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Skipping the first active meal appears to adversely alter reproductive function in female than male rats

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ABSTRACT

There is a growing consciousness about chrono-nutrition and its physiological functions. The human feeding pattern establishes three meals a day, meal timing however may not be adhered to. Previous studies have reported ovarian dysfunctions in breakfast skipping among females. In this study, the investigation was carried out on the effects of breakfast skipping on reproductive functions in the male rat and comparison, to the female rat. Eight-week-old animals (10 rats per group) were used to mimic post-adolescence. Rats are active at night thus the meal model was divided as follows. Female rats who had all three meals ($Control_F$), Female rats who had a no-first-active meal ($NFAM_F$), Male rats who had all three meals ($Control_M$), and Male rats who had a no-first-active meal ($NFAM_M$). All animals were fed the same amount of food every day. After the expiration of the four weeks experiment, serum testosterone, estrogen, Luteinising Hormone (LH) Follicle Stimulating Hormone (FSH), and prolactin (PRL) were quantified using ELISA. Sperm was also analyzed. There was a significant increase ($p < 0.05$) in the testosterone level and sperm count in the $NFAM_M$ compared to the $Control_M$ while the estrogen level was significantly reduced in the $NFAM_F$ compared to the $Control_F$. LH, FSH, and PRL levels were significantly reduced in the $NFAM_F$ compared to the $NFAM_M$. These findings further confirm that post-adolescent females are prone to breakfast skipping. The increase in testosterone levels and sperm count in the males establish that breakfast skipping might not interfere with the reproductive physiology in males as it does in females.

1. Introduction

Nutrition, genetics, and environmental factors play significant roles in the physiology of reproduction. Diets including sugars and fats have been implicated in reproductive dysfunctions (Plotan et al., 2013; Adekunbi et al., 2016; Oyelowo and Adegoke, 2016). The circadian timing system characterized by body temperature cycles, sleep-wake, and feeding behaviors (Dibner et al., 2010), plays a tremendous role in the make-up of individuals.

There are pieces of literature suggesting that nutrition could affect the health of females and males differently (Marino et al., 2011). Studies have constantly reported that women consume more fruits and vegetables, dietary fibers, and lower fat than men (Wardle et al., 2004; Westenhoefer, 2005), while men prefer beef to women (Cosgrove et al., 2005; McAfee et al., 2010). Besides nutrition, the circadian timing system which includes feeding behavior (Dibner et al., 2010) plays a tremendous role in the make-up of individuals.

Breakfast typifies the most important meal of the three meals a day which is well-known by most people. Breakfast-skipping appears very high in young adults due to lifestyle activities resulting in an increase in chronic diseases in the future. This has developed into a serious matter in the young (Pendergast et al., 2016). There are reports of young women skipping breakfast and showing higher occurrences of dysmenorrhea and reproductive dysfunction compared to those who took breakfast (Fujiwara, 2003; Fujiwara and Nakata, 2010; Abu Helwa et al., 2018). These studies show that breakfast skipping affects female reproductive functions. Regarding the issues of reproductive health especially fertility problems, it is important to examine routine dietary patterns even in males (Panth et al., 2018; Skoracka et al., 2020). According to a study by the World Health Organization (WHO), 20% of cases were attributed to male factors, (WHO, 1987) also, in some countries, 50% of infertility problems are attributed to males (Kumar and Singh, 2015). There is a paucity of information on the clear-cut effects of skipping breakfast on reproductive functions in males. Since breakfast skipping could predispose to the risk of reproductive dysfunction in females, this study was thus designed to compare the effects of skipping breakfast in males and females on reproductive functions in Wistar rats and draw out possible mechanisms of action.

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2. Materials and methods

2.1. Animals and experimental design

Male and female Wistar rats (six-weeks of age; and 10 rats per group) were obtained from the Central Animal House, University of Lagos. The animals were housed under a 14 h:10 h dark-light (DL) cycle at constant temperature and given access to food only in the dark period and water ad libitum. The animals were acclimatized to the lighting and feeding condition for two weeks before the commencement of the study. The dark/light pattern followed that the onset of darkness was referred to as Dark-Light Time 0 (DLT 0) while the onset of light was Dark-Light Time 14 (DLT 14). Eight-week-old animals were used to mimic post-adolescence. Rats are active at night thus the meal model was divided as follows. Female rats who had all three meals ($Control_F$), Female rats who had a no-first-active meal ($NFAM_F$), Male rats who had all three meals ($Control_M$), and Male rats who had a no-first-active meal ($NFAM_M$). Rats of each group were given the same total amount of food every day and were fed a standard caloric diet of 20.0% protein, 62.9% carbohydrate, and 7.0% fat, 3.95 kcal/g). The rats that were fed three times a day (Control group) were fed at DLT0–2 (33% of total), DLT6–8 (33% of total), and DLT12–14 (33% of total). In the NFAM (no first active meal) group, the rats were fed two times a day at DLT6–8 (50% of total) and DLT12–14 (50% of total) (Wu et al., 2011). The light-dark cycle was however not changed. All through the four weeks of the experiment, weekly body weight and daily amount of food ingested by each rat were measured using a scale balance. The total food intake was limited to ensure each rat could consume the entire amount of food during each limited feeding time of 2-h duration. Rats of each group were given the same amount of total food every day, which was increased week by week. This amount of total food was equal to approximately 70–80% of the amount of food consumed by ad libitum feeding rats of the same age. The stability of the estrus cycle of female rats corresponding to the post-adolescent stage was confirmed (Fujiwara et al., 2018). Post-adolescence was also confirmed in male rats (McCutcheon and Marinelli, 2009). All rats were killed under anesthesia by an intraperitoneal (i.p.) injection of sodium pentobarbital, on the first day of the fifth week. Experimental procedures relating to the use of animals were by the EU Directive 2010/63/EU for animal study and the study conformed with the Animal Research: Reporting of *In Vivo* Experiments (ARRIVE) guideline (2010) and ethical approval was obtained from the College of Medicine, University of Lagos Animal Care and Use Research Ethics Committee.

2.2. Biochemical assays

Testosterone, Luteinising Hormone (LH), and Follicle Stimulating Hormone (FSH) were assessed by enzyme-linked immunosorbent assay (ELISA) using ELISA assay kits (Acc-Bind Elisa microwell monoband (USA).

2.3. Sperm analysis

The analysis of sperm count, sperm motility, and sperm morphology was carried out as described in a previous study (Adekunbi et al., 2016) as follows: humanely, the caudal epididymis was harvested, and cut into pieces in 1 ml of 37 °C of normal saline solution. A drop of the solution was placed on a glass slide and covered with a coverslip and afterward placed under a microscope at x40. The sperm motility was based upon; oscillatory or stationary, slow progression or rapidly progressive, vibrating movements, and these were expressed in percentages. The sperm morphology was determined as follows: a smear preparation was made (with formal saline) and was stained with 1 percent eosin stain, and it was allowed to stand for 20–30 min to allow staining to occur. A hundred sperms per animal were morphologically examined at ×100 magnification, the abnormal sperms were categorized based on the presence of irregular heads, detached tails, midpiece bending, and double tails. The sperm count was done using the enhanced Neubauer hemocytometer and was expressed as million/ml of the suspension.

2.4. Statistical analysis

Data were presented as means ± SEM. Statistical analysis was carried out by two-way analysis of variance (ANOVA) supported by the Newman-Keuls test when pair-wise comparison was done between the groups. The analysis was done using version 5.0 (GraphPad Software, San Diego California, USA). The level of statistical significance was placed at $p < 0.05$.

3. Results

3.1. Effect of no first active meal (NFAM) on body weight and feed intake in male and female Wistar rats

There was a significant decrease in the feed intake of the NFAM female rats when compared to the NFAM male rats throughout the four weeks of breakfast skipping. The female rats that were fed the active meal (Control) had an increase in their feed intake compared to the Control male rats at week one, but by the fourth week, there was a significant reduction in feed intake of the Control female rats when compared to the Control male rats (Fig. 1) (see Fig. 2) (see Fig. 3) (see Fig. 4) (see Fig. 5) (see Fig. 6).

There was a significant decrease in the body weight of the NFAM female rats when compared to the NFAM male rats by week four. There was also a significant decrease in the body weight of the female rats that were fed the active meal (Control) compared to the Control male rats at weeks two and four.

3.2. Effect of no first active meal (NFAM) on serum hormonal profile in male and female Wistar rats

The testosterone level in the NFAM male rats was significantly increased compared to those who were fed the first active meal (Control), while the estrogen level in the NFAM female rats was significantly reduced compared to those who were fed the first active meal (Control).

The LH and FSH levels were not affected in both the NFAM males and females when compared to their controls respectively. The LH and FSH levels were however significantly reduced in the NFAM female rats when compared to the NFAM male rats as well as in the female rats who were fed the first active meal (Control) when compared to the male rats who were fed the first active meal (Control).

The prolactin level was significantly reduced in the NFAM female rats when compared to the NFAM male rats, but the level was significantly increased in the female rats who were fed the first active meal (Control) when compared to the male rats who were fed the first active meal (Control).

3.3. Effect of no first active meal (NFAM) on epididymal sperm characteristics in male Wistar rats

There was a significant increase in the sperm count of the rats who skipped the first active meal (NFAM) compared to those who ate the first active meal (Control). There was however no significant difference in sperm motility and abnormal sperm morphology in rats who skipped the first active meal (NFAM) compared to those who ate the first active meal (Control).

4. Discussion

This study examined the effect of skipping the first active meal and its consequent roles on reproductive functions in males and females. Breakfast skipping mimics the human habit. The experiment will

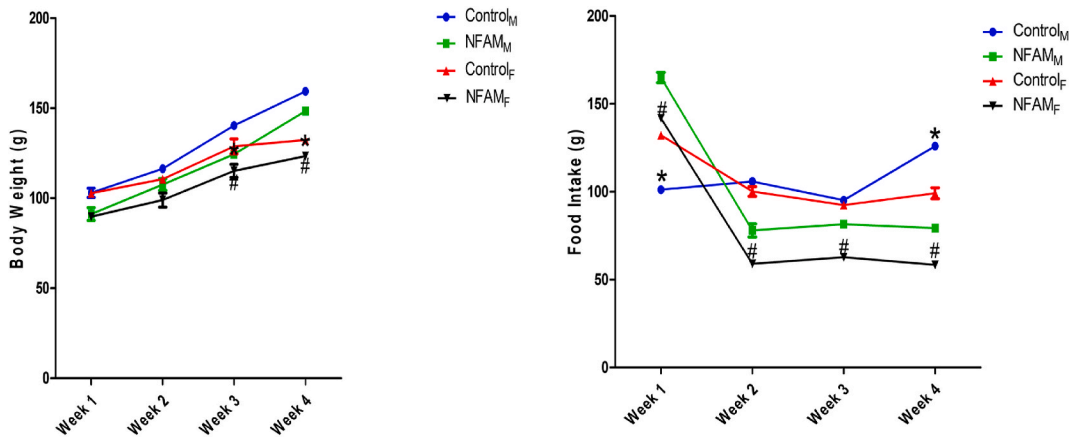

Fig. 1. Decreased mean body weights characterized NFAM female rats when compared to the NFAM male rats at week four, and a significant reduction in body weight was observed in Control female rats when compared to Control male rats at the second and fourth weeks. Values are expressed as mean ± SEM of 10 rats per group, *p < 0.05 vs control male, #p < 0.05 vs NFAM male. NFAM (No-first active meal). Throughout the experiment, decreased feed intake characterized NFAM female rats when compared to the NFAM male rats, while at week one significant increase in feed intake characterized female rats fed the active meal (Control) when compared to male rats fed the active meal (Control). At week four, however, a significant decrease in feed intake was observed in female rats fed the active meal (Control) when compared to male rats fed the active meal (Control). Values are expressed as mean ± SEM of 10 rats per group, *p < 0.05 vs control male, #p < 0.05 vs NFAM male. NFAM (No-first active meal.

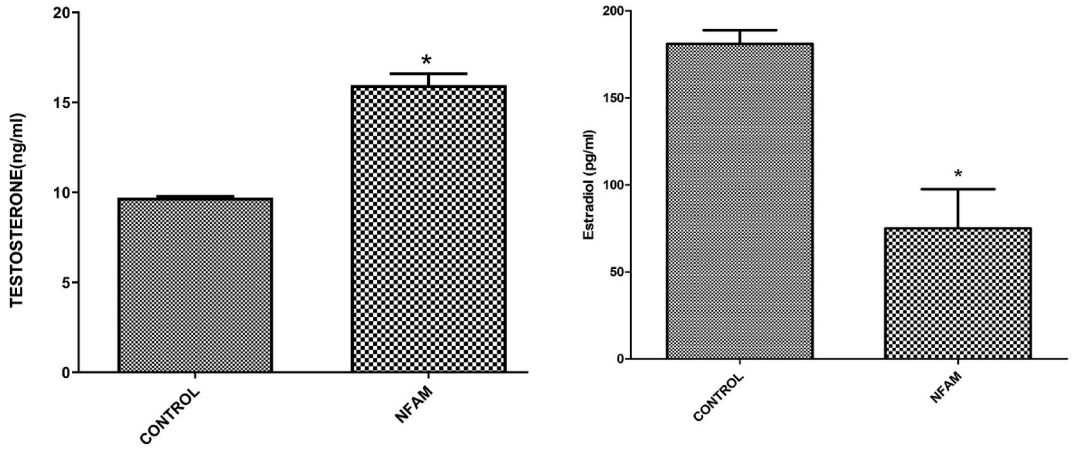

Fig. 2. Increased testosterone levels characterized male rats in the NFAM group when compared to the control group but a decrease in the estrogen level characterized female rats in the NFAM group when compared to the control group. Values are expressed as mean ± SEM of 10 rats per group, *p < 0.05 vs control. NFAM (No-first active meal).

corroborate and extend knowledge on the effects of skipping the first active meal of the day and more importantly the physiologic implications for both males and females in reproductive functions.

The NFAM female rats had reduced food intake when compared to the NFAM male rats from the first week of the experiment to the fourth week. The female rats who were not deprived of the first active meal (Control) also had reduced food intake compared to the control males by the fourth week of the experiment. This further confirms that the timing of food intake is a critical factor that influences female reproductive function (Fujiwara et al., 2018). Their study also reported reduced feed intake in the daytime-fed (non-active feed time) female rats and the night-fed (active feed time) female rats, which corroborates our findings. Our study however focuses on breakfast skipping in male and female rats. Body weight loss was recorded in the control female animals compared to the male rats in the second and fourth weeks. There was a significant increase in body weight of animals that were not deprived of the first active meal (control animals) in the relatively short term. By the fourth week of the study, food intake was reduced in the control females compared to the control males which resulted in a significant reduction in body weight by the fourth week, although the body weight reduction was observed in the second week of the study. This reduction in feed intake could be because meal duration but not frequency was significantly shorter in females than in males (Funabashi et al., 2009). The decrease in food intake and the corresponding reduction in body weight have been reported in situations like breakfast skipping (Hubert et al., 2000). Different feeding patterns affect female and male rats (Laviano et al., 1996) and these sex differences are found also in humans (Fukushima et al., 2015). The significant reduction in feed intake throughout the study in the NFAM group could be explained by the fact that rodents exhibit adaptive physiological and biochemical responses to food deprivation, for example, rodents reduce metabolism when deprived of food (Wang et al., 2006). There are neurons in the hypothalamus of the female rat which increase in situations such as fasting or breakfast skipping irrespective of the estrous day. This increase in neurons does not occur in male rats. The relationship between these sex differences in the neurons in the hypothalamus and fasting implies that there is a greater sensitivity of the female hypothalamus to metabolic cues (Fukushima et al., 2015). Again, the reduction in calorie intake could bring about reproductive dysfunction in females (Fujiwara et al., 2018). The reduction in food intake in the Control and NFAM female rats

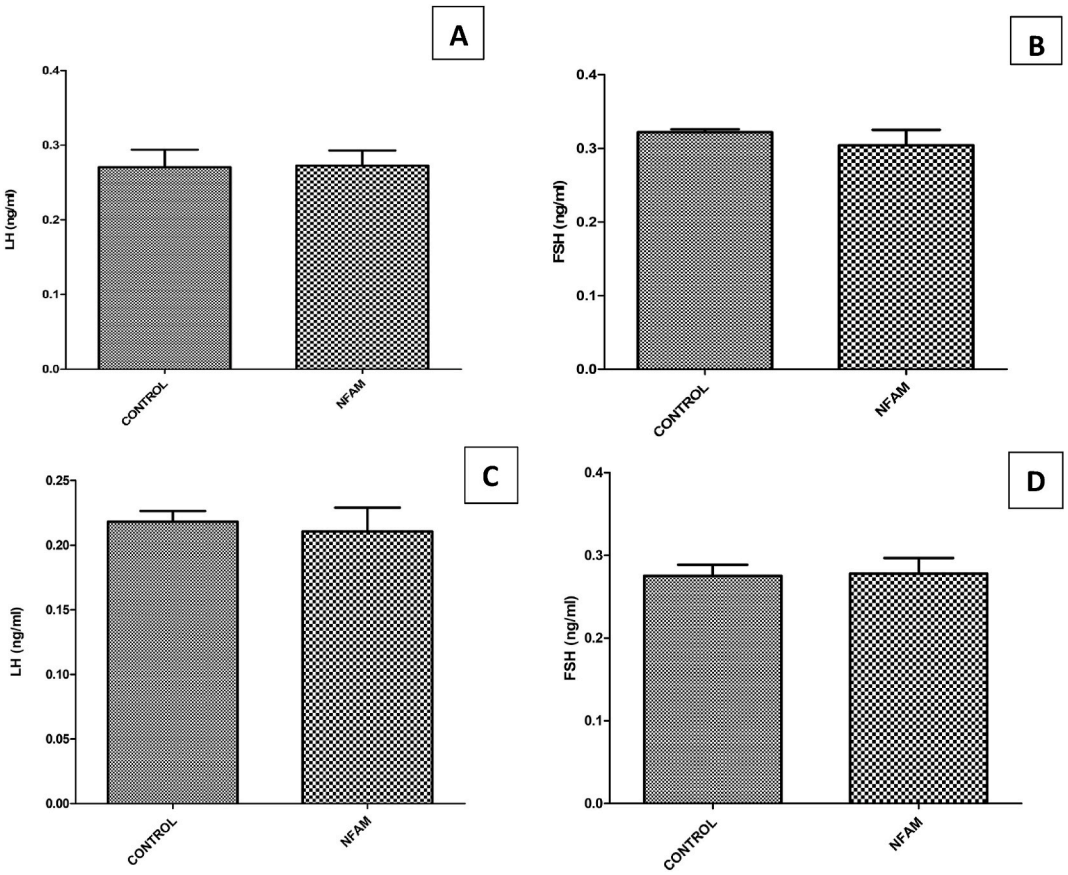

Fig. 3. A &B shows that the LH and FSH levels were not significant in the NFAM males compared to Control males. **C&D** shows that the LH and FSH levels were not significant in the NFAM females compared to the Control females. Values are expressed as mean ± SEM of 10 rats per group, *p < 0.05 vs control. NFAM (No-first active meal, Luteinizing Hormone (LH), Follicle-Stimulating Hormone (FSH).

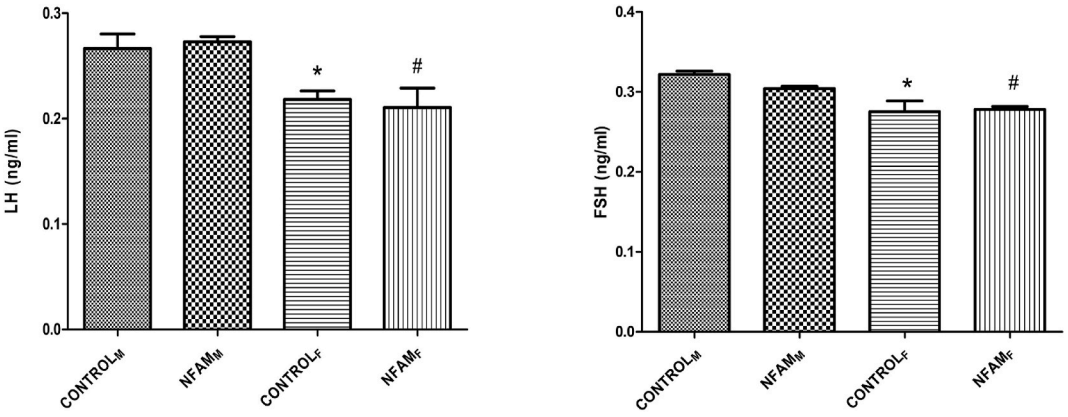

Fig. 4. The LH level was significantly reduced in the NFAM female rats compared to the NFAM male rats and the LH level was significantly reduced in the Control female rats when compared to Control male rats. Values are expressed as mean ± SEM of 10 rats per group, *p < 0.05 vs control male, #p < 0.05 vs NFAM male. NFAM (No-first active meal), Luteinizing Hormone (LH). The FSH level was significantly reduced in the NFAM female rats compared to the NFAM male rats and the FSH level was also significantly reduced in the Control female rats when compared to Control male rats. Values are expressed as mean ± SEM of 10 rats per group, *p < 0.05 vs control male, #p < 0.05 vs NFAM male. NFAM (No-first active meal), Follicle-Stimulating Hormone (FSH).

and subsequent body weight reduction in this post-adolescent period, could be because appetite loss during adolescent and post-adolescent phases are physio-pathologically significant in young women (Clarke et al., 2012; Misra and Klibanski, 2014).

Although extreme weights and body fat distribution influence the hypothalamic-pituitary-ovarian (HPO) axis, caloric restriction such as skipping breakfast could alter the HPO axis as observed in the study, with reduced body weights and a reduction in estrogen levels. Extreme weights and body fats interfere with endocrine as well as paracrine mechanisms involved in reproductive cycle control. When normal GnRH pulsatility is lost, there is usually an excessive aromatization of androgen precursors, DHEA, and testosterone to estrone in adipose tissue decreased levels of sex hormone-binding globulin (SHBG), and elevated production of leptin by adipocytes (Silvestris et al., 2018). In underweight individuals, however, GnRH pulsatility is affected by depletion of circulating leptin, too much cortisol, and neuropeptide Y

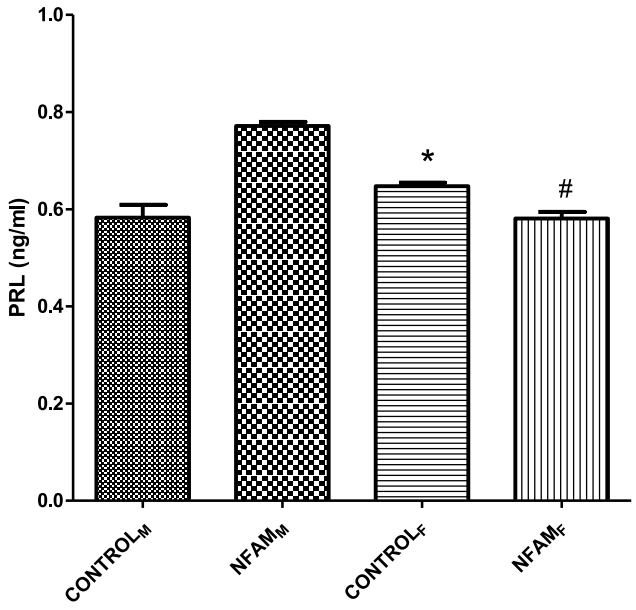

Fig. 5. The PRL level was significantly reduced in the NFAM female rats compared to the NFAM male rats, but the PRL level was significantly increased in the Control female rats when compared to Control male rats. Values are expressed as mean ± SEM of 10 rats per group, *p < 0.05 vs control male, #p < 0.05 vs NFAM male. NFAM (No-first active meal), Prolactin (PRL).

production raised centrogenic opioid and endorphin secretion which would invariably affect reproduction and fertility.

The level of testosterone was significantly higher in the no first active meal (NFAM) male group when compared to those who had their first active meal (Control), while the estradiol level was significantly lower in the no first active meal (NFAM) group when compared to those who were fed their first active meal (Control). The NFAM female rats were more affected by food intake and body weight than the males. Caloric intake such as in obesity has been linked to low serum testosterone levels (Hu et al., 2018). It does imply that low caloric intake like skipping breakfast, might be beneficial in the male in terms of reproduction and fertility as reported in this study. The increase in the testosterone level of the NFAM rats appears beneficial because testosterone is the primary androgen responsible for the development, growth, and maintenance of male reproductive functions and sexual characteristics (O'Shaughnessy et al., 2012).

The Luteinising hormone (LH) and Follicle-Stimulating hormone (FSH) levels which are part of the hypothalamic-pituitary-gonadal (HPG) axis were both non-significant in the NFAM males when compared to those who were fed their first active meal (Control), and in the NFAM females when compared to those who were fed their first active meal (Control) respectively. Ideally, as blood testosterone level rises, the luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels should decrease, but in this study, the testosterone levels increased while the gonadotropin levels were not affected indicating that the effects of breakfast skipping were directly on the testes. The estrogenic levels may also be acting directly on the ovaries. The LH and FSH levels were however significantly reduced in the NFAM female rats when compared to the NFAM male rats. The female animals fed the first active meal also had significantly reduced LH and FSH levels when compared to the male rats. The hypothalamic-pituitary-ovarian (HPO) axis is primarily responsible for controlling reproductive ability and the release of ovarian hormones in humans and animals (Nielsen and Herrera, 2017). Estradiol, progesterone, and testosterone hormones influence the negative-feedback loop regulating HPG axis activity. The gonadotropins stimulate the gonads. The estradiol level was reduced in the NFAM groups when compared to the control. This could be the reason for the reduced gonadotropin levels in the NFAM females compared to the NFAM males since LH is co-secreted alongside FSH by the gonadotrophin cells in the anterior pituitary. Also, LH release is stimulated by gonadotropin-releasing hormone (GnRH) and inhibited by estrogen and testosterone. Since LH helps to regulate the female cycle, its reduction in the NFAM females gives credence to the reason for cycle alteration in females skipping breakfast (Fujiwara et al., 2018). The proestrus phase corresponds to the human follicular stage, which is associated with a rise in circulating estradiol concentrations and little surge in prolactin levels which will lead to a rise in LH and FSH release (Heape, 1990).

Prolactin hinders the secretion of GnRH from the hypothalamus, thus decreasing the secretion of gonadotropins, a twist of events occurs to the level of prolactin in relationship to caloric intake. A study reported that in mice with lifelong hyperprolactinemia, there was increased food intake (Lopez-Vicchi et al., 2020). In this study, the female rats fed the active meal (control) had increased prolactin levels compared to the male rats fed the active meal while the female rats who were not fed the first active meal (NFAM) had reduced prolactin levels compared to the NFAM male rats.

Studies have reported ovarian dysfunction in females who skipped breakfast (Fujiwara, 2003; 2010, 2018). In this study, there was an increase in sperm count in the male rats who skipped breakfast compared to those who did not skip breakfast. Sperm count and quality are correlated with an increase in testosterone level (Sönmez et al., 2005), there was however no significant difference in the percentage of abnormal sperm morphology and sperm motility in the animals. Of all the semen parameters, sperm motility appears to be a strong predictive marker of male fertility potential (Dcunha et al., 2022) but it was not significant in this research, further studies are thus required in this area.

5. Conclusion

This study demonstrated that breakfast skipping alters the female reproductive function compared to the male reproductive function during the post-adolescent stage in rats. The hypothalamic-pituitary-gonadal (HPG) axis, like other parts of the brain, respond to sex steroids differently (Sisk and Foster, 2004; Bramen et al., 2012). The HPG axis could be modulated differently for the males and females regarding breakfast skipping. There are possibilities that human males are less affected than females. This study, to our knowledge, is the first to experimentally confirm that female rats are more prone to adverse effects along the hypothalamic-pituitary-gonadal (HPG) axis than male rats. Although these findings should not be applied directly to humans, this model can provide vital information to understand the mechanisms why female post-adolescent who skip breakfast exhibit reproductive dysfunctions, studies on human male post adolescents viz-a-viz skipping breakfast are also important. The reasons for these studies are so that the opposing effects of skipping breakfast during the post-adolescent phase on fertility in imminent adulthood which is a critical physiological stage should be expounded.

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CRediT authorship contribution statement

Oluwakemi T. Oyelowo: Conceptualization, Methodology, Software, Data curation, Writing – original draft, Validation, Writing – review & editing, Supervision. **Emmanuel O. Taire:** Visualization, Investigation, Software, Validation. **Olubunmi I. Ajao:** Visualization, Investigation, Software, Validation.

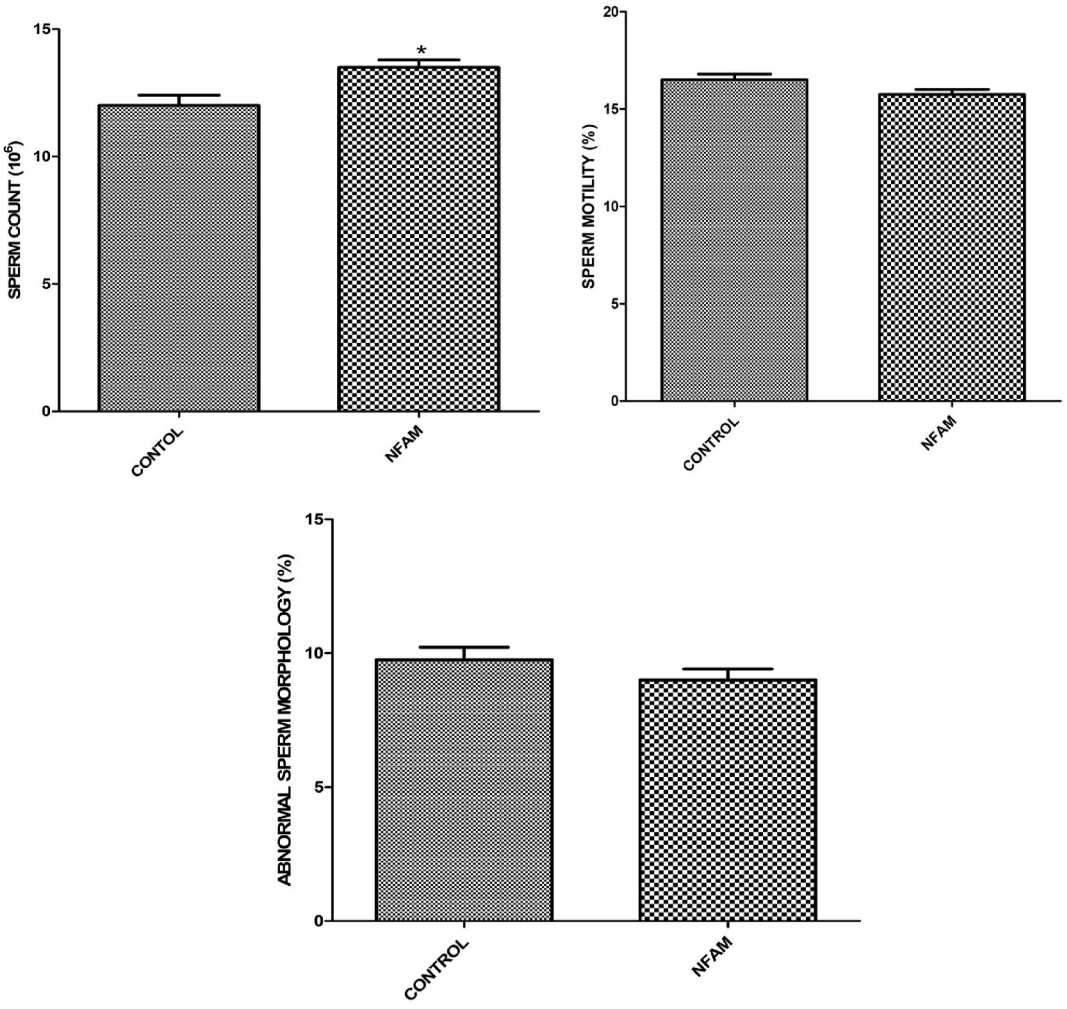

Fig. 6. The sperm count was significantly increased in the NFAM male rats when compared to the Control male rats. There were no significant differences in the percentage of sperm motility and percentage of abnormal sperms in the NFAM male rats when compared to the Control male rats. Values are expressed as mean ± SEM of 10 rats per group, *p < 0.05 vs control. NFAM (No-first active meal).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

NFAM	No first-active meal
LH	Luteinising Hormone
FSH	Follicle Stimulating Hormone
PRL	prolactin
i.p.	intraperitoneal

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