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Physiologic Effect of Ketogenic Diets on Hormonal Profiles in Stress-Induced Male Wistar Rats

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ABSTRACT

Aim/Objective: *The aim of this research was to determine the effects of starvation-induced stress on reproductive parameters of Wistar rats fed with ketogenic diets.*

Materials/Methods: *Forty healthy male Wistar rats acclimatized for 14 days, weighing 110-200g when weighed with Golding meter (USA) digital weighing scale. Group A was the normal control while Group B was also a control; they were fed with ketogenic diet and water ad libitum daily without stress induction. Group C&D were administered 15hrs ketogenic diet, 9 hours starvation daily and 6 hours KD, 18 hours starvation daily. The hormonal profiles were determined using Tiet and Layman methods.*

Results: *A significant decrease was observed in all three major hormones among the test groups considered in this study compared with the control group that was not subjected to starvation- induced stress. Comparing GP-B (control 2) fed with ketogenic diet and water ad libitum daily with GP-A (normal control 1) fed with standard diet and water ad libitum also shows a dcline in serum male hormones among KD-fed group with a significant p value in (LH) 18hours stress induced group. Regarding serum FSH, there was a significant (p-value ≤ 0.05) decrease among 9 and 18hrs stress-induced groups compared with the control while testosterone decrease was non-significant.*

Conclusion: *Starvation-induced stress with ketogenic-diet possesses antigonadotrophic consequences. We therefore recommend that further research on this starvation-induced stress should not be limited to reproductive parameters only but to wide range of parameters involving other body systems.*

Keywords: *Diet, ketogenic, hormones, LH, FSH*

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INTRODUCTION

Ketogenic diets have high fat concentration, low protein and very low carbohydrates. They enhance ketone bodies production due to breakdown of fat to produce energy [1]. KD are effective treatment for most metabolic diseases, cluding tumour growth [2]. Studies have shown that KD has curative benefits. It has been recommended as supplementary remedy for acne, convasant therapy etc [3]. [26-4]. KD also assist in reducing cholesterol levels in obese patients, and maintaining mood stability in bipolar disorder [5-6].Clinical trial, findings indicate that KD consumption for 20 days significantly reduced deposits of CO2 in the body [3]. Irrespective of its popular use, there have been some concerns on some possible consequences of the ketogenic diet on the whole body system. Since the ketogenic diet substitute's glucose with fat as the main energy source, the body is induced to activate a series of fat metabolic processes for energy acquisition [7]. Fat metabolic processes produce acetyl coenzyme A (Acetyl-CoA) as the principal product, which then enters the tricarboxylic acid cycle and becomes oxidized to produce ATP [8].

Acetyl-CoA that exceeds the activity of the citric acid cycle and/or the availability of oxaloacetate leads to a rise in ketone bodies (acetoacetate, β-hydroxybutyrate, and acetone). This process is known as ketogenesis [8].Ketone bodies from KD are acidic; hence rapid removal of acids via the kidneys may decrease bicarbonate ions (HCO_3^-) [9]. As a consequence, the significance of the KD reduced blood pH, resulting in ketoacidosis [10]. The effect of a high-fat diet on the function of important organs, such as the liver and kidneys, has been effectively studied using several animal models [11,12-13].High KD has been shown to alter renal lipid metabolism in mice, especially the balance between lipolysis and lipogenesis, resulting in the accumulation of lipid in the kidneys and, hence, renal dysfunction [14].

Figure 1: High Fat, Low Carbohydrate (Ketogenic) Diets (Photo Credit: Gillian Vann)

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MATERIALS AND METHODS

Ketogenic Diets

The Ketogenic diet preparation and the duration of administration were in accordance with [15]. Ketogenic diets are composed of 60% fats, 25% proteins, and 15% carbohydrates.

Preparation of the Ketogenic Diets

The ketogenic diet was prepared with a mixture of the Standard Diet and Margarine. 1kg of Margarine was added to 1kg of Standard Diet. Both components were hand-mixed thoroughly until no trace or sample of Margarine was noticed in the homogenous mixture.

LABORATORY ANIMALS USED

The animals used for this research were 40 healthy male Wistar rats with weights ranging from 110 to 200g using a Golden Meter USA scale calibrated in grams.

They were acclimatized for two weeks and sheltered in 4 cages of 10 per group, having access to natural light, air, rat feeds, and water ad libitum (for the control group, while the test-groups were subjected to hours of fasting before the administration of ketogenic diets). [16)

RESEARCH DESIGN

- Group A (Control 1): 24 hours SD and wateronly. No Starvation
- Group B (Control 2): 24 hours KD and water. No Starvation
- Group C: 15 hours KD and water. 9 hours' starvation daily
- Group D: 6 hours KD and water.18 hours' starvation daily

SAMPLE COLLECTION AND ANALYSIS

Five rats were sacrifice from each group with a 5ml of blood collected via cardiac puncture for hormonal analysis

RESULTS

Table 1: Comparing the mean values of hormonal assay in Wistar rats fed with ketogenic diet

Parameters	Control	9 Hours Starvation	18 Hours Starvation
Luteinizing hormone (ng/ml)	1.880 ± 0.24	1.680 ± 0.076	1.388 ± 0.048▪
Follicle stimulating hormone (ng/ml)	2.685 ± 0.42	1.910 ± 0.11	1.715 ± 0.13▪
Testosterone level (ng/ml)	1.313 ± 0.21	0.980 ± 0.13	0.9650 ± 0.17▪

**P < 0.05 indicates significant difference*

Table 2: Comparing the mean values of different hormonal assays in Wistar rats fed with standard diet and ketogenic diet

Parameters	Treatments	Control	9 Hours Starvation	18 Hours Starvation
Luteinizing hormone (ng/ml)	Standard Diet	2.323 ± 0.166	2.150 ± 0.27	2.200 ± 0.26
	Ketogenic Diet	1.880 ± 0.24	1.680 ± 0.076	1.388 ± 0.048
	P-values	0.178	0.146	0.022▪
Follicle stimulating hormone (ng/ml)	Standard Diet	2.953 ± 0.64	2.830 ± 0.25	3.255 ± 0.22
	Ketogenic Diet	2.685 ± 0.42	1.910 ± 0.11	1.715 ± 0.13
	P-values	0.738	0.015▪	0.000▪
Testosterone level (ng/ml)	Standard Diet	1.665 ± 0.45	1.275 ± 0.13	1.525 ± 0.41
	Ketogenic Diet	1.313 ± 0.21	0.980 ± 0.13	0.9650 ± 0.17
	P-values	0.499	0.160	0.250

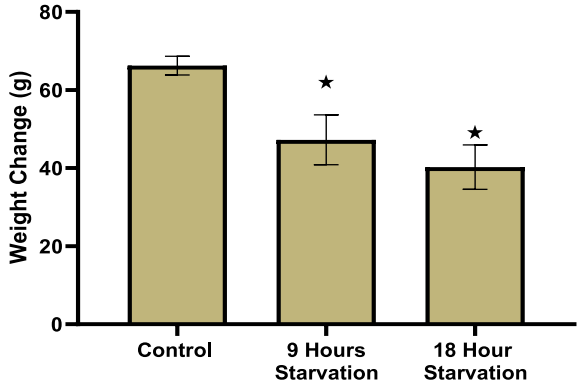

Figure 2: Effect of hours of starvation on the weight change of Wistar rats on ketogenic diets

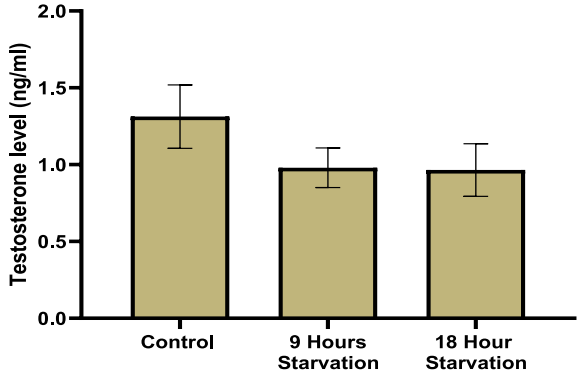

Figure 3: Effect of hours of starvation on the testosterone level of Wistar rats on ketogenic diets

There were no significant differences in 9 hours and 18 hours' starvation group compared with control.

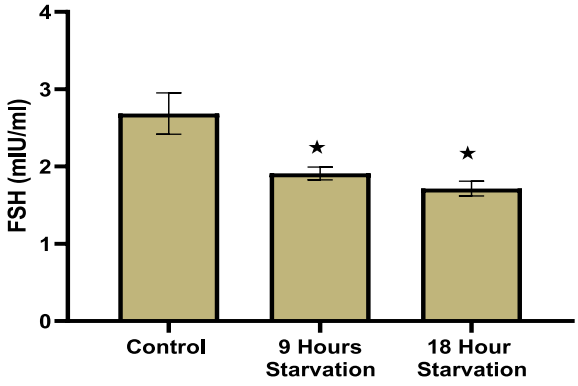

Figure 4: Effect of hours of starvation on FSH of Wistar rats on ketogenic diets

There were significant decreases in 9 hours and 18 hours starvation group compared with control, but there were no significant changes in 18 hours starvation compared with 9 hours starvation.

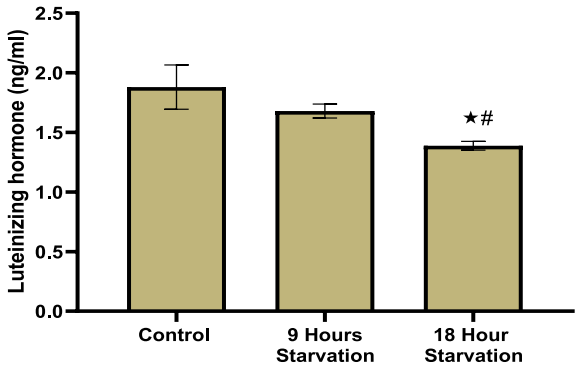

Figure 5: Effect of hours of starvation on LH in Wistar rats on ketogenic diets

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There was a significant decrease in 18 hours starvation compared with control and 9 hours starvation group, but there was no significant difference in 9 hours starvation compared with control.

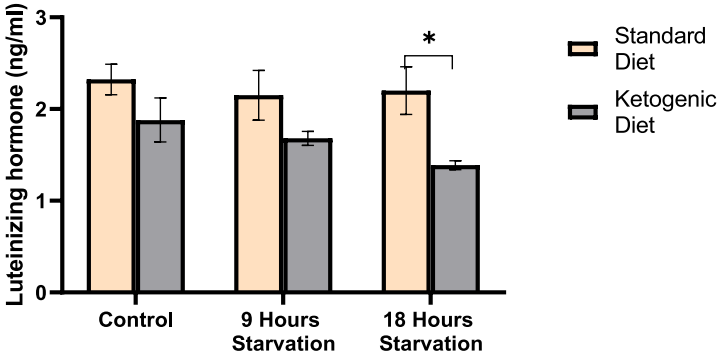

Figure 6: Effect of hours of starvation on the luteinizing hormone of Wistar rats on standard and ketogenic diets

There was a significant decrease in ketogenic diet group compared with the standard diet group at 18 hours' starvation, though there were no significant changes among group of ketogenic diet for control and 9 hours' starvation group compared with standard diet.

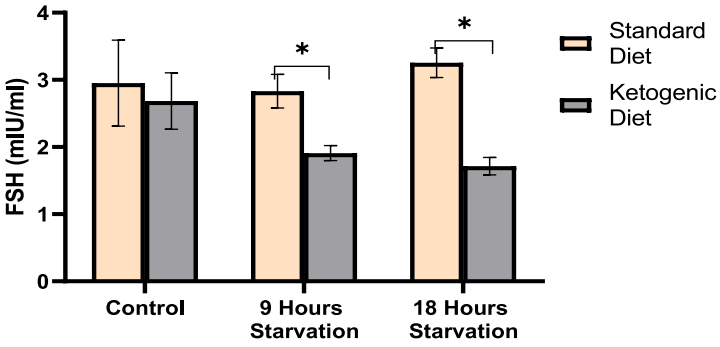

Figure 7: Effect of hours of starvation on the follicle-stimulating hormone of Wistar rats on standard and ketogenic diets

There were significant decreases in ketogenic diet group compared with standard diet group at 9 hours and 18 hours of starvation, though there was no significant change in the ketogenic diet group for control group compared with standard diet.

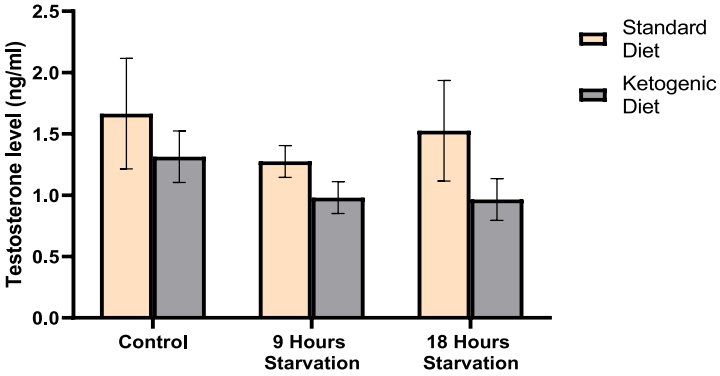

Figure 8: Effect of hours of starvation on the testosterone level of Wistar rats on standard and ketogenic diets

There were no significant changes in among group of the ketogenic diet for control, 9 hours, and 18 hours' starvation group compared with the standard diet.

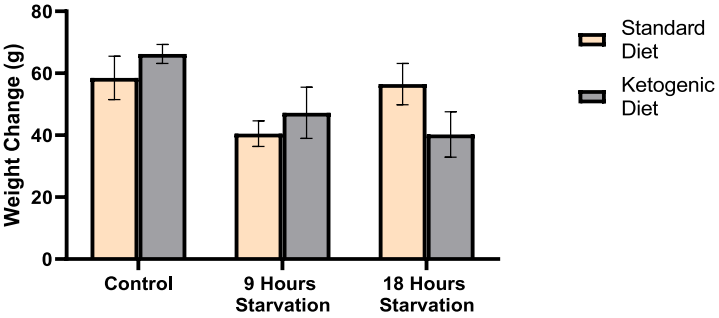

Figure 9: Effect of hours of starvation on the weight change of Wistar rats on standard and ketogenic diets

There were no significant changes in the group of ketogenic diet for control, 9 hours, and 18 hours' starvation group compared with the standard diet.

DISCUSSION

Body Weights in Wistar Rats Fed with Ketogenic Diet

There were significant decreases in the Body Weight Change of both the 9- and 18-hours starvation when compared with the Control in rats fed with Ketogenic diets. This shows that both prolonged starvation and high-fat (ketogenic) diet consumption contribute to the hypoglycemic effects of the rats' tissue and hence the significant loss of body weight, as it is the case with this study.

Mean Values of Body Weights in Wistar Rats fed with Standard Diet and Ketogenic Diet

The fact that there was no significant difference in mean Body Weights Change for the Control, the 9- and 18-hours starvation when the Standard diet was compared to the Ketogenic diet shows that both moderate and prolonged starvation have no significant effect on the mean Body Weights when rat fed with Standard diet were compared to those that were fed with Ketogenic diets. This is in contrast with the work of [17].whose findings revealed that rats treated with the ketogenic diet had a significant weight loss as a result of induced ketosis.

Hormonal Assays in Wistar Rats fed with Ketogenic Diet

Observation from the results of the present study shows that there is a unanimous decrease in the serum level of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testosterone (T) 42 days of intermittent starvation and feeding with ketogenic diets.LH and FSH are known as gonadotropins that attained stimulatory affinity with the Gonads, the male testes [18].

Testosterone acts on the Sertoli and peritubular cells of the seminiferous tubules and directly enhances spermatogenesis stimulation [19-21].In this light, both LH and FSH inhibit the gonads either from producing sperm or synthesizing a sufficient quantity of testosterone. FSH stimulates the various developmental phases from spermatogonia to spermatocytes and also maintains the spermatogenic processes, while both LH and FSH are necessary for meiotic development of the spermatids [22].Testosterone is necessary for meiosis and sperm development, in response to FSH [23-24].The significant decrease in serum LH in the group of 18 hours of intermittent starvation and ketogenic diet suggest that high-fat diet and prolonged starvation have inhibitory effects on the hypothalamic-pituitary-testicular axis. This will, in turn, lead to a concomitant decrease in Testosterone production by the Leydig Cell and hence a suppressive decrease in sperm cell maturation [25].

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Also, the significant decrease in serum FSH concentration in the 9 and 18hours- starved rats also portrays the inhibitory effect that the prolonged starvation and high-fat (ketogenic) diet exert on the hypothalamic-pituitary axis to decrease FSH secretion.
The decrements in the concentration of these gonadotrophic hormones suggest a direct inhibition of the anterior pituitary homogenesis. Testosterone is the major hormone of the gonads in males, produced by the Leydig cells in the testis. Also, in addition to LH and FSH, it is the major hormonal marker of androgenicity [26].The development and maintenance of male reproductive organs are also enhanced by testosterone [27-28].).In this study, although the testosterone of the starvation-induced stressed rats with the ketogenic diet is decreased but are not significant when compared with the control. The decrease in Testicular protein, cholesterol, and glycogen are not more marked [29].

CONCLUSION

Long-term starvation exerts appreciable decreases in the reproductive hormones, especially FSH and LH in starved rats fed with a ketogenic diet for a prolonged period of time. This study is among the first to successfully delve into investigations on starvation -induced stress, standard diet, ketogenic diet on reproductive function. Prolonged starvation exerts significant detriment on body weight, even though standard or ketogenic feeds were given without limitation after the starvation period. This was the case because although starved rats tend to eat more vigorously than their un-starved counterparts, nutrients lost during extensive starvation could not be completely recovered.

Conflict of Interest: None

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