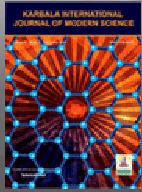

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Modulation of Hypothalamic–Limbic Circuits Regulating Appetite in Response to Health Lifestyle in Obese Adults

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Background: Overeating leads to obesity a low-grade inflammatory disease. In this context, aguati-related neuropeptide (AgRP) and ghrelin are pivotal players in appetite regulation, while chemerin is an adipose tissue-secreted adipokine that contributes to low-grade inflammation associated with obesity. **Objective:** This study used a healthy lifestyle program designed for each obese participant to identify diet-related neuro-hormonal changes in appetite regulation. **Design, Setting, and Participants:** This a longitudinal quasi-experimental controlled study was conducted from 1st December 2024, to 30th July 2025, at University of Anbar. The sample included 100 participants, 50 obese (weight between 100–140 kg) and 50 healthy participants with normal weight. All participants are between 20 and 40 years old. Obese participants underwent body composition assessment using the InBody device and undergoing a 6-month of healthy intervention. Measurements of each of the three variables: appetite-stimulating neuropeptide (AgRP), ghrelin, and chemerin, were performed for obese participants pre- and post-intervention, while these variables were measured for the healthy control group once. **Results:** Pre-intervention, obese participants showed lower concentrations of AgRP and ghrelin compared to healthy control, while chemerin was elevated. Post-intervention for 6-months, AgRP and ghrelin concentrations increased in obese participants but remained lower than normal levels, while chemerin levels decreased but remained higher than normal levels in healthy control. Significant correlations also emerged between the studied variables. Conclusion: Undergoing to a healthy lifestyle, combining a balanced diet and physical activity, rebalances the neural circuits regulating appetite and energy, providing a potential long-term strategy for managing obesity and improving metabolic health.

Keywords

Obesity; Gut-brain axis; AgRP; Ghrelin; Chemerin

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RESEARCH PAPER

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Conclusion: **Undergoing to a healthy lifestyle, combining a balanced diet and physical activity, rebalances the neural circuits regulating appetite and energy, providing a potential long-term strategy for managing obesity and improving metabolic health.**

Keywords: Obesity, Gut-brain axis, AgRP, Ghrelin, Chemerin

1. Introduction

Obesity considered one of the most notable global health challenges of the 21st century. In spite of the obesity is often defined as the result of an imbalance between energy intake and expenditure, recent evidence suggests that it is a complex neuro-metabolic disorder that goes beyond simple fat accumulation to include a dysfunction in the functional integration between the gastrointestinal tract, adipose tissue, and the central nervous system [1].

The gut-brain axis represents a bidirectional communication network linking gastrointestinal tract (GIT) and the central nervous system (CNS). This axis depends on neural and hormonal cues which includes gut-derived hormones and neuropeptides released by the HT, enabling a continuous interexchange of information regarding nutrient ingestion and the regulation of energy homeostasis [2].

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GIT is a dynamic sensory system that acts as a main interface between an individual and its internal and external environment, sensing a broad range of mechanical, chemical, microbial, and immunological stimuli, pathogens, and toxins. Thus, it contributes to regulating integrated responses aimed at keeping body homeostasis [3].

Enteroendocrine cells (EECs) are main sensors in this axis, lied along the intestinal epithelium and discovering nutrients, mechanical, and microbial stimulates by specialized receptors. When induced by nutrients, these cells produce and secrete intestinal hormones such as GLP-1, PYY, and CCK, which set appetite and the metabolic response following food intake [4]. Recent studies have detected that a specialized kind of these cells, renowned a neuropod cells, has the capability to connect directly with the vagus nerve by rapid cues similar to neurotransmitters as glutamate, providing an active channel for transferring input from the gut to the brain in near-instantaneous period [5].

Gut hormones appear appears to be a primary means of transmitting signals from the gastrointestinal tract to the brain centers responsible for regulating appetite, by what is known as the gut-brain axis. Such inputs can be transported to the CNS either by vagal or non-vagal afferent nerve signaling or straight by blood stream [6]. Neural networks distributed throughout the forebrain and brainstem control eating behaviors and maintain energy balance. In the HT, balance feeding behavior is unified. Herein, the arcuate nucleus (ARC), the paraventricular nucleus (PVN), the ventromedial nucleus (VMN), the dorsomedial nucleus (DMN), and the lateral hypothalamic area (LHA) play a key role in control of energy homoeostasis [7].

During fasting or starvation, the hormone ghrelin is secreted from the stomach, stimulating NPY/AgRP-producing neurons in the hypothalamus, which release peptides that enhance the feeling of hunger and activate eating behavior. After eating, enteroendocrine cells secrete peripheral satiety hormones, such as GLP-1 and PYY, which stimulate POMC/CART-producing neurons in the hypothalamus to secrete peptides that suppress appetite and promote feelings of fullness [8]. In addition, leptin, a hormone secreted from adipose tissue, promotes the same neural pathways in the hypothalamus, enhancing the effect of peripheral satiety hormones on inhibiting food intake and regulating energy balance [9].

Numerous scientific evidence proposes that consuming foods high in fat and sugar promotes activity in the dopamine reward pathways, alternating appetite control signs to favor increased food intake for longer times. This behavior resulting from the activation of the reward system is known as "reward-driven overeating" or "get back for more" where the desire to continue eating is stimulated despite the natural feeling of fullness [10]. With repeated exposure to high-calorie foods, there is a persistent overriding of normal hormonal signals of satiety, resulting in decreased neuronal sensitivity to GLP-1, PYY, and leptin, and increased influence of ghrelin and NPY/AgRP, which prolongs meal duration and gradually shifts the "set point" for energy balance and body weight (Fig. 1) [11].

So, assessing healthy lifestyle interventions is critical to understanding how to reprogram these

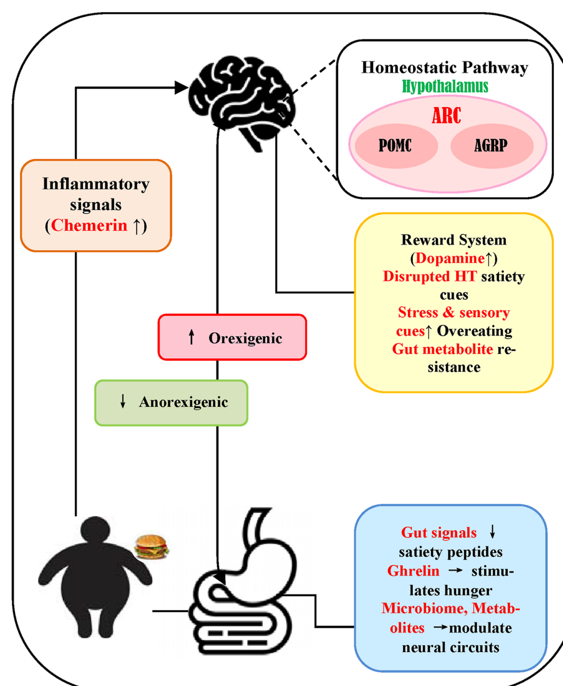


Fig. 1. A model of brain-gut interactions and systemic inflammation in appetite regulation when overindulging in palatable foods. This diagram illustrates how overeating affects the gut-brain axis. Hormonal signals secreted by the gut are transmitted to the brain via the vagus nerve and the bloodstream, where they encounter resistance from gut neurotransmitters. Disruption of the brain circuits responsible for appetite regulation, particularly in (ARC, leads to increased hunger and decreased satiety. In addition, systemic inflammatory signals (such as tyrosine) emanating from the gut, adipose tissue, liver, and immune cells contribute to this imbalance, leading to a vicious cycle of overeating and increased fat accumulation. The diagram also reflects the influence of the reward system (dopamine) and sensory and psychological signals that can override homeostatic control mechanisms. Up arrows: mean increase, down arrows: mean decrease. Abbreviation: ARC: the arcuate nucleus of the hypothalamus. POMC: Proopiomelanocortin, AgRP: Aguati-related peptide.

neuro-hormonal circuits and achieve a sustainable balance in the regulation of hunger and satiety.

This study aimed to evaluate the impact of six-month adherence to a healthy lifestyle on neuro-hormonal markers associated with appetite regulation in obese individuals, by measuring appetite peptides as ghrelin and AgRP. This study could help elucidate the underlying mechanisms behind restoring the stability of the gut-brain axis, which might pave the way for the improvement of more precise and effective therapeutic strategies in the future.

2. Material and methods

2.1. Study inclusion criteria

The study included adults (males and females) aged 20–40 years. Participants were classified as:

- Obese participants (BMI $\geq$30 kg/m^2) without associated chronic diseases or endocrine disorders, with mild insulin resistance and increased fasting insulin allowed.
- Healthy control with normal weight (BMI 18.5–24.9 kg/m^2) free from chronic diseases and endocrine disorders.
- Follow-up group: The same sample of obese participants who were re-evaluated after 6 months of adherence to a healthy lifestyle intervention that included healthy dietary modifications and regular exercise.

2.2. Study exclusion criteria

Those with: acute illnesses, renal/liver failure, uncontrolled endocrine disorders (as untreated hypo/hyperthyroidism), use of medications affecting appetite, recent weight loss surgery, pregnancy, individuals who taking hormonal supplements.

2.3. Body composition assessment

Body composition was assessed in obese participants at baseline using the InBody device, including body weight (BW), High (H), visceral fat (VF), body fat (BF), body fat percentage (BFP%), skeletal muscle mass (SMM), basal metabolism rate and (BMR). These measurements were used to characterize the sample and examine associations with the variables studied.

2.4. Study design

A longitudinal quasi-experimental controlled design was adopted to assess impact of a structured healthy lifestyle, including a balanced healthy diet and regular exercise, applied to obese participants in comparison with a healthy control group. The study involved three time points: (1) baseline measurements of the healthy control group (2) baseline measurements of the obese group pre-intervention, and (3) re-evaluation post-intervention in the same obese participants, to evaluate changes in appetite-related neuropeptides, immunity markers, and hormonal concentrations (Fig. 2). All procedures were performed in the university of Anbar laboratories.

2.5. Primary and secondary outcomes

Variables related to appetite regulation (ghrelin and AgRP) and the immune indicator chemerin were adopted as primary outcomes of the study. Secondary outcomes included body composition in obese participants at baseline, including BW, H, BF, BFP, VF, SMM, BMR, with their relationship to gender examined. All data were collected using reliable measurement tools and were statistically analyzed to assess differences and associations between variables.

2.6. Intervention

The study protocol included a 6-month program that included a healthy diet and regular exercise 3–5 days a week, aiming to promote weight loss

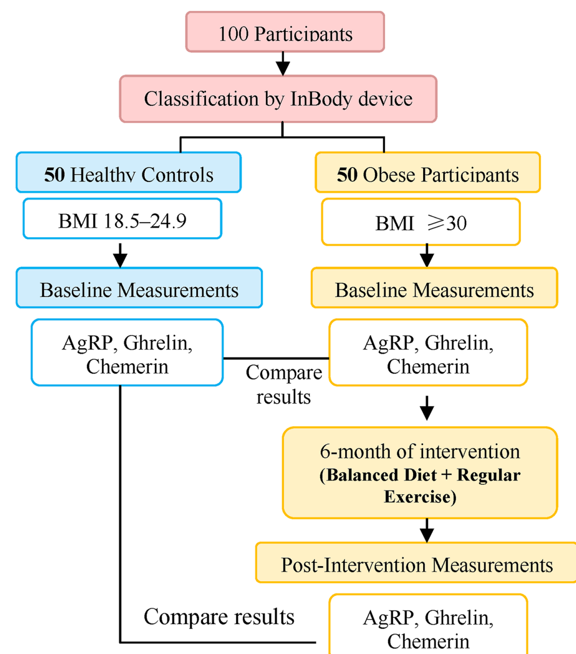


Fig. 2. Study flow chart.

and improve health indicators in obese participants. The protocol did not include any pharmacological interventions, surgical procedures, or fat-reducing techniques (as laser), but rather was restricted to dietary and lifestyle modifications. Very low-calorie diets (VLCDs) were excluded due to their likelihood of providing inadequate micronutrient intake, which may result in adverse health consequences. The diet was designed by a certified nutritionist, taking into account individual differences in body composition as determined by the InBody device, as well as each participant's specific nutritional needs. The diet was low-cost, easy to implement, and widely scalable without the need for advanced resources. For clarity, it has been summarized by the researcher in the visual schematic (Figs. 3 and 4).

2.7. Sample collection

Blood samples were collected from 50 normal weight and 50 obese (pre-intervention) participants after an overnight fast by vein puncture by using a sterile medical syringe. The blood samples were put down in a gel tube free of coagulants and left at the room temperature. Then, the samples underwent centrifugation process at 3500 rpm for 15 min. The serum samples for Aguati-related peptide, ghrelin, and chemerin concentrations tests were stored at 2–8 °C until was measured according to the manufacturer.

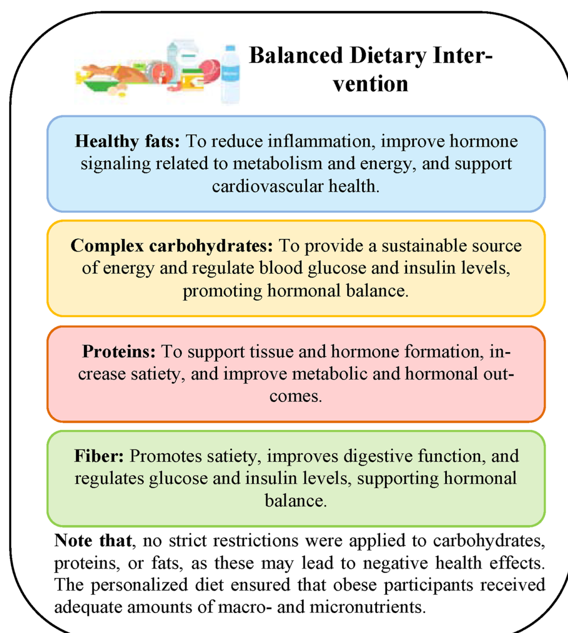


Fig. 3. The importance of different nutrients on hormonal balance.

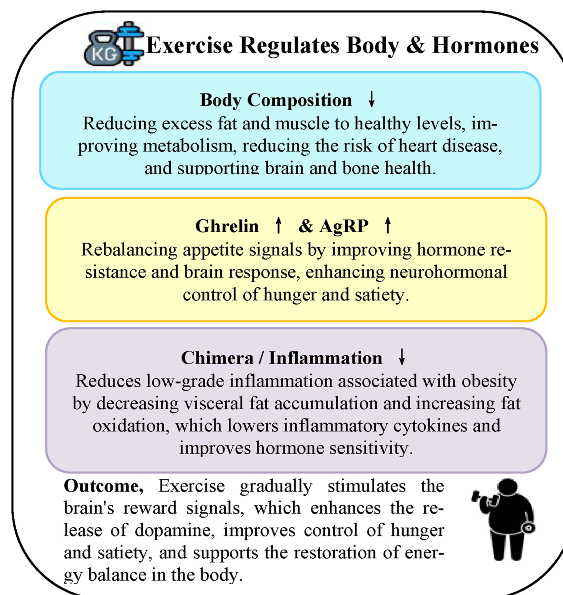


Fig. 4. The importance of exercise on body compositions and hormonal balance.

After six month of undergoing healthy lifestyle, blood samples were collected from obese participant. While, specimens from the normal weight participants were collected once.

2.8. Variable assessment

Serum concentrations of AgRP, ghrelin, and chemerin were determined using commercial ELISA kits according to the manufacturer's protocols. Specifically:

- AGRP concentration was determined by commercial Quick Step Human AGRP ELISA Kit from SunLong Biotech, China.
- Ghrelin concentration was measured using Human Ghrelin Sandwich ELISA kit from SunLong Biotech, China.
- Chemerin concentration was measured using FineTest Human Chemerin ELISA kit (Cat. No: EH0092), China.

2.9. Statistical analysis

Statistical analysis were performed using SPSS version 24 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 9 (GraphPad Software, San Diego, CA, USA). Data were presented as mean ± SD or for continuous variables. Comparisons among the three groups were assessed using one-way ANOVA followed by the Least Significant

Difference (LSD) post hoc test. Pearson's correlation analysis was used for correlation analysis between variables. Logistic regression was used to determine predictors of obesity status. Receiver operating characteristic (ROC) curve and area under the curve (AUC) analyses were applied for assess the discriminative ability of study variables between groups. Subgroup analyses were conducted according to age categories and sex. Statistical significance was set at p less than 0.05.

3. Results and discussion

Scientific evidence indicates that obesity arises as a result of the interaction between genetic factors, which determine the physiological and behavioral response to food, and recent environmental factors, such as the availability of high-calorie foods and a sedentary lifestyle, influence eating behavior and physical activity and thus determine energy balance and body weight [12].

3.1. Body compositions

Statistical analysis results showed a significant relationship between sex and the body composition means of obese participants pre-intervention ($P < 0.05$). Male had higher body weight (BW), high (H), skeletal muscle mass (SMM), and basal metabolism rate (BMR), while female had higher body fat (BF), body fat percentage (BFP%), and waist-to-hip ration (WHR). No significant differences were observed in VF between the sexes (Table 1, Fig. 5).

Table 1. Relation between body measurement with sex for obese participants.

Variables	Sex	Mean	Std. Deviation	p-value
Weight (kg)	Male	110.04	16.71	0.0001
	Female	95.52	12.61	
Length (cm)	Male	178.45	6.92	0.0001
	Female	161.25	7.22	
Body fat (kg)	Male	33.52	5.025	0.0001
	Female	40.55	7.286	
BFP%	Male	30.98	5.443	0.0001
	Female	37.76	7.713	
WHR	Male	0.934	0.163	0.231
	Female	1.172	1.519	
BMR (Kcal)	Male	2227.90	105.09	0.0001
	Female	1682.07	201.63	
Visceral fat (kg)	Male	13.526	5.329	0.523
	Female	14.159	3.997	
Skeletal Muscle (kg)	Male	34.87	2.318	0.0001
	Female	26.12	2.453	

*Significant differences (p-value less than 0.05), Abbreviation: BFP%: Body fat percentage, WHR: Waist to Hip ratio, BMR: Basal metabolism rate.

Marked sex differences in body composition indicate the influence of hormonal factors on tissue distribution. The higher SMM and BMR in males is explained by the stimulating effect of testosterone on muscle protein synthesis, while the BFP% and BF in females is associated to the impact of estrogen on promoting fat storage for metabolic and reproductive purposes. These results are consistent with the studies that suggests that males tend to have greater muscle mass, while females exhibit a higher propensity for fat accumulation, which is reflected in gender differences in energy metabolism and metabolic risk [13,14].

3.2. Appetite-stimulating neuropeptide

AgRP concentrations were low pre-intervention and increased at post-intervention, yet remained lower than normal levels (Table 2).

The Fig. 6 show the concentrations of AgRP in healthy control and obese group (pre- and post-intervention). Differences across groups were analyzed by one-way ANOVA follow by LSD post hoc test.

The results of the statistical analysis did not show a significant relationship between the age groups and mean concentrations of AgRP in obese participants pre-intervention ($P < 0.05$) (Fig. 7a).

In contrast, statistical analysis results presented a statistically significant relationship between gender and the mean concentrations of AgRP peptides in obese participants before the intervention ($P < 0.05$). Female recorded higher concentrations of AgRP than male (Fig. 7b).

The results showed that the AUC value of AgRP pre-intervention was 0.899, indicating high predictive power, while post-intervention it was 0.848, indicating continued strength in predicting weight and appetite changes (Fig. 8) (Tables 3 and 4).

AgRP acts as a MC4R inhibitor for stimulating food intake. Under normal physiological conditions, AgRP concentrations increased in response to low energy stores, and reduce when adequate energy is available in the body, thus acting as a fine regulator of energy homeostasis. However, the results of the current study recorded increased AgRP concentrations in obese participants, which might seem contradictory to the traditional function of this peptide in stimulating appetite [15].

Within the domain of neuronal and hormonal dynamics of energy regulation, which involves an complex network between peripheral signals and central neural circuits in the HT, this decrease in AgRP concentrations can be explained. In

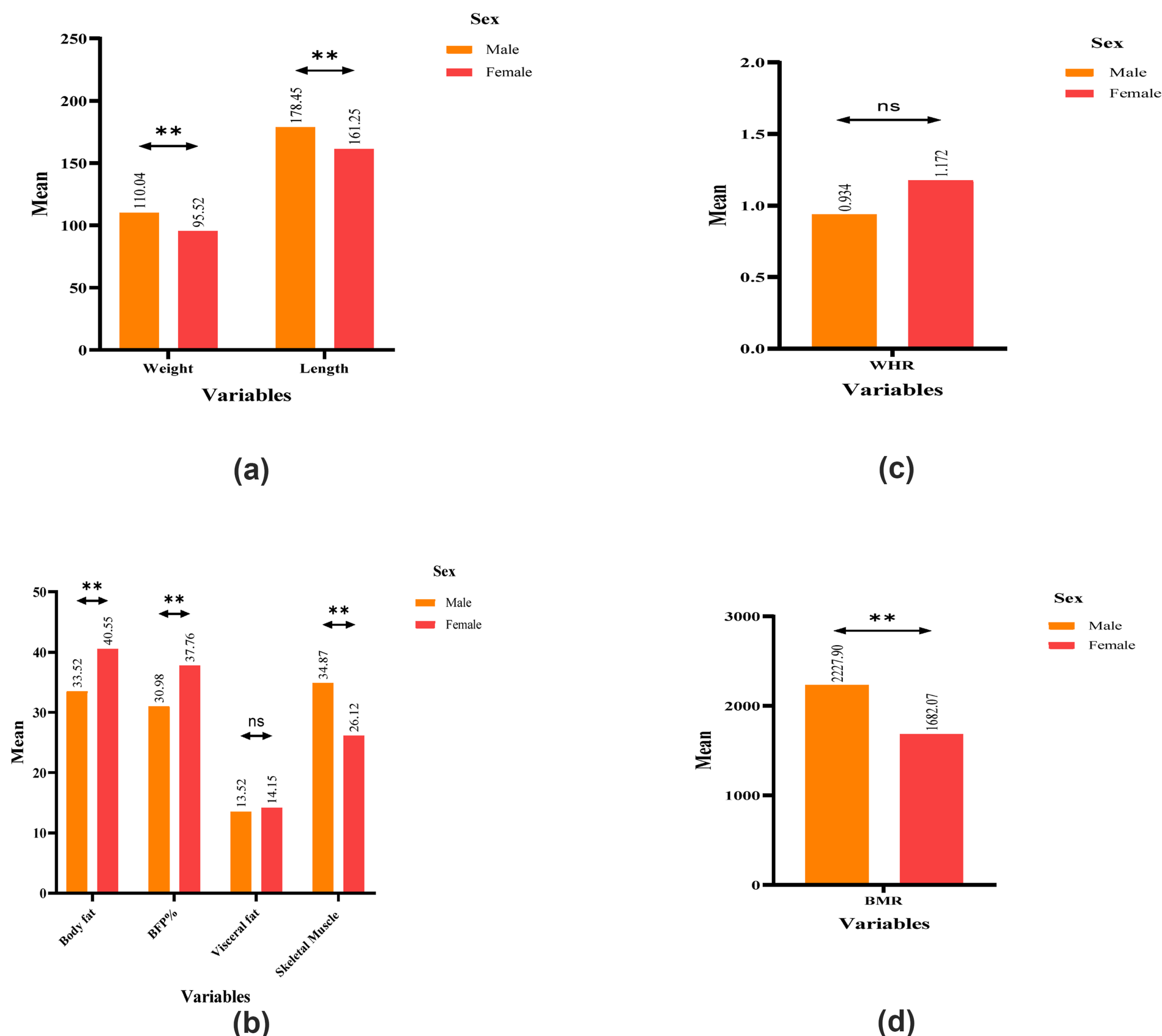


Fig. 5. a. Relation between sex and weight, and length in obese participants pre-intervention. b. Relation between sex and body fat, BFP%, visceral fat, and skeletal muscle in obese participants pre-intervention. c. Relation between sex and WHR in obese participants pre-intervention. d. Relation between sex and BMR in obese participants pre-intervention.

obesity, the persistent energy excess resulting from overeating, deactivate hunger cues via over-stimulating satiety hormones, as leptin and insulin. These hormones connect to their receptors on AgRP-producing neurons in the ARC, inhibiting their activity, so decreasing peptide secretion until in the presence of declined energy metabolism [16].

Table 2. Mean ± standard deviation of study variables in healthy controls, obese participants pre-intervention, and 6 months post-intervention.

Variables		Healthy Control (n = 50)	Obese group (n = 50)		F	p-value
			Post-intervention	Pre-intervention		
AgRP (ng/L)	Mean ± SD	34.78 ± 11.8 a	15.75 ± 4.41 b	19.34 ± 4.01 c	87.56	0.0001
	Min. − Max.	10.0–56.91	9.0–30.0	8.83–36.0		
Ghrelin (ng/ml)	Mean ± SD	46.3 ± 7.09 a	19.53 ± 7.53 b	25.61 ± 7.97 c	173.1	0.0001
	Min. − Max.	20.02–59.3	9.02–61.3	15.2–67.2		
Chemerin (Pg/ml)	Mean ± SD	187.2 ± 88.1 a	315.1 ± 81.9 b	234.4 ± 73.3 c	194.3	0.0001
	Min. − Max.	8.21–29.54	23.54–41.2	19.94–35.0		

*Significant differences (p-value less than 0.05), Abbreviation: a: control group, b: Obese group before, c: Obese group after, Different superscript letters (a, b, c) indicate statistically significant differences between groups, SD: Standard deviation, Min.: Minimum, Max.: Maximum, AgRP: Agouti-related peptide.

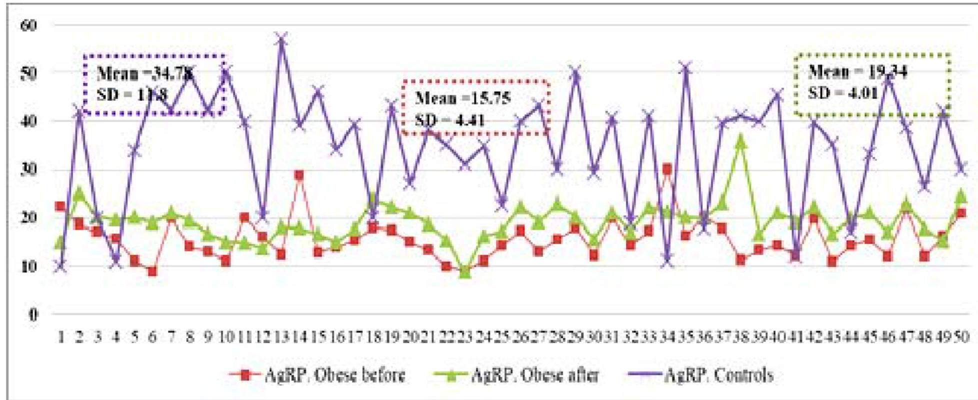
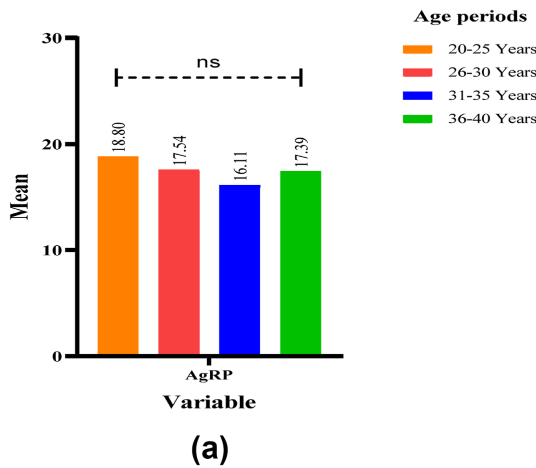


Fig. 6. Serum concentrations of AgRP healthy and obese participants, before and after the lifestyle intervention.

Functional resistance to ghrelin, the primary stimulator of AgRP secretion, plays an additional role in the decreased levels of this peptide. In chronic obesity, despite disturbances in energy sensing or a perceived sense of hunger, ghrelin's ability to stimulate AgRP cells is reduced, leading to decreased AgRP secretion. This referencing a disruption in neuro-hormonal communication between actual hunger sigs and central energy control cues, within the body's energy-execs environment. So, decreased AgRP does not refer complete appetite suppression, but rather reverberates a complex adaptive dysfunction in appetite and energy regulation paths, confirming that obesity is a



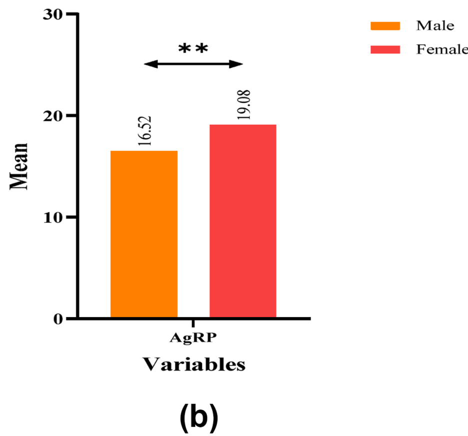
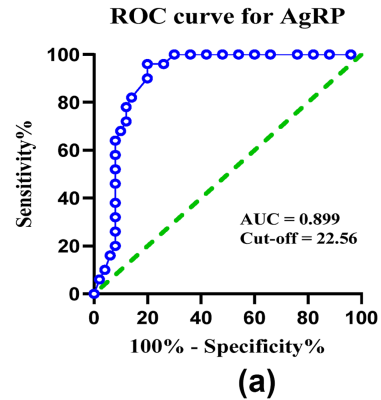


Fig. 7. a. Relation between AgRP and age periods in obese participants pre-intervention. b. Relation between AgRP and sex in obese participants pre-intervention.



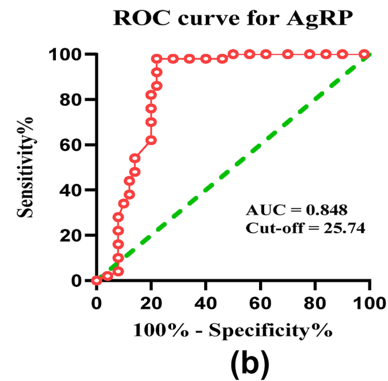


Fig. 8. a. ROC curves for AgRP in obese participants pre-intervention. b. ROC curves for AgRP in obese participants post-intervention.

Table 3. Area under curve (AUC) and ROC curve for study variables comparison between obese participants pre-intervention with control group.

Variables	AUC	Specificity %	Sensitivity %	Cut-off	p-value
Chemerin	0.855	80	94	226.13	0.0001
AgRP	0.899	96	80	22.565	0.0001
Ghrelin	0.973	98	94	35.215	0.0001

multi-level disturbance in central energy homeostasis, and not simply an increase in calorie intake [17].

The statistical results of the correlation analysis showed a strong, significant positive correlation between ghrelin and AgRP concentrations in the obese group pre-intervention ($r = 0.40$, $p < 0.002$). This correlation reflects the functional connection between ghrelin, which plays a key role in stimulating appetite, and AgRP, a neuropeptide in regulating energy intake, supporting the complementary role of these two factors in the neurohormonal of energy regulation.

In addition, HT inflammation and endoplasmic reticulum stress restrict the fast restoration of leptin/STAT3 sensitivity, whilst constant impairments in leptin transfer across the BBB by tanycytes, beside a slowly reversible epigenetic mark on the POMC promoter, further retard full normalization. So, a more gradual improvement would be expected with longer follow-up periods exceeding 6 months to achieve complete recovery [18].

Previous study in obese rodent models have shown that the metabolic interventions can dynamically change AgRP neurons activity. In the present study, AgRP concentrations increased slightly post-intervention, but stayed below healthy control values. This partial increases likely refers compensatory activation of AgRP neurons to return energy homeostasis, impacted by functional heterogeneity among neuron subgroups. As well as, the intrinsic orexigenic role of AgRP ensures sustained partial activity, highlighting the gradual and incomplete normalization of orexigenic cues post-intervention [19].

The increased AgRP concentrations in females compared to males are attributed to a complex interaction between estrogen signaling and the function of neural circuits in the ARC. Estrogen hormones link to estrogen receptor alpha (ERα) presented in the neurons surrounding AgRP/NPY neurons within the ARC. This connecting modulates the responsiveness of these neurons to peripheral signs (leptin and insulin) conveying the body's energy store and nutritional levels information, and also impacts the production and secretion of AgRP peptide. As a result, the activity of appetite-stimulating neural paths may increase under specific metabolic conditions [20].

Table 4. Area under curve (AUC) and ROC curve for study variables comparison between obese participants post-intervention with control group.

Variables	AUC	Specificity %	Sensitivity %	Cut-off	p-value
Chemerin	0.720	62	84	199.82	0.0001
AgRP	0.848	98	78	25.74	0.0001
Ghrelin	0.959	98	92	39.115	0.0001

Logistic analysis showed that AgRP was the utmost effective variable on health intervention response in obese participants, with elevated AgRP associated with lower probability of response (O.R = 0.755, $p = 0.012$). In contrast, Ghrelin showed a significantly smaller effect (O.R = 0.890, $p = 0.049$), while Chemerin was not significantly related with response ($p = 0.553$). These results point that appetite-regulating peptides play a greater role than inflammatory markers in predicting improved results post-intervention (Table 2).

3.3. Hormonal regulation of appetite

Ghrelin concentrations were low pre-intervention and increased at post-intervention, yet remained lower than normal levels (Table 2).

The Fig. 9 show the concentrations of ghrelin in healthy control and obese group (pre- and post-intervention). Differences across groups were analyzed by one-way ANOVA follow by LSD post hoc test.

The results of the statistical analysis did not show a significant relationship between the age groups (Fig. 10a)and sex with mean concentrations of ghrelin in obese participants pre-intervention ($P < 0.05$) (Fig. 10b).

The results showed that the AUC value of ghrelin pre-intervention was 0.973, indicating high predictive power, while post-intervention it was 0.959, indicating high predictive power, ghrelin also had the highest predictive power compared to studied variables (Fig. 11) (Tables 3 and 4).

The results of the current study confirm the findings of a previous study by Xin and his team, [21], which indicated lower ghrelin concentrations in obese adolescents. This decrease has been explained by a complex balance between factors that increase ghrelin secretion, such as low blood insulin concentration, and factors that reduce ghrelin concentration, such as hyperinsulinemia, increased glucose levels, insulin resistance, and obesity itself [22].

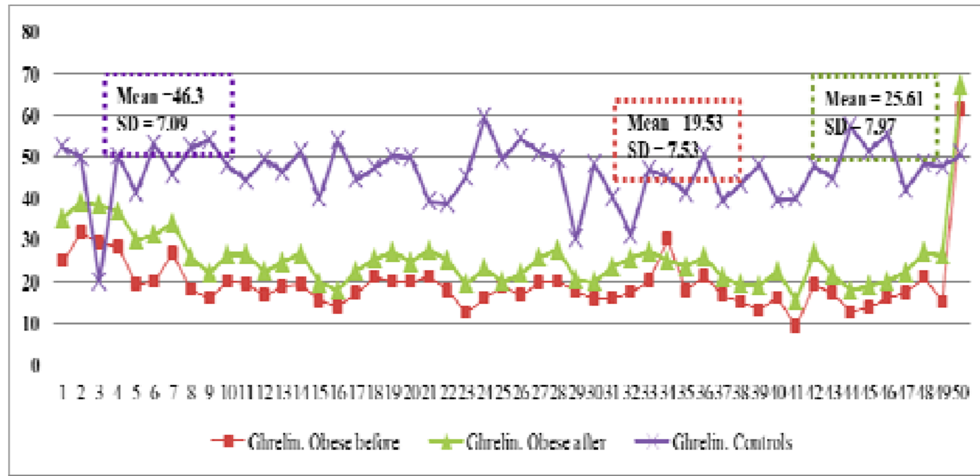
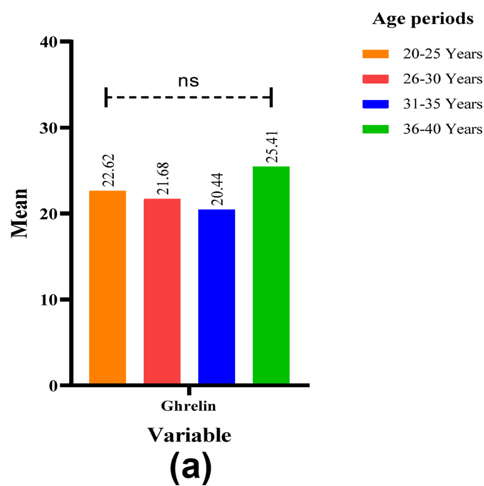


Fig. 9. Serum concentrations of ghrelin healthy and obese participants, before and after the lifestyle intervention.

Ghrelin, secreted primarily from X/A cells in the stomach fundus, stimulates appetite by activating AgRP/NPY cells and inhibiting POMC neurons in ARC [23]. In obesity, chronic overfeeding and increased leptin and insulin concentrations suppress ghrelin secretion and decrease the sensitivity of its GHS-R in the ARC and VTA, reflecting a case of neural resistance to ghrelin [24].



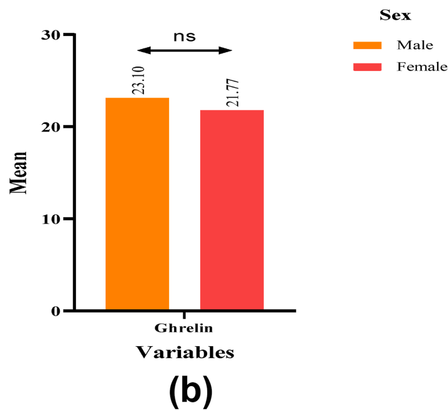
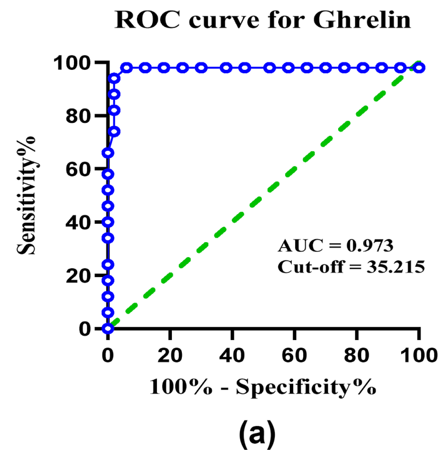


Fig. 10. a. Relation between ghrelin and age periods in obese participants pre-intervention. b. Relation between ghrelin and sex in obese participants pre-intervention.



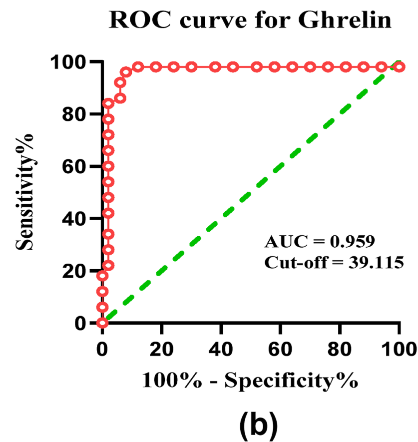


Fig. 11. a. ROC curves for ghrelin in obese participants pre-intervention. b. ROC curves for ghrelin in obese participants post-intervention.

The results of the statistical analysis showed a strong positive correlation between ghrelin and AgRP pre-intervention ($r = 0.40$, $p = 0.002$), reflecting that any relative variability in ghrelin is associated to the functional activity of AgRP/NPY neurons, which signals the continued integration between peripheral and neural cusses, even in the presence of low concentrations of these two indicators [25].

The observed increase in ghrelin after intervention in the current study is consistent with the known pattern of hormonal adaptation in non-surgical weight loss. Scientific evidence shows that energy restriction and weight loss increase total ghrelin as a compensatory response to hunger, as observed in studies of dietary-induced weight loss and in recent meta-analyses of healthy diet and physical activity interventions. These results reflect a partial improvement in the regulation of hunger signals via the gut-brain axis without significant hormonal disruption [26].

The results of bariatric surgery studies, specially sleeve gastrectomy (SG) and gastric bypass (RYGB), are inconsistent with the current study. SG shows a sharp decline in ghrelin post-fundoplication, while RYGB shows biphasic pattern with a short-term characterized by decrease followed by a relative increase [27]. In current study, lifestyle intervention and fat loss lead to an increase in ghrelin, which remains below normal. This rise is attributed to a normal physiological adaptive response to non-surgical weight loss.

3.4. *Inflammation indicator*

Chemerin concentrations were high pre-intervention and increased at post-intervention, yet remained higher than normal levels (Table 2).

The Fig. 12 show the concentrations of chemerin in healthy control and obese group (pre- and post-intervention). Differences across groups were analyzed by one-way ANOVA follow by LSD post hoc test.

The results of the statistical analysis did not show a significant relationship between the age groups and mean concentrations of chemerin in obese participants pre-intervention ($P < 0.05$) (Fig. 13-a). In contrast, statistical analysis results presented a statistically significant relationship between gender and the mean concentrations of chemerin in obese participants before the intervention ($P < 0.05$). Female recorded higher concentrations of chemerin than male (Fig. 13-b).

The results showed that the AUC value of chemerin pre-intervention was 0.855, indicating high predictive power, while post-intervention it was 0.720, reflecting the continued predictive power of chemerin as an indicator of low-grade inflammation in participants with obesity (Fig. 14) (Tables 3 and 4).

The significantly elevated chemerin concentration in the serum of obese individuals may be attributed to the expansion of white adipocytes, which are the main source of this adipokine. The hyperplasia of white adipocytes is joined by the partial cleavage of some of their precursors, which increases the total mass of adipose tissue and thus leads to the activation of intracellular inflammatory pathways, especially NF-κB and STAT3, which are the main drivers of chemerin production and accumulation in blood [28].

The results of present study are consistent with previous studies, where Zhang et al. [29], showed an relationships between BMI and chemerin, while Aravindraj et al. [30] focused on VF and BMI. In contrast, the current study showed that chemerin was more strongly associated with BF, BFP ($r = 0.65$,

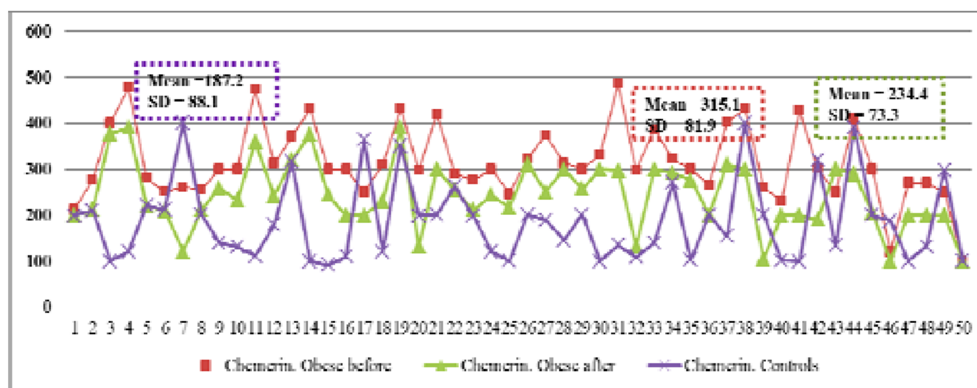


Fig. 12. Serum concentrations of chemerin healthy and obese participants, before and after the lifestyle intervention.

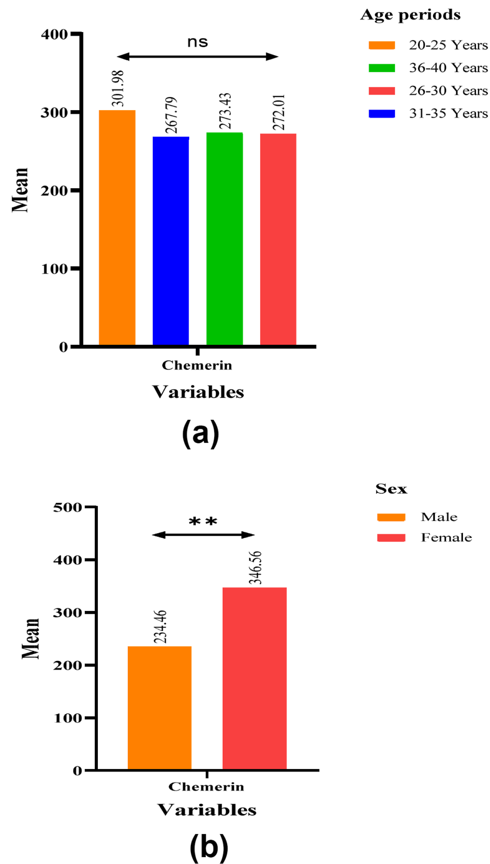


Fig. 13. a. Relation between chemerin and age period in obese participants pre-intervention. b. Relation between chemerin and sex in obese participants pre-intervention.

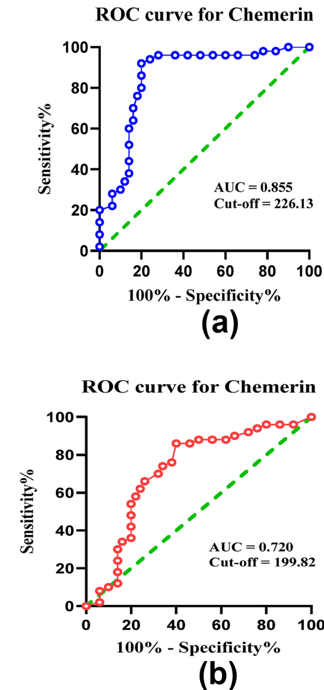


Fig. 14. a. ROC curves for chemerin in obese participants pre-intervention. b. ROC curves for chemerin in obese participants post-intervention.

$p = 0.0001$; 0.68, $p = 0.0001$) respectively, suggesting that the amount of fat itself plays a direct role in determining the secretion of this adipokine. On the other hand, the current study showed a negative correlation between muscle mass and chemerin concentrations ($r = -0.756$, $p = 0.0001$), indicating that muscles may play an opposite role in regulating the inflammatory environment associated with obesity.

After the intervention, the results of the present study showed a decrease in chemerin concentrations in obese individuals. These results are consistent with previous study, where it was found that weight loss resulting from Roux-en-Y Gastric Bypass (RYGB) and following low calorie-formula diet led to a clear decrease in chemerin levels in obese individuals. The study includes 128 obese patients, showed a significant decrease in chemerin levels after 12 months of weight loss, whether through surgical intervention or through a conservative program based on a low-calorie diet (LCD), with the decrease being more pronounced in the RYGB group [31,32].

In contrast, a recent study by Erdem et al. [33] showed that following a low-fat diet for 12 weeks did not lead to a significant decrease in chemerin, despite improvements in other inflammatory markers. These differences between studies reflect that the response of chemerin to weight loss may be influenced by sample characteristics, duration of follow-up, and severity of change in BMI, highlighting the need for additional longitudinal studies to determine whether its decrease represents a direct response to weight loss or is related to other metabolic factors.

The findings of the current study, which revealed higher chemerin concentrations in female, are consistent with previous literature indicating that women have higher total body fat than men. Studies have suggested that this difference is associated with higher circulating levels of chemerin, with adipose tissue showing higher expression of chemerin mRNA in women compared to men [34]. For example, the Chemerin Gene Expression study found that chemerin mRNA levels in subcutaneous tissue were higher in female than in male, compared to visceral tissue [35]. Furthermore, review studies have noted that female sex hormones, particularly estrogen, influence adipocyte function and regulate the secretion of adipokines as chemerin [36].

Table 5. Logistic regression analysis for obese patients before as a dependent variable and obese patients after intervention toward the research parameters.

Variable	Coefficient (B)	P value	O.R	95 % CI
AgRP (ng/L)	−0.281	0.012	0.755	0.606−0.941
Ghrelin (ng/ml)	−0.116	0.049	0.890	0.793−0.999
Chemerin (pg/mL)	−0.004	0.553	0.996	0.984−1.008

Also, higher circulating chemerin values have been observed in female in several clinical populations, such as patients with hypertension and type 2 cervical cancer [37]. Although the strength of the effect varies between studies, the trend toward female prevalence remains after adjusting for some confounding factors [38].

Logistic regression analysis was performed on all variables under study to determine which were most strongly associated with obesity status pre- and post-intervention (Table 5). The analysis showed that both AgRP and ghrelin were significantly associated with obesity status, as the negative values of the regression coefficient (B) showed an inverse relationship between their levels and the probability of obesity, indicating that higher concentrations are associated with a lower risk of obesity. In contrast, chimerines showed little to no significant correlation, suggesting that their effect on the statistical model was limited. These results confirm the modulatory role of both AgRP and ghrelin in regulating appetite and weight, and highlight their remarkable response to changes resulting from adopting a healthy lifestyle.

4. Conclusion

The current study results show that 6-months of a healthy lifestyle in obese adults resulted in effective modification of the hypothalamic-limbic circuits responsible for appetite regulation and energy homeostasis, with significant increases in AgRP and ghrelin concentrations and a slight improvement in chemerin as adipokine. These results support the idea that lifestyle interventions can reorganize the neuro-hormonal balance in patients with obesity, emphasizing the importance of combining proper nutrition and physical activity as the basis of any sustainable treatment strategy.

Ethics information

The study was approved by the Institutional Ethics Committee at University of Anbar (Approval No. 223, Date 24/2/2024). Written informed consents were signed by all participants. All procedures done in accordance with the international ethical standards for research including human participants. The study was done in accordance with Declaration of Helsinki.

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Conflicts of interest

The author declare that they have no competing interests.

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