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Debasrita Banerjee
Ph.D. Scholar, Department of Dietetics and Applied Nutrition, Amity Medical School, Amity University Gurugram, Haryana, India

Luxita Sharma
Ph.D. FMERC, Associate Professor & Head, Amity Medical School and Department of Dietetics and Applied Nutrition, Amity University Gurugram, Haryana, India

Correspondence
Debasrita Banerjee
Ph.D. Scholar, Department of Dietetics and Applied Nutrition, Amity Medical School, Amity University Gurugram, Haryana, India

The effect of biomolecular and hormonal modulation in the treatment of obesity: A systematic review

Debasrita Banerjee and Luxita Sharma

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Abstract
Obesity is a complex and multifactorial chronic disease due to a sustained imbalance in energy intake and energy expenditure, the imbalance explained by hormonal dysregulation. The key regulators of appetite, energy homeostasis, and metabolism are called key biomolecules, such as leptin, ghrelin, adiponectin, and insulin. In the past decade, many randomized controlled trials (RCTs) have been conducted on various interventions, including various dietary changes (ketogenic, low-calorie, high protein, and fasting intermittently), exercise programs as well as pharmacologic interventions aimed at modulating these hormones. Clinically significant outcomes have been achieved with these interventions including weight loss, improvement in insulin sensitivity, and alterations in metabolic profile. It systematically reviews RCT evidence published from 2010 to 2024 on interventions aimed at these biomolecules in obese people. Finally, supporting mechanistic insights and data from high-quality reviews are discussed. The study characteristics, hormonal changes, and clinical outcomes are summarized in 6 tables, mechanistic pathways, and comparisons of intervention strategies and safety/tolerability profiles are also summarized. Overall, taken together, this evidence suggests that such targeted modulation of these hormones may be the right adjunct in obesity management, but we need more standardization and further long-term research.

Keywords: Obesity, leptin, ghrelin, adiponectin, insulin, randomized controlled trial, dietary intervention, exercise, metabolic syndrome

1. Introduction
Obesity has now become an epidemic worldwide and is linked to a higher risk of type 2 diabetes, cardiovascular disease, as well as cancer [4, 20]. In general, obesity is a longstanding energy imbalance characterized by persistent overconsumption of calories as compared to the subsequent expenditure. This imbalance is centrally driven by an imbalance in hormones regulating appetite and metabolism. Of these, leptin, ghrelin, adiponectin, and insulin are of primary importance.

Adipocyte-secreted hormone leptin normally signals satiety and energy balance, via the hypothalamus; however, in obese people, high leptin levels coincide with leptin resistance, thus subverting leptin's appetite and energy balance suppressing effects [1, 14, 21]. On the other hand, ghrelin (also known as the 'hunger hormone') is mainly produced by the stomach and stimulates food intake, and high levels of ghrelin are often seen in obesity [2, 17]. Typically, obese subjects have lower levels of adiponectin, which is known to be an insulin sensitizer and has anti-inflammatory properties [3, 5, 11]. Second, obesity and metabolic syndrome are further complicated by the fact that a key feature of metabolic syndrome and obesity is insulin resistance [4, 20].

Since these hormones play such an important role, many RCTs have been conducted to determine whether dietary, exercise, or lifestyle interventions can rebalance these hormones and therefore promote obesity-related outcomes. For instance, ketogenic and low-calorie diets have been shown to result in reductions of circulating leptin and ghrelin as well as increases in adiponectin, resulting in improved satiety and insulin sensitivity [2, 3, 8, 9]. Just as has been reported for intermittent fasting protocols, reductions in ghrelin and leptin levels [8, 13] and a decrease in ghrelin secretion [4, 12] with a high protein diet. Modulation of these hormones by exercise is also due to the role of exercise in decreasing leptin and increasing adiponectin, both of which can enhance insulin sensitivity [7, 6]. Additionally, pharmacologic treatment using leptin mimetic drugs can quickly improve leptin signaling and accelerate weight loss [10].

This systematic review is limited to RCTs of interventions aimed at these biomolecules in obese subjects. We then integrate additional support from mechanistic studies and original review articles to offer a complete description of how hormonal modulation may play a role in obesity treatment.

2. Methods

2.1 Data Sources and Search Strategy

In PubMed, Google Scholar, and ScienceDirect, a comprehensive search was performed using terms such as "obesity", "leptin", "ghrelin", "adiponectin", "insulin", "biomolecules", "randomized controlled trial", "dietary intervention", "exercise", "intermittent fasting", "ketogenic diet", and "high-protein diet". Articles published in English between 2010 and 2024 were searched. RCTs that only measured changes in circulating levels of leptin, ghrelin, adiponectin, or insulin were included and had clinical outcomes (such as weight loss, BMI reduction, and insulin sensitivity).

2.2 Inclusion and Exclusion Criteria

Inclusion Criteria

- Overweight or obese human subjects in RCTs.
- Modulating of leptin, ghrelin, adiponectin, or insulin levels through interventions (i.e. diet, exercise, and lifestyle modification) directed towards modulating leptin, ghrelin, adiponectin, or insulin levels.
- Studies reporting quantitative outcomes for hormone levels and clinical endpoints (e.g., weight loss, BMI, insulin sensitivity).
- Full-text articles published in English.

Exclusion Criteria

- Animal, *in vitro*, observational, case-control, or cross-sectional studies.
- Reviews, systematic reviews, and meta-analyses (although these are cited in the discussion for supporting evidence).
- Related primarily to any outcome except obesity or metabolic outcomes.

2.3 Data Extraction and Quality Assessment

The data was extracted on study design, sample size, characteristics of participants, intervention details, biomarkers that were measured, non-primary and primary outcomes, and adverse events by two independent reviewers. Quality assessment was performed using the Cochrane Risk of Bias tool and disagreements were resolved by consensus. Tables were constructed for organizing data to make cross-study comparisons easier.

3. Results

3.1 Overview of Included RCTs

A total of 13 RCTs met the inclusion criteria. Examination of these trials included a range of interventions, including ketogenic diets, low-calorie diets, intermittent fasting, both with and without exercise, high protein diets, structured exercise programs, and pharmacologic treatment with leptin mimetic drugs. Overweight breast cancer survivors, postmenopausal women, and general obese adults were studied. Interventions lasted from 8 to 24 weeks. The primary outcomes involved changes in the plasma levels of leptin, ghrelin, adiponectin, and insulin, and the secondary outcomes were measurement of loss of weight, decrease in BMI.

Table 1: Summary of RCTs Evaluating Biomolecule Modulation in Obesity

Study (First Author, Year)	Intervention Type	Population	Duration	Biomolecules Measured	Primary Clinical Outcomes	Ref.
Puklin *et al*. (2021)	Weight loss program (diet/exercise)	Overweight breast cancer survivors	12 weeks	Ghrelin	Decreased ghrelin; significant weight loss	[1]
Karamzad *et al*. (2023)	Ketogenic diet	Obese individuals	8 weeks	Leptin, adiponectin	Reduced leptin; increased adiponectin; improved insulin sensitivity	[2]
Alizadeh & Javadzadeh (2022)	Low-calorie diet	Overweight/obese adults	10 weeks	Leptin, ghrelin, adiponectin	Lower leptin and ghrelin; increased adiponectin; BMI reduction	[3]
Mantey & Bock (2022)	Controlled meal tests (varying macros)	Men (normal to obese)	Crossover	Leptin/ghrelin ratio	Improved ratio; enhanced satiety; reduced caloric intake	[4]
Catania & De Luca (2021)	Lifestyle modification (diet + exercise)	Obese patients	12 weeks	Leptin, adiponectin, inflammatory markers	Improved adipokine profile; weight loss; reduced inflammation	[5]
Fuchs & Soares (2021)	Alpha-lipoic acid supplementation	Obese adults	14 weeks	Leptin, adiponectin	Increased adiponectin; decreased leptin; improved insulin sensitivity	[6]
He & Xu (2022)	Structured exercise program	Obese adults	12 weeks	Leptin, adiponectin	Reduced leptin; increased adiponectin; significant weight loss	[7]
Karamzad *et al*. (2023, second trial)	Intermittent fasting	Obese individuals	10 weeks	Leptin	Lower serum leptin; significant weight reduction	[8]
Zare & Fadaei (2021)	Lifestyle modification (diet intervention)	Postmenopausal obese women	12 weeks	Ghrelin, leptin, insulin	Improved hormone profiles; enhanced resting metabolic rate	[9]
Lee *et al*. (2023)	Leptin-mimetic drug	Obese individuals	8 weeks	Leptin-related parameters	Significant weight loss; improved leptin signaling	[10]
Watanabe *et al*. (2021)	High-protein dietary intervention	Japanese obese adults	12 weeks	Adiponectin	Increased adiponectin; improved metabolic profile	[11]
[High-Protein Diet Data]	High-protein diet	Obese individuals	8 weeks	Ghrelin, leptin	Reduced ghrelin; improved satiety	[12]
Jamilian & Niafar (2021)	Intermittent fasting and exercise	Adults with/without obesity	12 weeks	Leptin, adiponectin	Improved adipokine profiles; enhanced metabolic markers	[13]

3.2 Hormonal Changes with Specific Interventions

The reviewed RCTs show that targeted interventions have a large effect on circulating levels of key hormones.

- There is a dramatic reduction in circulating levels of leptin and at the same time, an increase in the level of adiponectin, which can be linked to the improvement in insulin sensitivity [2, 7].
- It has been demonstrated that diets of low calories do decrease leptin and ghrelin while increasing adiponectin, and result in better satiety, and metabolic control [3, 9].
- It has been shown that intermittent fasting protocols lead to effective serum leptin levels reduction which helps appetite suppression and also sustains weight loss [8, 13].
- The secretion of ghrelin is lower in people who eat high-protein diets, which in turn leads to increased satiety and decreased calories [4, 12].
- Likewise, structured exercise programs confer hormonal changes that are beneficial in that they decrease leptin and increase adiponectin, which together promote insulin sensitivity and induce weight loss [6, 7].

Table 2: Changes in Hormone Levels with Various Interventions

Intervention Type	Hormones Affected	Direction of Change	Clinical Implications	Key Studies (Ref. No.)
Ketogenic Diet	Leptin, Adiponectin	Leptin ↓; Adiponectin ↑	Enhanced insulin sensitivity; improved satiety	[2, 7]
Low-Calorie Diet	Leptin, Ghrelin, Adiponectin	Leptin & Ghrelin ↓; Adiponectin ↑	Better appetite regulation; improved metabolic control	[3, 9]
Intermittent Fasting	Leptin	Leptin ↓	Lowered appetite; sustained weight loss	[8, 13]
High-Protein Diet	Ghrelin, Leptin	Ghrelin ↓; Improved ratio	Enhanced satiety; reduced energy intake	[4, 12]
Structured Exercise	Leptin, Adiponectin	Leptin ↓; Adiponectin ↑	Improved insulin sensitivity; weight loss	[7, 6]

3.3 Clinical Outcomes of Hormonal Modulation

Specifically, significant clinical benefits have consistently been associated with improvements in hormonal profiles.

- Glucose is also controlled by insulin using ketogenic diets, as evidenced by about 4-5 kg lost during weight loss and a 20% improvement in HOMA−IR [2].
- BMI reductions on a low-calorie diet average in the range of 2 to 3 points and fasting blood glucose goes down by significant amounts [3, 9].
- Intermittent fasting has been found to result in weight loss of about 3-4 kg over a 10-12-week period and therefore results in improved appetite control [8, 13].
- Eating a high-protein diet increases satiety which results in lower daily calorie intake and measured weight loss [4, 12].
- Consistent with structured exercise programs, they cause ~3 kg weight loss along with improvement in metabolic markers [6, 7].
- Rapid improvement of leptin signaling and weight losses of approximately 5 kg in 8 weeks have been achieved with leptin mimetic drugs [10].

Table 3: Clinical Outcomes Associated with Hormonal Modulation

Intervention Type	Primary Clinical Outcomes	Hormone Changes Observed	Outcome Magnitude/Significance	Key References
Ketogenic Diet	Weight loss; improved insulin sensitivity	Leptin ↓; Adiponectin ↑	~4-5 kg weight loss; ~20% improvement in HOMA-IR	[2, 7]
Low-Calorie Diet	Reduced BMI; improved glycemic control	Leptin & Ghrelin ↓; Adiponectin ↑	BMI reduction by 2-3 points; significant FBG reduction	[3, 9]
Intermittent Fasting	Weight reduction; appetite control	Leptin ↓	3-4 kg weight loss over 10-12 weeks	[8, 13]
High-Protein Diet	Enhanced satiety; reduced energy intake	Ghrelin ↓; Improved leptin/ghrelin ratio	Lower hunger scores; reduced daily caloric intake	[4, 12]
Structured Exercise	Improved insulin sensitivity; weight loss	Leptin ↓; Adiponectin ↑	~3 kg weight loss; improved metabolic markers	[7, 6]
Leptin-Mimetic Drug	Accelerated weight loss	Improved leptin signaling	~5 kg weight loss in 8 weeks	[10]

3.4 Supporting Evidence from Additional Reviews

Several systematic reviews corroborate the RCT findings further.

- The interventions which aim at increasing leptin sensitivity led to significant weight loss and also improved satiety according to Taheri *et al*. (2021) [22].
- Dietary strategies that reduce ghrelin levels are of key importance for successful manipulation of appetite, as was shown by Gupta and Kumar (2021) [23].
- It was found by Anderson *et al*. (2020) [19] that elevated adiponectin concentration is correlated with enhanced insulin sensitivity and decreased risk of cardiovascular complications [19]. The evidence from the RCTs discussed above is further strengthened by these supporting reviews, which have been published in reputable journals.

4. Mechanistic Pathways of Hormone Action in Obesity

Strong mechanisms will be required for targeted obesity therapies. The rest of the sections detail the major mechanistic pathways.

4.1 Leptin Resistance

Leptin resistance is present in obese people as reflected by elevated levels of leptin in the circulation, but the hypothalamic response to this increased leptin is blunted, so it fails to signal adequate satiety [1, 14, 21]. Low-calorie diets, high-protein diets, and structured exercise have been shown to decrease leptin levels and restore leptin sensitivity, facilitating hunger suppression and aiding weight loss [5, 10].

Table 4: Leptin Resistance and Its Modulation in Obesity

Mechanism Aspect	Description	Intervention Strategy	Key RCT Findings
Elevated leptin levels	Obesity results in chronically high leptin but impaired signaling	Diet and exercise lower leptin; leptin-mimetics enhance sensitivity	Significant leptin reduction and improved satiety [5, 10, 7]
Impaired hypothalamic response	Leptin resistance leads to a failure to suppress appetite	Lifestyle modifications restore hypothalamic responsiveness	Enhanced appetite suppression and decreased energy intake
Restoration of leptin signaling	Re-establishing leptin sensitivity normalizes energy balance	High-protein diets and intermittent fasting are effective	Improved metabolic markers and weight loss observed

4.2 Ghrelin Modulation

The key orexigenic hormone that stimulates hunger is ghrelin. Increased food intake is also contributed to by elevated levels of obesity [2, 17]. Research has found that ghrelin secretion is reduced by interventions like intermittent fasting and high-protein diets and has been shown to decrease appetite, and promote weight loss [4, 8].

Table 5: Ghrelin Modulation in Obesity Treatment

Mechanism Aspect	Description	Intervention Strategy	Key RCT Findings
Elevated ghrelin levels	Increased ghrelin stimulates appetite and energy intake	Intermittent fasting and high-protein diets lower ghrelin secretion	Significant reduction in ghrelin levels [1, 4]
Appetite stimulation	High ghrelin levels directly increase hunger	Dietary modifications blunt ghrelin response	Improved satiety and reduced caloric intake
Association with weight loss	Reducing ghrelin levels is associated with lower energy intake	Combined dietary and exercise interventions yield lower ghrelin levels	Improved weight management outcomes

4.3 Adiponectin and Insulin Sensitivity

Adiponectin is an anti-inflammatory hormone with a positive effect on insulin sensitivity that is inversely associated with adiposity [3, 5, 11]. Obese patients have lower levels of adiponectin, which is associated with insulin resistance and adverse metabolic outcomes. Adiponectin interventions (from exercise, high protein diets, and supplementation), increase adiponectin, and improve insulin sensitivity and metabolic profiles [6, 11].

Table 6: Adiponectin Modulation and Clinical Outcomes

Mechanism Aspect	Description	Intervention Strategy	Key RCT Findings
Reduced adiponectin levels	Obesity is associated with low adiponectin, leading to insulin resistance and inflammation	Exercise, high-protein diets, and nutraceutical supplementation increase adiponectin	Increased adiponectin correlates with improved insulin sensitivity [6, 7,11]
Anti-inflammatory effects	Adiponectin reduces inflammatory cytokine production	Lifestyle modifications enhance adiponectin levels	Lower inflammatory markers and improved metabolic profiles
Impact on insulin sensitivity	Higher adiponectin levels improve glucose uptake and insulin action	Integrated interventions lead to better metabolic outcomes	Significant improvements in glycemic control and weight loss observed

5. Discussion

5.1 Integration of RCT Evidence

In summary, in the 13 RCTs reviewed herein, there is strong evidence that interventions that affect key biomolecules yield favorable hormonal and clinical outcomes in obesity. Leptin and ghrelin levels are commonly decreased by ketogenic and low-calorie diets, which increase adiponectin, and subsequently, improve satiety, increase insulin sensitivity, and cause weight loss [2, 3, 8, 9]. In particular, intermittent fasting is effective in reducing serum leptin levels, which in turn reduces appetite and induces continued weight loss [8, 13]. In addition, high-protein diets decrease ghrelin secretion, which results in even more satiety and less caloric intake [4, 12]. In 2013, the results from structured exercise programs providing lower leptin and increased adiponectin play an important role in lowering insulin sensitivity and improving overall metabolic health [8, 6, 7]. In addition, leptin-mimetic drugs have been shown to rapidly improve leptin signaling and weight loss [10].

5.2 Supporting Evidence from Additional Reviews

Several high-quality systematic reviews and meta-analyses corroborate the findings from these RCTs. Therefore, interventions that increase leptin sensitivity have been found to improve satiety and result in weight loss by Taheri *et al*. (2021) [22]. According to Gupta and Kumar (2021) [23], dietary modifications that decrease ghrelin are essential for effective appetite regulation. In Anderson *et al* (2020) [19], it was shown that higher adiponectin levels are strongly associated with better insulin sensitivity and a lower risk of cardiovascular events. The additional evidence from the literature such as this further supports the use of hormone-targeted interventions in obesity management.

5.3 Mechanistic Implications

The development of obesity is to a large extent based on the interactions between leptin, ghrelin, adiponectin, and insulin. A major cause of overeating in obesity is leptin resistance, a condition in which high levels of leptin are unable to suppress appetite [1, 14, 21]. Restoring leptin sensitivity by interventions such as low-calorie and high-protein diets and structured exercise is therefore vital. Interventions that deplete ghrelin such as intermittent fasting and high protein diets work to suppress appetite [2, 17, 4] because elevated ghrelin drives hunger. In addition to improving insulin sensitivity, adiponectin levels are

increased not only but also have anti-inflammatory effects and enhance metabolic health [3, 5, 11]. Taken together, these mechanistic programs highlight the need for a multi-component approach to the treatment of obesity.

5.4 Clinical Implications

The capacity to control these hormones has promising utility as an adjunct to traditional obesity therapies clinically. With the consistent decrease in leptin and ghrelin and the increase in adiponectin, we experience improved satiety, less caloric intake, enhanced insulin sensitivity, and a huge amount of weight loss. Links have been made between better glycemic control and improved lipid profiles and the consequent reduction of diabetes and cardiovascular disease risk with such hormonal changes. Nevertheless, the variability of the protocol used in RCTs suggests the necessity for standardized treatment to improve patient outcomes.

5.5 Future Directions

Future research should address the following areas:

1. Heterogeneity: One of the potential reasons for the poor reproducibility might be related to heterogeneity of studies and therefore there is a need to standardize intervention protocols (e.g., fixed calorie deficits, specific macronutrient ratios, fixed exercise regimens).
2. Advanced analysis will be done (such as metabolomics and proteomics) to understand more about the molecular pathways that these interventions affect to modulate the hormone levels.
3. Large-scale, multicenter RCTs conducted over a long period are required to assess the durability of hormonal change over time and its subsequent clinical effects.
4. Investigations into genetic and environmental factors that affect an individual's hormonal response can be used for personalized interventions in Personalized Medicine.
5. Lifestyle Modifications and Pharmacologic Agents (e.g., Leptin Mimetics): In some cases, exploring the potential of combination therapies using lifestyle modifications in concert with pharmacologic agents (e.g., leptin mimetics) may circumvent resistance mechanisms and capitalize on additional therapeutic benefits.

5.6. Limitations

There are, however, several limitations despite the encouraging evidence. As the RCTs reviewed vary widely in the characteristics of their participants, durations of their intervention, and methods of measuring outcomes, there is little sense in making direct comparisons. Till now most studies have had short durations precluding understanding of the long-term sustainability of hormonal modulation and clinical improvement. Furthermore, although hormonal change is major, the data supporting the translation of hormonal change into durable clinical benefit requires further documentation.

6. Conclusion

We show that modulation of key hormones, leptin, ghrelin, adiponectin and insulin through dietary, exercise and lifestyle interventions represent a promising adjunct strategy for the treatment of obesity, through this systematic review. RCT evidence shows that ketogenic diets, low calorie diets, intermittent fasting, high protein diets, structured exercise programs, and leptin mimetic drugs all change hormone levels and improve satiety, reduce caloric intake, improve insulin sensitivity, and cause significant weight loss. They are strongly associated with positive metabolic consequences and a reduced risk of future obesity related complications, that are likely influenced by these hormonal improvements. Nevertheless, these interventions need to be further standardized and long-term research is needed to optimize these interventions and validate their long-term efficacy and safety. Together, these biomolecules are modulated in a valuable way that adds to the management of obesity on a comprehensive level, and in the future may play a role in personalized treatment strategies.

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