Iraqi Journal of Veterinary Sciences

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Physiological effect of leptin and time-restricted feeding-in reproductive value of female rat

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Article information

Article history:
Received 23 May, 2024
Accepted 13 September, 2024
Published online 29 September, 2024

Keywords:
Leptin
Time-restricted feeding
Female
FSH
LH

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Abstract

The female must expend far more energy during reproduction than the male needs. Given that reproduction requires energy utilization, it makes sense that physiological control mechanisms associated with appetite and nutrition would also be connected. This research evaluated leptin's capacity to alleviate the effects of time-restricted feeding (TRF) in female. Twenty-four adult female rats, weighted 175-200g were divided randomly into four groups; the control group (G1) was given DW, and the (G2) group injected i.p. leptin hormone (50µg/kg BW) with normal diet. (G3) TRF group regimen from (8:00 a.m.-3:00p.m.) diet with water free, (G4) TRF with leptin groups injected i.p. leptin (50 µg/kg BW) regimen from (8:00 a.m.-3:00p.m.) diet with water-free. At the end of the research (8 weeks), Rats were sacrificed serum collection for FSH and LH estimation using ELIZA technology, Ovaries were processed for hematoxylin and eosin staining. Results showed that decreased significantly P≤0.05 in body weight in time- restricted feeding (TRF) with leptin, leptin and TRF, decreased significantly P≤0.05 in ovarian weight of leptin and TRF with leptin. FSH and LH hormone increased significantly P≤0.05 in the leptin group, TRF and TRF with leptin. Histological changes in the treated group showed many primary and secondary follicles with many large antral follicles and corpora luteum, and TRF showed normal follicles. In conclusion, time- restricted feeding promotes the reproductive function of female rats with ovarian hormones and leptin stimulates FSH and LH hormones. This is probably the agent that brings about the beginning of puberty.

DOI: 10.33899/ijvs.2024.150110.3684,

Introduction

Leptin, is a peptide 16-kDa hormone at most generated from adipose tissue, while other organs and tissues such as the ovary, pituitary gland, bone, muscle, abdomen, and tissue lymphoid may create smaller quantities, maybe for local effect which has large and complex metabolic signaling potential. A growing understanding exists that high plasma leptin levels are associated with various of metabolic illnesses (1). Leptin regulates glucose, lipid, and bone metabolism as well as neuroendocrine and immunological activities and energy homeostasis (2). Within fasting, levels of circulating leptin rapidly decline. A lower leptin concentration stimulates the expression of Plasma Agouti-Related Protein (AgRP) and Neuro peptide (NPY) and inhibits Pro-Opiomelanocortin (POMC) and Arcute nucleus (CART), thereby raising the intake of food and diminishing energy expenditure (3). Leptin acts in the CNS in the hypothalamus (4). The central role is to arrange mechanisms of satiety and appetite leading to reduced cravings and decreased food intake. Conversely, it raises lipid oxidation and energy expenditure, therefore participating in thermogenesis processes (5). leptin can regulate the production and release of GnRH in the hypothalamic arcuate (ARC) nucleus (6) The leptin gene-deficient animals do not secrete enough GnRH. (7). Leptin receptor expression is either absent or very low in the ARC nucleus of GnRH neurons (8). Consequently, the leptin hormone regulates

puberty independently but directly affect GnRH neurons (9). However, leptin may impact NPY neurons, indirectly affecting GnRH neuron activity (10). Time-Restricted Feeding (TRF) It is a feeding model that restricts eating intake to a certain amount of time without affecting the amount or quality of nutrients (11).TRF reduces the access to food during the active period and is a dietary technique that has emerged as a viable intervention for decreasing insulin resistance and other indicators of overall health, It has been promoted for weight loss and body fat reduction, TRF can reduce body fat while maintaining lean mass in animals (12). In rodents, the axis reproduction, which involves the cyclic expulsion of reproductive hormones, drives one of at least two oscillatory systems that interact to organize the estrous cycle. The other oscillatory system is stimulated by the involvement of regulatory cells in the ovaries and hypothalamic nuclei. The suprachiasmatic nucleus (SCN) controls the circadian system, the second oscillatory system (13). In addition, the ovary is essential for the estrous cycle's hormonal regulation (14). It establishes the time for the ovary's sensitivity to hormones and the hypothalamic-pituitary-gonadal axis' timing for the rush of LH in the ovulation process (15). Various approaches have been investigated in experimental and clinical research to avoid or reverse circadian disruption. These approaches include scheduled food, exercise, melatonin administration, and dexamethasone administration, when paired with the activity phase, scheduled feeding has been demonstrated to be a potent entraining signal. In research projects, time-restricted feeding (TRF) (16). Females must expend far more energy during reproduction than do males. Given that reproduction requires energy expenditure, it makes sense that the physiological regulatory systems controlling appetite and nutrition would maintain a connection (17).

This research aims to investigate how well leptin counteracts the effects of TRF on the ovary and function of female rats.

Materials and methods

Ethics approval

The official consent for the committee for this study's research design is within Veterinary College, Mosul University, in compliance with institutional policies regarding the keeping and using animals in the study UM.VET.2023.061.

Experimentation design

In this investigation, 24 female rats, aged 21 days, were used. Rats- were kept and fed similarly in the University of Mosul's College of Veterinary Medicine's Animal House Unit. The normal lab circumstances include a 12-hour light/dark cycle, a temperature of 22±4ºC, and a humidity of 55%. The animals were divided into four equal treatment groups at random, the control group (n=6) orally got normal saline solution. In the first group (G1) rats were treated with leptin hormone intraperitoneally injected (i.p.) at a dose of 50µg/kg BW (18). The second group (G2) is the Time-Restricted Food (TRF) group (19). Rat in the third group (G3) were treated with leptin hormone and TRF. At the end of the handling period (8 weeks), all animals of treatment were euthanized with inhalation by ether prior to being sacrificed by dislocation of the neck and exsanguination.

Samples collection

After anesthetized rats, blood samples from the retro-orbital plexus were instantly obtained by microcapillaries, and allowed to clot; then cervical animals were sacrificed by dislocation. The serum samples were centrifuged at 3000 rpm for 15 minutes, and supernatants were transferred into the epindrof tubes while kept within -25°C for the hormonal analysis. Subsequently, a midline incision in abdomen was performed. The abdominal cavity was opened, and the ovaries were excised and cleansed in saline, weighed, and instantly fixed in 10% neutral buffered formalin for one day. The relative weights were taken from (weight of ovary /BW ×100, as in g/100 g BW) (20,21).

Processing and dissection of the ovary

Each group's ovaries (n=12) were dissected and cleansed to remove any adhering tissues. Ovaries that had just been cleansed were directly submerged in 10% neutral buffered formalin until infused with paraffin. After that, non-sequentially, each ovary's midsections were treated at 5 m using a handheld microtome (22).

Processing of tissue and staining

Segments of the ovary were stained immediately with Gills hematoxylin II and 1% aqueous eosin (H&E) as in per routine protocol (23).

Biochemical analysis

The concentration of Follicle Stimulating Hormone (FSH) for rat Cat: ELK1315 hormone ELISA, rat Luteinizing Hormone (LH) hormone Cat: ELK2367 were measured using an enzyme-linked immune sorbent assay, Kits were conducted according to the manufacturing company (ELK Biotechnology company) that depended on the technique of the quantitative sandwich enzyme immunoassay (24,25).

feeding schedule and diet

Twenty-four rats were fed a standard diet. The control and leptin groups were fed an ad libitum normal diet throughout the day. TRF and TRF with leptin were administered according to a schedule every day for 60 days, from 8:00 a.m. to 3:00 p.m., and given only water.

Statistical analysis

A one-way analysis of variance was used to examine the data, and Duncan's multiple range test (SPSS version 24, USA) was then used to assess group differences. Results were given as the mean ± standard error of average. Values at P<0.05 can considered significantly different (26).

Results

Weight of animals

The result showed a decreased significant P≤0.05 in the weight of the animals in the group TRF and a group of TRF and leptin hormone compared with the control and leptin group, and there was no significant difference between the leptin and control group in 6 weeks of experiments. In 12 weeks of experiments, the group of TRF with leptin decreased significantly P≤0.05 in the weight of the animals in comparison with groups of leptin and control, whereas there was no significant difference in comparison with the TRF group; Leptin and TF groups had no significant difference in comparison with the control group. (Table 1).

Weight of ovary

The weight of the ovary fell significantly by P≤0.05 in the leptin group and TRF with the leptin group in compared to the control and TRF groups However, these groups did not differ significantly from one another. The TRF group and the control group were identical (Table 2 and Figure 1).

Table 1: Leptin and TRF's effects on female body weight

Groups	Means (g/ BW) ± Standard Error		
	zero	6 weeks	12 weeks
G1	197.3±7.5[a]	233.6±3.2[a]	231.6±1.8[a]
G2	197.6±2.4[a]	218.0±5.5[a]	131.3±1.2[a]
G3	197.3±2.9[a]	183.0±9.8[b]	199.6±5.6[ab]
G4	179.6±2.0[a]	188.0±6.4[b]	180.6±4.0[b]

Different letters in one column indicate a significant difference between groups at P≤0.05.

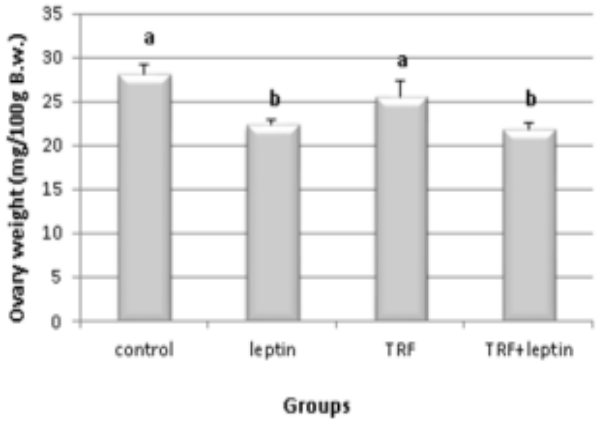

Figure 1: leptin and TRF effects on female rats' ovarian weight.

Table 2: Leptin (µg/kg) and TRF's effects on female rats' ovarian weight, FSH and LH concentration

Groups	Ovary weight (mg/100g)	FSH (ng/ml)	LH (ng/ml)
Control	28.06±1.15[a]	32.63±2.26[b]	3287.33±122.46[b]
Leptin	22.31±0.55[b]	6571±3.05[a]	6528.00±616.37[a]
TRF	25.52±1. 86[a]	37.89±4.14[b]	5493.67±140.6[ab]
TRF+Leptin	21.86±0.7[b]	37.89±7.07[b]	4005.33±515.5[b]

Different letters in one column indicate a significant difference between groups at P≤0.05.

Follicular stimulating hormone concentration

Figure 2 showed an increase significantly of P≤0.05 in the FSH concentration in the leptin group treatment compared with control, TRF, and TRF with leptin, while there was no significant difference in TRF and TRF with leptin groups. The TRF groups and TRF with leptin were not significantly different from the control groups (Table 2).

Luteinizing hormone concentration

Results show a significant increase in P≤0.05 in the LH hormone concentration in leptin and TRF treated groups compared to control and TRF with leptin, At the same time, there were no significant difference between TRF with leptin and the control group (Table 2 and Figure 3).

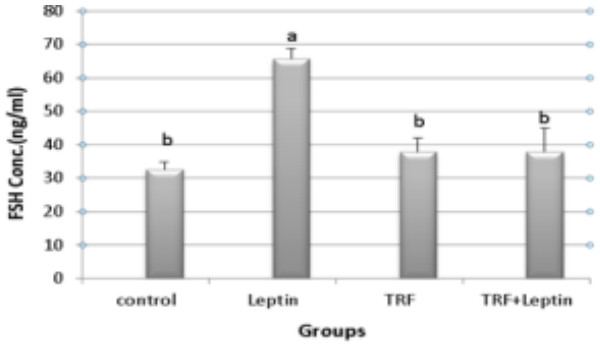

Figure 2: Leptin and TRF Effects on follicular stimulating hormone concentration in female rats

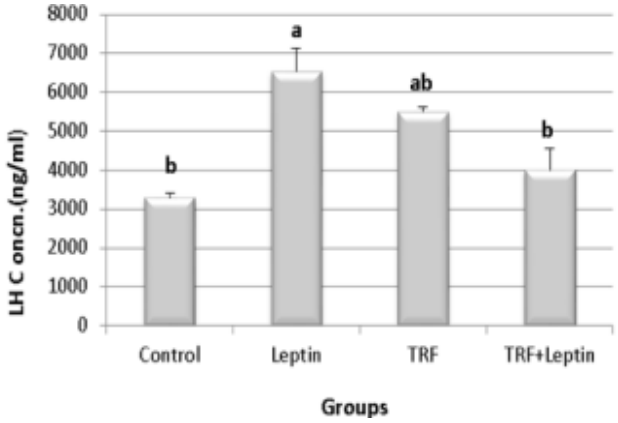

Figure 3: Leptin and TRF Effects on Luteinizing hormone concentration in female rats.

Ovarian histology

A histological slice of the control group's rat ovary reveals one layer of flattened pre-granulosa cells encircling the oocyte in a normal primary follicle to Well-developed primary follicles, degenerative luteal cells with vacuolation in the corpus luteum in leptin treated groups (Table 3). There are many primary and secondary follicles with many big antral follicles and corpora luteum. Antral follicles show vacuolation in granulosal layers and ooplasm enclosed by disarrangements and zona pellucida thinning. TRF groups show normal primary follicles, Severe congestion of blood vessels, and many corpora luteum. In groups of TRF with leptin showing natural aspect of the ovary and moderate congestion in blood vessels, various numbers of follicles primary, secondary, and antral follicles with corpus lutetium (Figures 4-17).

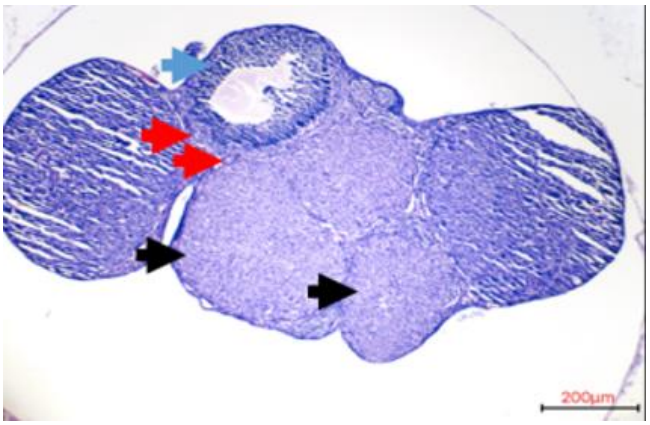

Figure 4: Histological section from the rat ovary of control group. Small primordial follicles are difficult to detect (red arrows). Antral follicles (blue arrow). corpora luteum (black arrows). (200µm H&E).

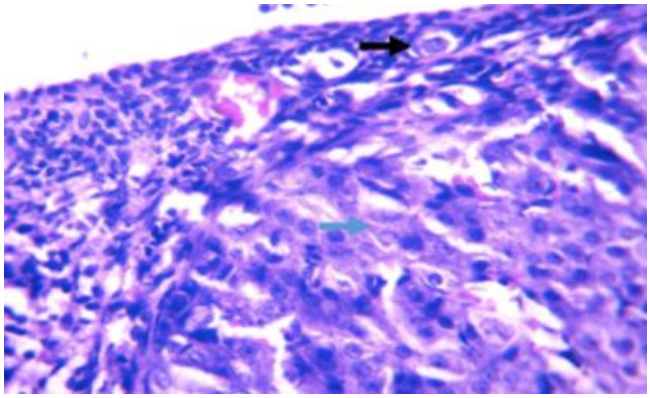

Figure 5: Rat ovarian histological section of control. The oocyte was surrounded by a single layer of flattened pre-granulosa cells in a normal primary follicle. The Corpus luteum and blood vessels appear normally (blue arrow). (20µm H&E).

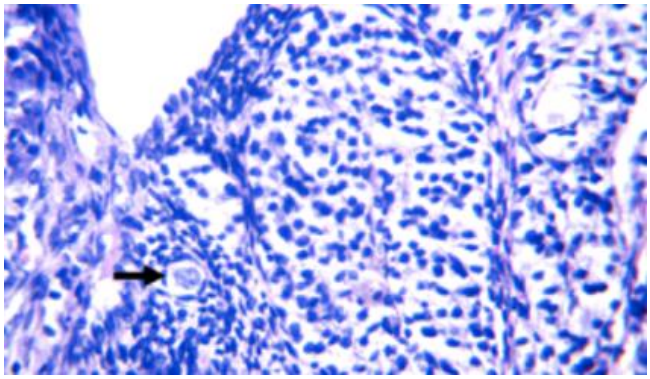

Figure 6: Histological section from the rat ovary of control group. Well-developed primary follicles (black arrow). (20µm H&E).

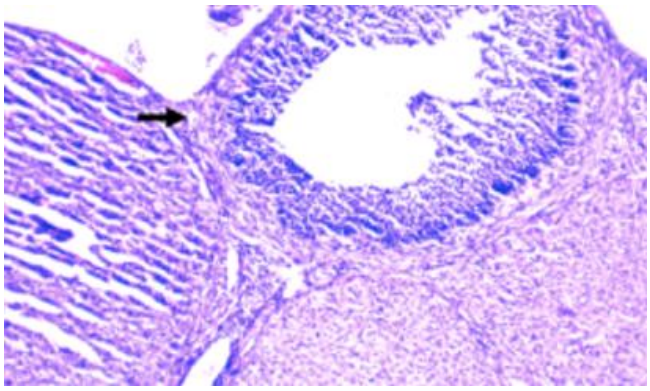

Figure 7: Histological section of the rat ovary in control group. Normal primary follicle as well as single layer of flattened pre-granulosa cells surrounding the oocyte (black arrow). Corpus luteum and blood vessels appear normally (blue arrow). (100µm H&E).

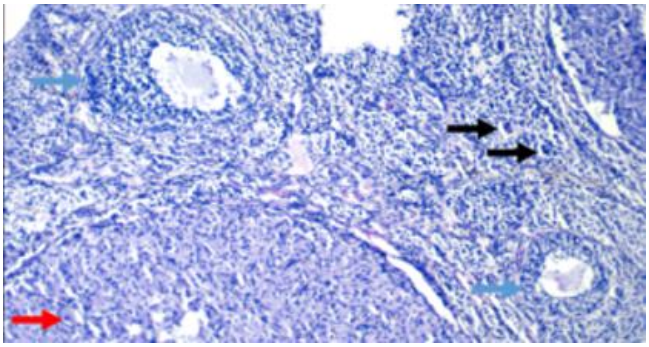

Figure 8: Histological section from the rat ovary of group 2 treated with leptin. There are many primary and secondary follicles (black arrows) with many large antral follicles (blue arrows). corpora luteum (red arrow). (200µm H&E).

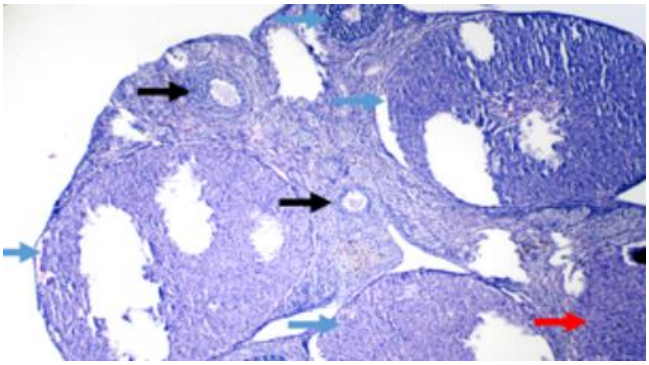

Figure 9: Histological section from the rat ovary of group 2 treated with leptin. There are many primary follicles as well as one of flattened pre-granulosa cells layer surrounding the oocyte (black arrows). Many of large growing follicles, antral follicles of different sizes (blue & red arrows). (100µm H&E).

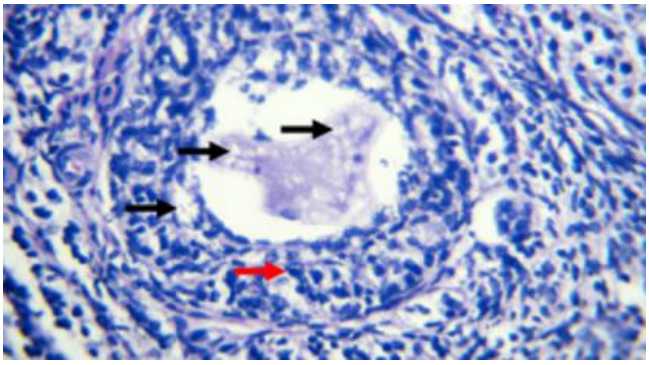

Figure 10: Histological section from the rat ovary of group 2 treated with leptin. Antral follicles showing vacuolation in granulosal layers and ooplasm (black arrows) enclosed by disruptions and thinning of zona pellucida (red arrow). (20µm H&E).

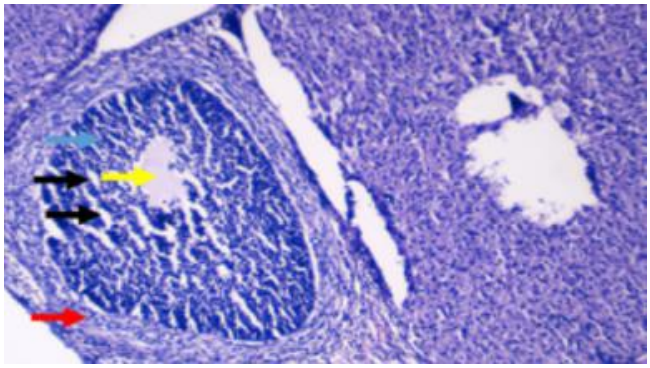

Figure 11: Histological section from the rat ovary of group 2 treated with leptin. Large antral follicles contain oocyte (yellow arrow) and presence of antral spaces in granulosa cells (black arrows), granulosa cells (blue arrow), theca interna (red arrow). (20µm H&E).

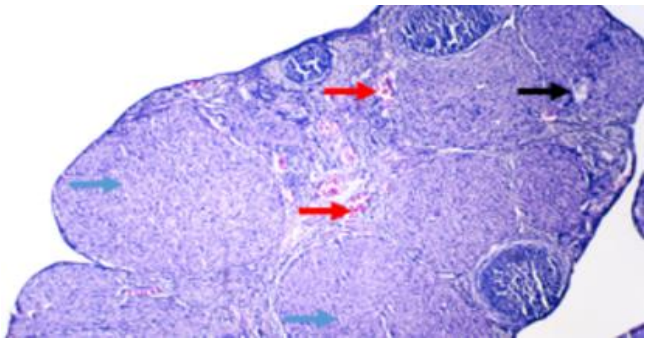

Figure 12: Histological section from the rat ovary of group 3 after time-restricted feeding. showing normal ovarian stroma and some follicles (black arrow), Severe congestion of blood vessels (red arrows), with many corpora luteum (blue arrows). (200µm H&E).

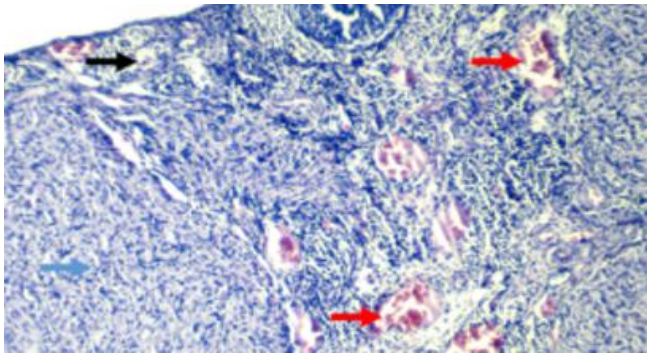

Figure 13: Histological section from the rat ovary of group 3 after time-restricted feeding. showing normal primary follicle (black arrow), Severe congestion of blood vessels (red arrows), with many corpora luteum (blue arrows). (100µm H&E).

Table 3: The histopathological changes of ovaries in adult female rats

Variables	Control	Leptin	TRF	TRF+Leptin
Vascular congestion	Absent -	Absent-	Moderate ++	Mild +
Antral space in granulosa cells	Absent -	Absent -	Mild +	Moderate ++
Interstitial fibrosis	Absent -	Absent -	Absent -	Absent -
Single layer of flattened pre-granulosa cells	Absent -	Absent -	Mild +	Moderate ++

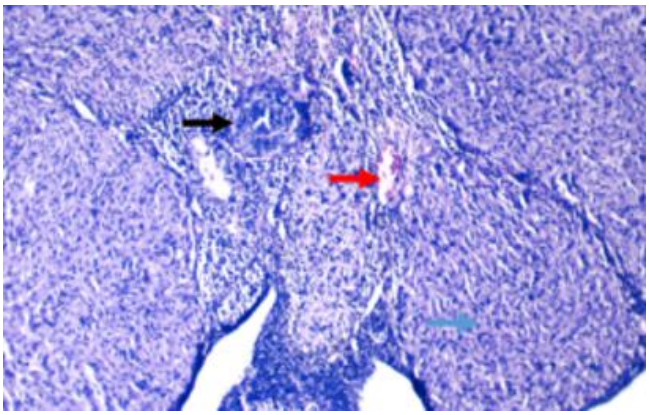

Figure 14: Histological section from the rat ovary of group 3 after time-restricted feeding. showing normal secondary follicle (black arrow), congestion of blood vessels (red arrows), there are many corpora luteum (blue arrow). (100µm H&E).

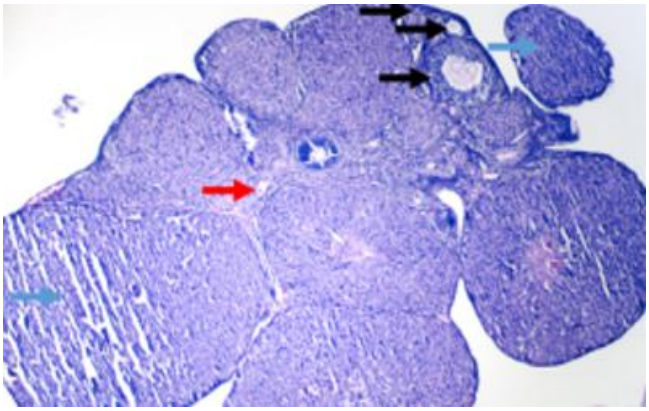

Figure 15: Histological section from the rat ovary of group 3 exposed to leptin and time-restricted feeding. Normal appearance of the ovary and moderate congestion in blood vessels (red arrow), various numbers of follicles (primary, secondary and antral follicles (black arrows) with corpus lutetium (blue arrows). (200µm H&E).

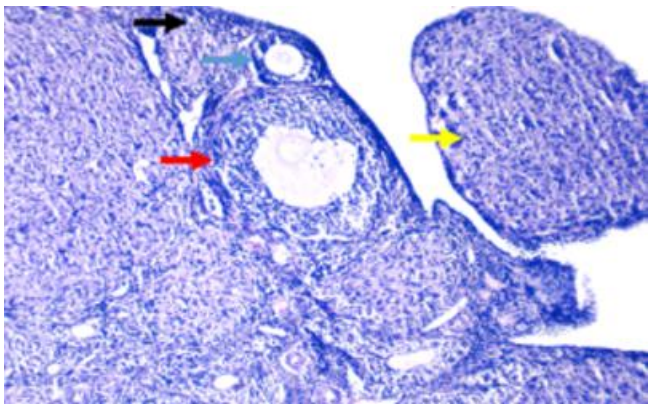

Figure 16: Histological section from the rat ovary of group 3 exposed to leptin and time-restricted feeding. Primordial follicle as well as one layer of pre-granulosa that has flattened cells enclosed the oocyte (black arrow), primary follicle and two layers of follicular cells (blue arrow), antral follicles with many layers of follicular cells (red arrow) and corpus lutetium (yellow arrow). (100µm H&E).

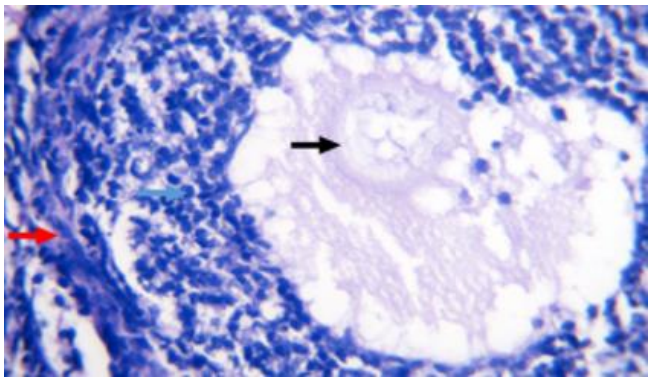

Figure 17: Histological section from the rat ovary of group 3 exposed to leptin and time-restricted feeding. Large antral follicles contain oocyte (black arrow) and presence of antral spaces in granulosa cells (blue arrow), theca interna (red arrow). (20µm H&E)

Discussion

Leptin hormone plays a crucial function in regulating satiety with supporting healthy reproductive functions. This current study showed that groups treated with leptin hormone significantly decreased in animal body weight compared to the control group. Leptin effects on food intake, and probably by an intermediary of various neuronal populations, the hypothalamus arcuate nucleus (ARH) is crucial region (27). Leptin influences food intake in the ARH

by acting least in two different neuronal groups: the proopiomelanocortin (POMC) prohormone and the cocaine and amphetamine regulated transcript (CART) are susceptible to the leptin response. Leptin activates ARH POMC/CART neurons, which typically prevent food intake resulting in greater satisfaction (28). The Leptin hormone enters the brain through the blood-brain barrier and causes neuronal inhibition within the hypothalamus because of anorexia (29). Exogenous leptin administration starts in obese persons to decrease food intake (30). The TRF groups' results indicated a significant decrease in animal body weight in compared to the control group. When an animal is starved and under food restriction, and body weight will decrease, the extent of weight loss relies mainly on the period the animal has been starved. A decrease in weight can be referred to decrease in food and water exhaustion. The parameter for weight, which is influenced by external factors, is considered a crucial component for the advancing biological activities (31). Body weight decreased in time-restricted feeding for 8 hours in obese objects. A study showed that rats on the TRF regimen gained less weight and were less obese than diet-matched ad-lib rats (32). In TRF with leptin, the animal's weight is decreased significantly in compared with control, leptin and TRF groups; this effect may be because of the Synergistic effect of leptin and TRF to decrease the body's weight. The ovary's weight significantly decreased in leptin and TRF with leptin in compared with control and TRF groups. The cause might be their impact on the whole-body weight, which results in weight reduction in ovarian weight. The result demonstrated the leptin hormone causes an increase in the concentration of FSH and LH hormone concentration in female rats. Leptin receptors occur throughout the body, including the pituitary gland and hypothalamus. The cause of the concentration of the hypothalamic-pituitary axis's leptin receptors is that, indirectly Leptin may affect on GnRH neurons (33). The leptin treatment increases the concentration of FSH and LH hormone, which may be because of the indirect action of the leptin hormone in the hypothalamus, which influences to GnRH neurons. Gonadotropin synthesis in the pituitary may be stimulated via leptin directly or indirectly through alteration of the sensitivity of the pituitary to GnRH (34).

The result showed that TRF did not affect the FSH and LH concentration and remained within the normal value, Fasting can enhance ovarian function by lowering insulin and glucose levels (35). The six-week intervention of eight hours of TRF resulted in significant reductions in AMH, FSH, LH, E2, prolactin, total and free testosterone, and DHEAS levels (36). In fasting animals, TRF the leptin hormone, led to improved FSH and LH hormone concentration and returned its value to normal as in the control group. Leptin a mediator in the communicating nutritional status information to the brain regions that regulate the reproductive system's function (37,38). The hypothalamic-pituitary axis's high leptin receptor density suggests that leptin mostly affects GnRH neurons indirectly (39). So, LH and FSH production and release were effectively stimulated by leptin at lower and moderate leptin concentrations. These results are consistent with many studies, with both a positive and a negative correlation between leptin and gonadotropins in cultured female rat pituitary cells (40). The results of study indicate that leptin plays vital role in controlling gonadotropin secretion by stimulating hypothalamic and pituitary actions by augmenting both FSH and LH release from anterior pituitaries of adult male and female rats (41). The researchers studied the effects of time-restricted diet (from 10:30 p.m. to 6:30 a.m.) in mice that this the FSH and LH levels (42). The production of corpus luteum is promoted by TRF, At the same time, cyst formation is inhibited, according to ovarian histology.

Conclusion

Time-restricted feeding restores the female reproductive function of rats with ovarian hormone and leptin stimulates FSH and LH hormones. This may be the agent that gets to the onset of puberty.

Conflict of interest

Conflicts of interest are not disclosed by the author.

Acknowledgement

The author is grateful to the University of Mosul's College of Veterinary Medicine for providing the necessary resources and assistance.

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التأثير الفسيولوجي للبتين وتقنين الغذاء في المعايير التناسلية لإناث الجرذان

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الخلاصة

تصرف الإناث طاقة زائدة أكثر من الذكور خلال التكاثر. مع العلم أن التكاثر يتطلب استخدام الطاقة، فمن المنطقي أن تكون اليات السيطرة الفسلجية المتعلقة بالشهية والتغذية تكون مرتبطة مع التكاثر. الهدف من البحث تقييم قدرة هرمون اللبتين على التقليل من تأثير تقنين الغذاء في إناث الجرذان. تم تقسيم ٢٤ من إناث الجران البالغة، وزنها ١٧٥-٢٠٠ غم عشوائيا الى أربع مجاميع. المجموعة الأولى (ك١) السيطرة أعطيت ماء المقطر. المجموعة الثانية (ك٢) حقنت بهرمون اللبتين بجرعة (٥٠ ميكروغرام/كغم من وزن الجسم) داخل الصفاق. المجموعة الثالثة (ك٣) هي تقنين الغذاء بنظام (٨ صباحا -٣ مساءا) والماء يكون حرا. المجموعة الرابعة (ك٤) تقنين الغذاء بنظام (٨ صباحا -٣ مساءا) والماء يكون حرا مع حقن هرمون اللبتين بجرعة (٥٠ ميكروغرام/كغم من وزن الجسم داخل الصفاق). في نهاية فترة البحث (٨ أسابيع) قتلت الحيوانات وجمع مصل الدم لتقدير مستوى الهرمون المحفز للجريبات والهرمون اللوتيني باستخدام تقنية الاليزا، عولجت المقاطع المبيضية بصبغة الهيماتوكسيلين والايوسين لدراستها نسجيا. أظهرت النتائج انخفاضا معنويا في وزن الجسم في مجموعة تقنين الغذاء مع هرمون اللبتين مجموعة هرمون اللبتين ومجموعة تقنين الغذاء، انخفاضا معنويا في وزن المبايض في مجموعة هرمون اللبتين ومجموعة تقنين الغذاء مع هرمون اللبتين. ارتفاع معنوي في الهرمون المحفز للجريبات والهرمون اللوتيني في مجموعة هرمون اللبتين، تقنين الغذاء ومجموعة تقنين الغذاء مع هرمون اللبتين. أظهرت التغييرات النسجية في مجموعة هرمون اللبتين العديد من جريبات مبيضية أولية وثانوية مع الجريبات الغارية والجسم الأصفر وأظهرت مجموعة تقنين الغذاء جريبات مبيضية طبيعية. نستنتج من ذلك أن تقنين الغذاء تعزز الوظيفة التكاثرية لإناث الجرذان مع هرمون المبيض المحفز للجريبات والهرمون اللوتيني واللبتين وربما يكون هذا هو العامل الذي يؤدي إلى بداية البلوغ.