naturally by the pineal gland and also by the retina, skin, intestine, testicles, and ovary [13, 14]. According to previous research, MT organizes a variety of biological pathways, including circadian rhythms, hormone secretion, and modulation and reproduction [15, 16]. MT effects on reproductive hormone levels vary according to physiological conditions and animal species [17].

MATERIALS AND METHODS

Experimental animals

The twenty-four adult male Albino rats were provided by the Iraqi Center for Cancer Research and Medical Genetics/Ministry of Higher Education and Scientific Research. These rats were between the ages of 3 and 4 months, and their weights ranged from 190 to 240 g/bw).The animals were housed in the Animal House of Thi-Qar University College of Education for Pure Science, and the room was under conventional conditions of temperature (24±1_C) under a 12-hour light/dark cycle. Before the experiment began, the rats were given 10 days to acclimate and were given free access to food and water.

Experimental design

Following the acclimatization period, the animals were divided into four groups of six rats each. The first group (the control group) was given 0.5 mL of distilled water only. The second group was given metoclopramide 5 mg/kg b.wt orally using gavage for 21 days to induce hyperprolactinemia according to [18]. The third group was given BRC at 2.5 mg/kg b.wt intraperitoneally [18] for 28 days. The fourth group was given MT 2.5 mg/kg intraperitoneally for 28 days [12].

Sperm count examination

The sperm count was calculated after removing the caudal epididymis from the left and right samples. It was then cut into small pieces, mixed with Ringer's solution, and set aside for 2 minutes. 10 µL of the sperm suspension were collected and placed in the hemocytometer. It was instantly examined under a microscope at x40 magnification [19].

Sperm viability examination

10 µL of the semen suspension in Ringer's solution was gathered, put into the object's glass, and then combined with one drop of 2% eosin. After homogenization, it was covered with a cover glass. The stained cells were examined under a 40x magnification microscope. The live sperm were clear (unstained), whereas the dead sperm absorbed the stain (red color). Sperm viability is measured in percentages [19].

Sperm motility examination

The hemocytometer was loaded with ten µL of the semen suspension in Ringer's solution. Under the microscope at x40 magnification, any moving or immovable spermatozoa were immediately examined. motile sperm cells are defined by their progressive and non-progressive movement. It was determined by dividing the number of motile sperm cells by the total number of sperm cells counted.

Histopathological examination

The testes were fixed in a formalin solution (10%) for 48 hours. They were then treated (washed with water, passed through ascending grades of alcohol, cleared in xylene, and embedded in paraffin wax at (70 ^{0}C).5µm of tissue thickness was

mounted on clean glass slides and stained with hematoxylin and eosin according to [20].

The Statistical Analysis

All data are expressed as the mean ± standard deviation . One-way analysis of variance was used to compare the differences between groups while multiple comparisons were performed by Tukey's test as a post-hoc test $P \leq 0.01$was considered statistically significant.

RESULT

The effect of MT and BRC on sperm parameters in male rats with hyperprolactinemia

The results shown in Figure 1 show the effect of MT and BRC on sperm count in male rats induced by hyperprolactinemia. The G1 revealed a significant increase ($P \leq 0.01$) compared with all other groups. The G2 showed a significant decline compared with the G3 and G4. Similarly, the G3 showed a significant decrease when compared to the G4.As for the result of sperm vitality in Figure 2, G1 showed a significant increase ($P \leq 0.01$) compared with all groups. The G2 indicated a significant decline compared with the G3 and G4. The results also showed that the G3 significantly decreased with the G4. The results related to sperm motility in Figure 3 revealed that the G1 showed a significant increase ($P \leq 0.01$) compared with all groups. As for the G2, it declined significantly with the G3 and G4, as well as the G3 decreased significantly with the G4.

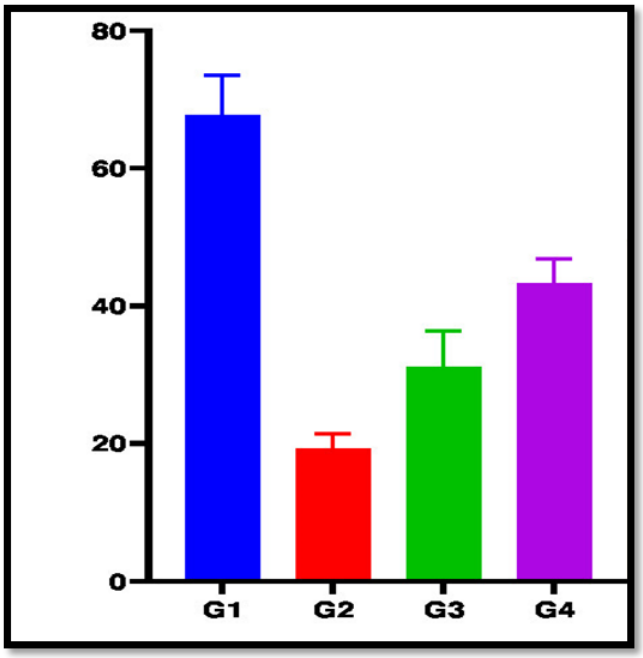


Figure (1) shows sperm count in all groups

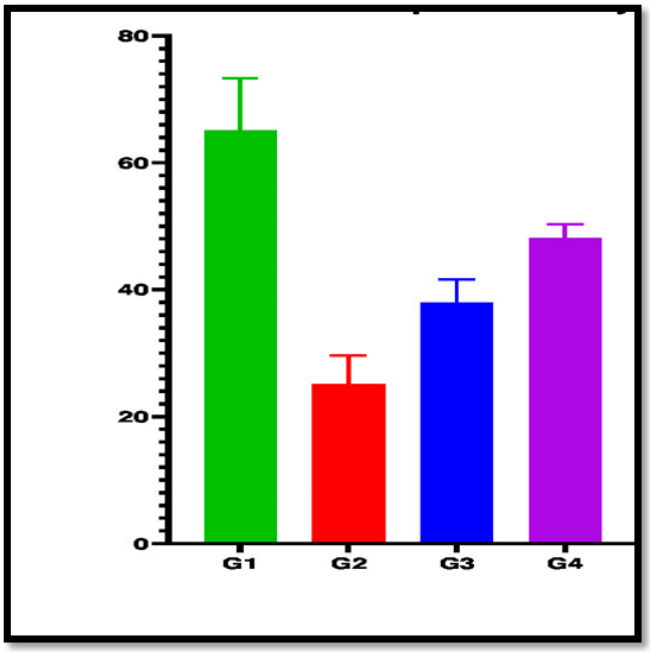


Figure (2) shows sperm viability in all groups

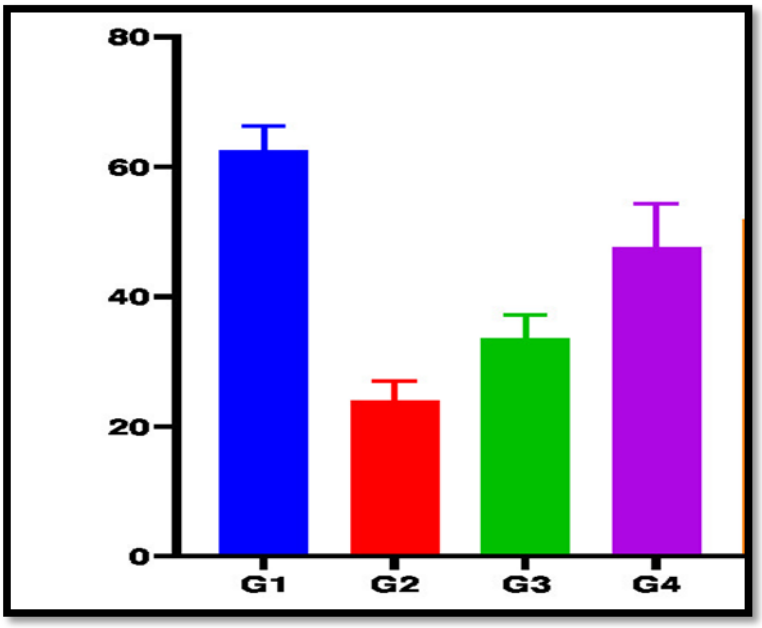
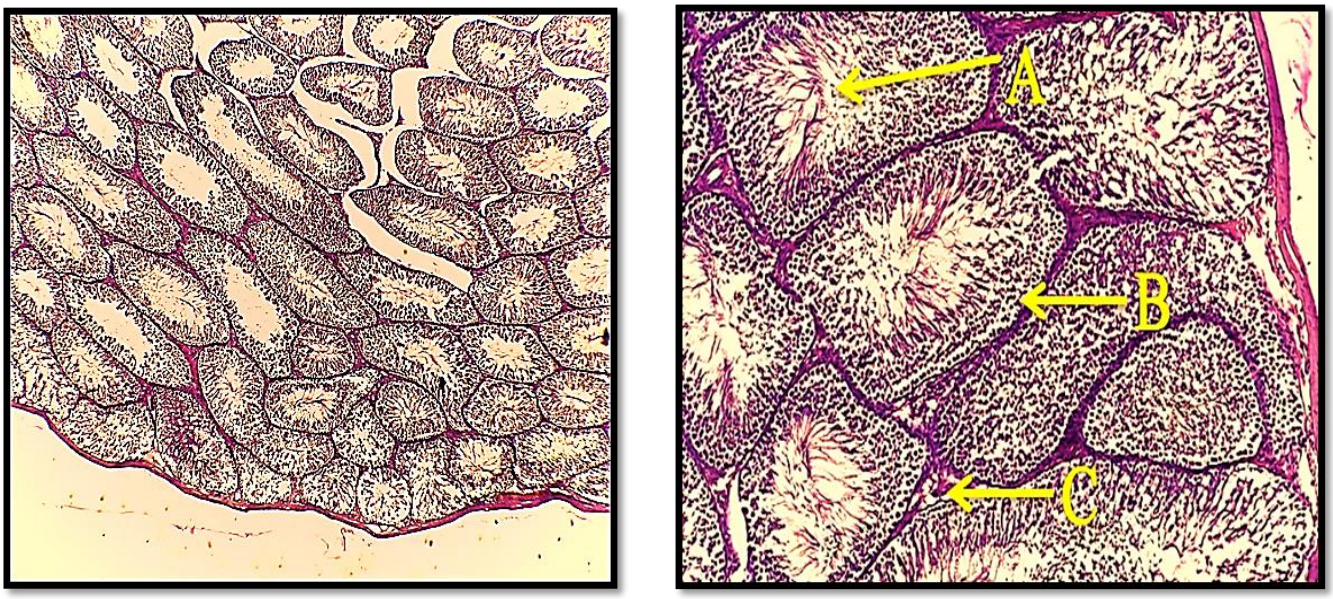


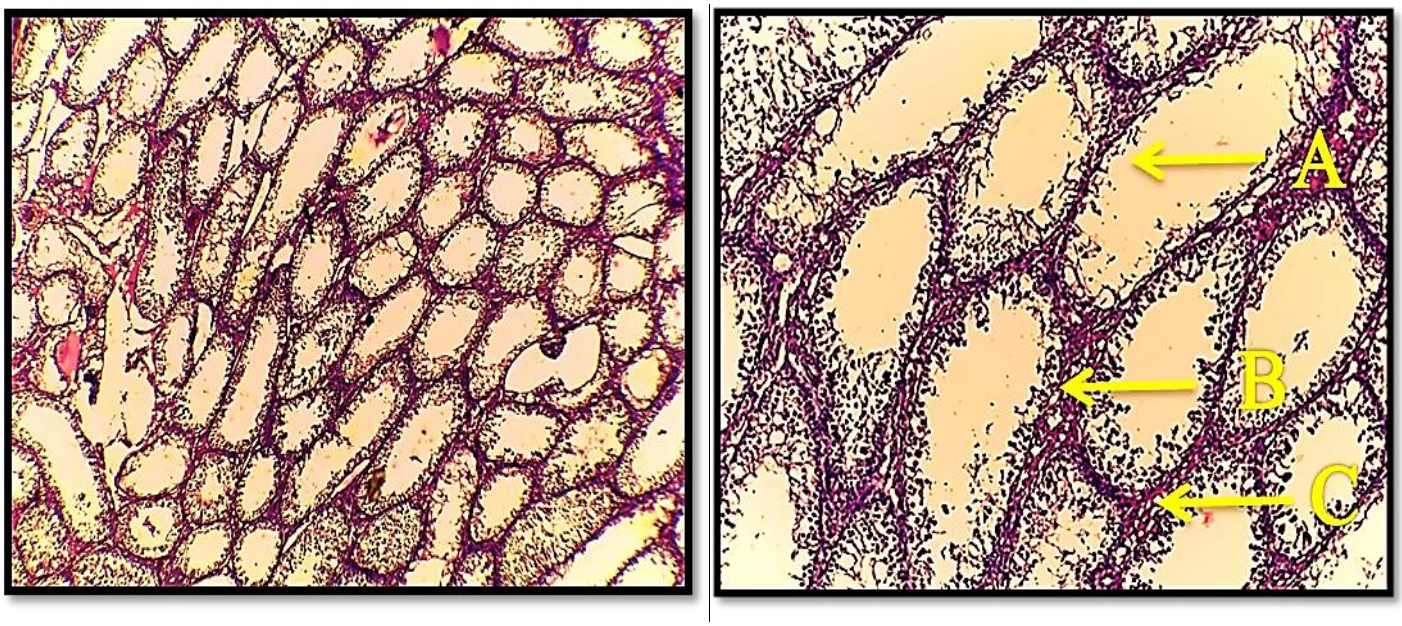
Figure (3) shows sperm motility in all group

Histological changes

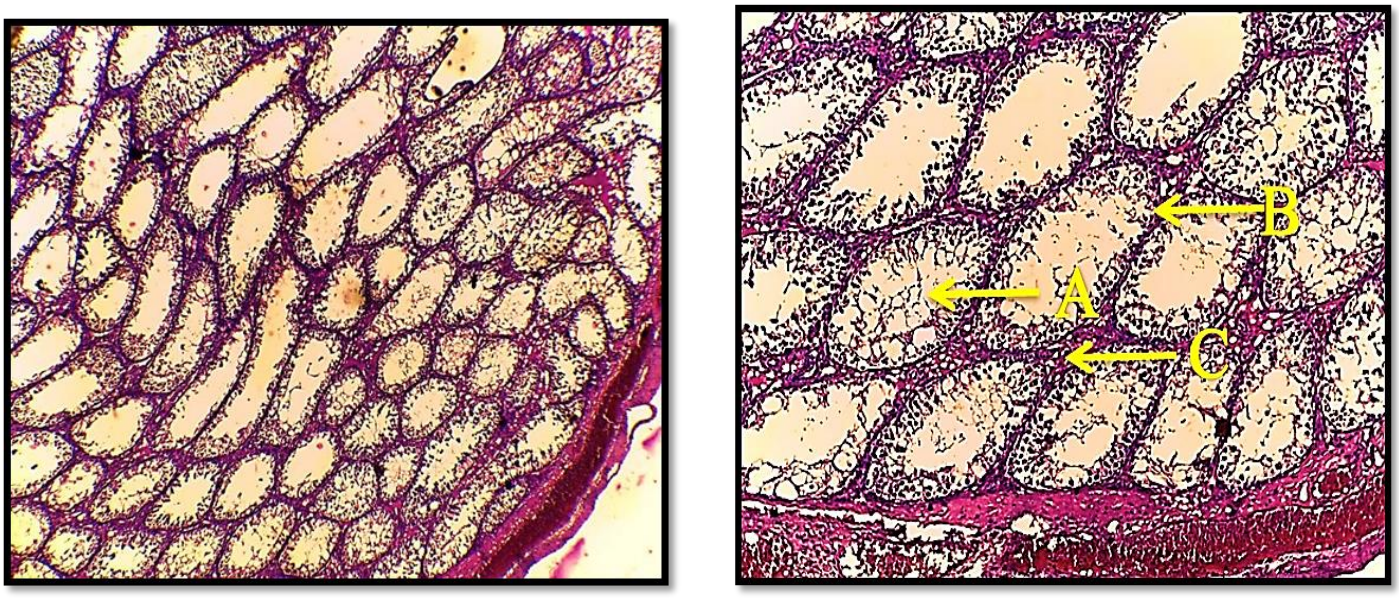
Histological examination of the control group showed testis Capsule containing normal seminiferous tubules that appear circular or almost circular with normal histological structure, a lumen with closely arranged seminiferous tubules, surrounded by stroma containing tiny clumps of leydig cells, and no edema in interstitial tissue. The presence of a high proportion of spermatozoa inside tubules indicates spermatogenesis and spermiogenesis are normal processes. The induced hyperprolactinemia group showed tubular degeneration and shrinkage, as well as many atrophic seminiferous tubules, thickening in the basement membrane, Sloughing and vacuoles in the epithelial cells were also observed, and an absence in all germ cells was observed (arrest of maturation). The third group, which received BRC had seminiferous tubules with a few layers of spermatogenic cells (mild hypo spermatogenesis) and thickening of the tubular basement membrane. As for the MT-treated group, MT showed more positive effects on spermatogenesis. The seminiferous tubules appeared normally with many layers of spermatogenic cells and a reasonable number of sperm.



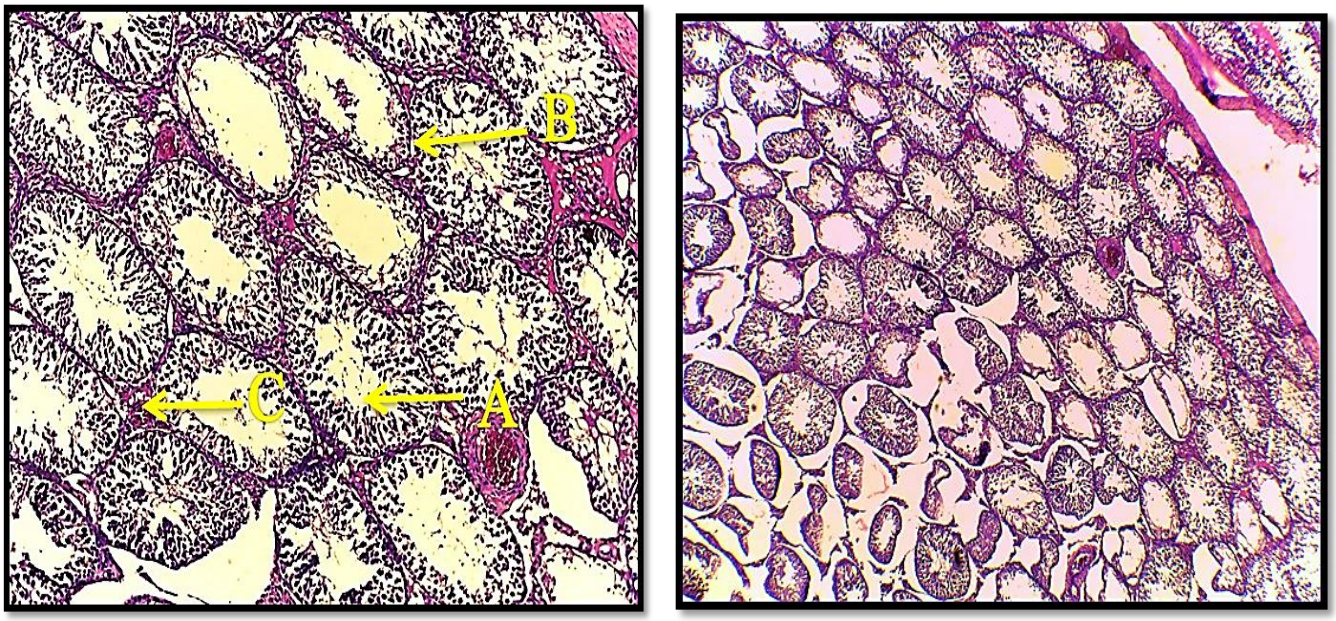
A-Transverse section of control testis (Group 1) showing sperm tails (A), seminiferous tubules (B), and interstitial tissue (C) (100X and 400X, H & E).



B-Transverse section of the testis (Group 2) demonstrating the absence of sperm (A), semi
tubules (B), and interstitial tissue (C) (100X and 400X, H & E).



C-Transverse section of testis (Group 3) showing sperm (A), seminiferous tubules (B), and interstitial tissue (C) (100X and 400X, H & E).



D-Transverse section of testis (Group 4) showing sperm (A), seminiferous tubules (B), and interstitial tissue (C) (100X and 400X, H & E).

DISCUSSION

The current study compares the efficacy of melatonin supplementation versus BRC for lowering prolactin levels and improving fertility in hyperprolactinized rats. BRC has side effects that include postural hypotension, which may be accompanied by dizziness and syncope, Raynaud's phenomenon, and vomiting, and less frequently, nasal congestion, flushing, and cramps [8]. Furthermore, melatonin is pleiotropic, adjusting numerous physiological parameters in numerous organs [21]. The results of this study revealed that melatonin is more effective than BRC for increasing fertility and improving testicular tissue

damaged by hyperprolactinemia. Hyperprolactinemia is a common and treatable cause of male infertility ,that responds well to dopamine agonist drugs [22, 23].

Prolactin has also been linked to changes in sexual function, such as ejaculation, desire, and orgasmic experience perception, resulting in erectile impairment [24, 25]. According to [22], erectile dysfunction was reported in 88% of hyperprolactemic males. In the current study, the hyperprolactinemia group showed sperm count, viability, and motility were all reduced. The reason for this decrease is that hyperprolactinemia may cause disorders in the hypothalamus and pituitary gland, and thus the secretions of these glands affect the reproductive system and the process of sperm formation in the testicles. According to [26], hyperprolactinemia prevents the pulsatile secretion of gonadotrophin releasing hormone (GNRH), resulting in decreased pulsatile release of follicle stimulating hormone (FSH), luteinizing hormone (LH), and testosterone, and thus an arrest of spermatogenic activity, decreased sperm motility, and altered sperm quality. It eventually leads to secondary hypogonadism and infertility.As [27] mentioned, hyperprolactinemia also has a direct impact on spermatogenesis and steroidogenesis by acting on receptors for prolactin found in Sertoli and Leydig cells in the testes, resulting in primary hypogonadism and infertility.

In the hyperprolactinemia group treated with BRC, there was a decrease in prolactin levels and an increase in sperm parameters. The reason for this improvement in semen parameters can be attributed to the pharmacological activity of BRC on the hypothalamus and pituitary gland and its action against prolactin. BRC administration may oppose a prolactin-induced bulk on the action of gonadotrophins on the testicles, and thus a reduction in levels of prolactin may lead to an improvement in sperm parameters and fertility [28]. Our study results correspond to those of [29], who investigated the effects of BRC in hyperprolactinemia patients and found that prolactin secretion was reduced and spermatogenesis, which had been disrupted, was restored to normal.

In the hyperprolactinemia group treated with MT, there was a considerable improvement in sperm parameters when compared to the other experimental groups. The reason for the increase in sperm parameters may be due to the anti-oxidative activity of MT and thus the protection of sperm from oxidative damage, resulting in an increase in sperm counts and an improvement in their quality. According to [30] and [31], MT has been shown to conserve sperm cells from ischemia and ameliorate sperm abnormalities due to its antioxidative characteristics. However, aside from its antioxidant capabilities in testicular cells, the specific mechanism of action is uncertain [32]. On the basis of MT binding sites identified in various parts of the reproductive organs, it is reasonable to suppose that MT performs its functions not only as an antioxidant but also through direct interaction with its receptors on steroidogenic cells [33].As explained by [34], it possesses receptors in the testes and hence controls testicular functioning directly. This may be due to the effectiveness of the naturally occurring endogenous MT and the exogenous MT administered in the current study directly on the testicle and its vital processes. MT created by the pineal gland into the blood is taken up by the testis, where it directly controls testicular function [35, 36] Furthermore, melatonin can also be produced by the testes [37, 38]. These results correspond with [39], who stated that MT could improve sperm motility. On the other hand, the findings of numerous studies contradicted our findings in this study. According to [40], MT has a deleterious influence on the forward advancement of sperm and the quality of sperm motility in rats. Furthermore, [41] discovered that melatonin reduced spermatozoal motility in a dose-and time-dependent manner in bulls. The reason proposed by researchers may be due to the effect of MT on spermatogenesis being due to a lack of testosterone.MT binds to its receptor MT1 and activates a Gi protein, and it lowers cAMP and calcium

levels. These consequences lead to a decrease in testosterone release, an important hormone for spermatogenesis [42, 43,44].

CONCLUSIONS

The results of the current study concluded that melatonin has an effective and positive role in improving semen parameters and protecting testicular tissue from damage caused by hyperprolactinemia and returning it to its normal state.

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Received: May 15, 2023/ Accepted: June 10, 2023 / Published: June 15, 2023
Citation: Mizban, N.A.; Saleh, H.S. Evaluation differential effects of melatonin versus bromocriptine in protection fertility for rats with hyperprolac-tinemia. Revista Bionatura 2023;8 (4) 63. http://dx.doi.org/10.21931/RB/CSS/2023.08.04.35