Hormonal Regulation in the Obese Population

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The rising epidemic of obesity, which is associated with type 2 diabetes and cardiovascular disease among other chronic health problems, has resulted in approximately 40% of the U.S. population being classified as obese. Only 28% of Americans meet the exercise standards set by the CDC and research has failed to show that one clear diet strategy can cure obesity. The Standard American Diet (SAD) is characterized by high consumption of processed and refined foods, animal-based foods, added sugar, fat, and sodium, while low in fruits, vegetables, whole grains, and lean protein. This has led to abnormally high levels of blood glucose and increased adiposity that results in a loss of the homeostatic regulation of weight balance. Recent research into peptide hormones has led to the popularity of GLP-1 receptor agonists as a new class of weight loss drugs that may help bring the body closer to homeostatic weight balance. Nutritional supplementation, however, can also have an effect on GLP-1 and hormonal weight regulation without pharmacologic intervention and its associated side effects.

Keywords Obesity, hormones of obesity, ghrelin, leptin, incretin, insulin, cortisol, metabolic syndrome, GLP-1, gymnema sylvestre, berberine, probiotics, intermittent fasting.

METHODS

A literature search was performed utilizing PubMed, Medline, and the Cochrane Library databases. The search terms included origins of obesity, obesity statistics, hormones involved in obesity, insulin and its effect on glucose, insulin and obesity, insulin and diabetes, mechanism of action of GLP-1, GLP-1 and incretin, natural ways to increase GLP-1, herbs that promote appetite suppression, drug-nutrient interactions of GLP-1 agonists. Inclusion criteria consisted of a limit of 75 free and full-text articles, meta-analyses, opinion articles, and systemic reviews for background.

LITERATURE REVIEW

The focus of this literature review was to examine obesity and its effects on health over the last four decades. A review of the literature was conducted on dietary recommendations and why obesity rates continue to increase. The literature frequently referenced the effects of various hormones and their influence on obesity. Some hormones have a direct effect while others seem to have an indirect effect on obesity. The literature often references type-2 diabetes (T2DM) and this was included with a specific focus on the incretin effect. There are 2 amino acids, 1) gastric inhibitory peptide (GIP) and 2) glucagon-like-peptide-1 (GLP-1), known as incretins. In comparing the 2 amino acids GLP-1 seemed to have a more profound effect on weight loss and management of T2DM. The review of the literature was limited to GLP-1. A class of drugs known as GLP-1 Agonists has been developed to help patients better manage diabetes and obesity. Studies are favorable to the use of pharmaceutical GLP-1 agonists but seem to be inconclusive on the long-term side effects. There are also natural ways to increase GLP-1 and several studies have looked at natural ways to lower insulin, raise GLP-1, lower blood glucose, and increase satiety without the use of GLP-1 agonists.

DISCUSSION

35% of adults are now living with obesity according to data from the Centers For Disease Control in 2022[1]. Obesity-related diseases place a burden on the healthcare system that was estimated to be $173 billion as of 2019[2]. Compared to healthy adults, those suffering from obesity are at risk for many serious health diseases including but not limited to, all-cause mortality, hypertension, dyslipidemia, type 2 diabetes, osteoarthritis, cancer, liver disease, depression and other mental disorders, and low overall quality of life.

Thousands of studies have been conducted on obesity and its origins[3]. While there is little consensus on the actual cause, many theories have been put forth with no clear unified theory of obesity. Among the popular theories of weight gain, there is a diverse set of causes which include, but are not limited to[3,4,5,6,7,8,9,10]:

- Calories in vs calories out
- Dietary fat
- Sugar consumption
- Red meat
- Refined Carbohydrates
- Dairy Products
- All Carbohydrates
- Wheat
- Gluten
- Genetics
- Leptin Resistance
- Lack of exercise
- Lack of sleep
- Poverty
- Wealth
- Gut Health
- Prescription Drugs
- Endocrine Disruptors
- Fast Food
- Foods

Hormones are chemical messengers that regulate body

systems[11]. A potential link to the various theories of obesity may be to consider the regulatory effects of hormones and how the endocrine system may influence obesity[12]. One of the most studied effects of hormonal changes is the consumption of excess sugar and its effect on insulin[13]. However, insulin is not the only hormone that has been studied in relation to obesity. Other hormones that might influence obesity are those involved in appetite regulation, blood sugar levels, and stress levels[13].

APPETITE REGULATION

Ghrelin

Ghrelin is a 28 amino acid peptide produced primarily by gastric mucosa. It is a growth hormone that acts on the hypothalamus and will stimulate appetite and induce feelings of hunger[14]. Ghrelin is manufactured primarily in the stomach but is also found in lower concentrations in the pancreas, placenta, kidney, and pituitary[14]. It is homeostatic, increasing in times of starvation and decreasing in times of food abundance[15]. Evidence suggests it can also influence glucose levels, lipid metabolism, and insulin secretion[16].

After meal ingestion, in normal healthy individuals, plasma levels of ghrelin decrease in response to increased plasma levels of glucose and insulin, increasing the time before there is a signal for hunger. In normal healthy individuals, ghrelin produces feelings of hunger to stimulate food intake and fat storage in times of starvation to maintain blood glucose levels[17].

In contrast, obese nondiabetic humans in the postprandial state do not seem to see the suppression of ghrelin, most notably in the presence of hyperinsulinemia[16]. Humans with a BMI > 43 Kg/m2 exhibited 60% lower fasting ghrelin concentrations and no suppression of ghrelin after meal ingestion. This suggests food intake fails to suppress ghrelin levels in obese humans, therefore contributing to overeating[17].

The peptide hormone GLP-1 is produced in the intestinal epithelial L-cells[18]. It has an opposing effect to ghrelin and reduces food intake[19]. It primarily acts in the intestines and stimulates insulin secretion in response to glucose. It also decreases gastric emptying and may have therapeutic benefits in regulating ghrelin.

Some natural holistic approaches can be employed to control ghrelin including:

- Avoiding crash diets or starvation diets
- Avoiding refined high carbohydrate diets
  High-carbohydrate foods and foods that are highly processed seem to have a reduced ability to delay gastric emptying which causes levels of ghrelin to rise and induce hunger[20].
- Eating nutrient-dense foods
  Protein seems to have the greatest effect in controlling Ghrelin levels, possibly because of delayed gastric emptying and lower insulin levels[20].
- Get adequate sleep[21]
- Exercise
  High-intensity exercise such as HIIT training was more effective than steady-state aerobic exercise[22].

Leptin

Leptin is a peptide hormone released from adipose tissue. Leptin enters the brain through the cerebrospinal fluid via the blood-brain barrier (BBB) eventually acting on the hypothalamus[23]. In a state of normal weight balance, leptin will increase to signal the inhibition of hunger. The result is less food intake and increased energy expenditure to balance the energy surplus[23]. If the CNS detects a decrease in leptin, hunger will increase along with energy-sparing mechanisms of decreased nervous system tone, decreased thyroid function, reduced reproductive hormone levels, lower energy expenditure, and lowered growth hormone secretion[23.]

The blood-brain barrier protects the brain from toxic substances and helps regulate the passage of nutrients and hormones between the blood and the brain. It is suggested that high saturation levels of leptin could lead to a downregulation of the leptin receptors at the BBB[24]. This leads to a reduced signaling for bodyweight regulation (decreases in hunger, longer length of satiety, etc.) and further weight increases.

Leptin resistance is the alteration of the tissue sensitivity to leptin and the response of the brain to leptin[25]. Pathologically high levels of leptin are considered a marker of leptin resistance leading to diet-induced obesity[25]. Studies have shown that as circulating levels of leptin rise above 25-30 ng/mL in response to adipose tissue accumulation, the level of leptin that crosses the blood-brain barrier does not increase[25].

As adipose tissue increases an increase in circulating leptin is observed[26]. In theory, high levels of circulating leptin would signal a decrease in hunger. What is observed is that obese individuals continue to experience hunger and a diminished signal to stop eating. This would indicate that obesity is not associated with leptin deficiency but rather the lack of ability of cells to be receptive to leptin.

When leptin levels are reduced by either genetic strategies or monoclonal anti-leptin antibodies, leptin sensitivity is restored as well as reduction in food intake and weight loss[26]. Treating obese people with exogenous leptin has been unsuccessful in most cases of diet-induced obesity[27]. This is generally thought to be due to high levels of circulating leptin already present.

Peptide hormones such as GLP-1 may exert positive effects on leptin[28]. Leptin and GLP-1 have similar effects that reduce food intake. Anini et al showed that leptin stimulates GLP-1 secretion and may be linked to impaired GLP-1 secretion in obese individuals[28]. They found that leptin resistance resulted in lower secretion of GLP-1 and that leptin is a physiological regulator of GLP-1. Therefore, enhancing GLP-1 may reduce excess leptin levels in obese individuals and contribute to a reduction in leptin resistance along with restoring the leptin response[29].

Natural and Holistic Ways to Reduce Leptin Resistance

- Eat whole foods that are high in fiber, high in protein, and contain healthy fat.
  This can lead to weight loss and restore leptin sensitivity[30].
- Practice intermittent fasting such as 16:8[31]
- Exercise
  High-intensity exercise such as HIIT training was more effective than steady-state aerobic exercise[32].
- Studies have shown that very few supplements directly affect leptin.
  However, resveratrol seems to limit leptin expression in adipocytes and may protect against the effects of obesity[33].

  Gymnema sylvestre may also reduce leptin levels in individuals with metabolic syndrome[34].

BLOOD SUGAR LEVELS

Insulin

Insulin is a polypeptide storage hormone synthesized in the β-cells of the pancreas. Its function is to maintain normal blood glucose levels in response to a stimulus of glucose[35]. Intake of food, especially glucose, causes the release of insulin. Insulin lowers blood glucose levels by stimulating the storage of excess glucose in the liver and uptake into muscle and fat. If there is no intake of food, insulin levels drop. Insulin levels vary and are released in bursts as a response to food intake. In obesity, the level of insulin remains high and relatively constant. Eventually, the cells become resistant to insulin.

Insulin resistance is a decreased glucose transport and metabolism in adipocytes and skeletal muscle with an impaired hepatic suppression of glucose output[36]. As the cells release signals for more glucose the brain responds by making more insulin to increase the cellular glucose uptake. Hyperinsulinemia can cause insulin resistance by downregulating insulin receptors. High levels of insulin resistance eventually leads to type 2 diabetes and obesity[36].

Insulin and Its Effects on Hormones

The pancreas maintains blood glucose levels within a very narrow range of 4-6mM[37]. This process uses various hormones to maintain homeostasis. Researchers found that ghrelin is produced in the pancreas (<1% of islet cell production) and will inhibit glucose-stimulated insulin secretion in healthy normal-weight individuals[37]. Hyperglycemia causes insulin secretion and decreases the secretion of ghrelin[38].

Insulin and ghrelin levels appear to have a close interrelationship in body weight regulation. In the presence of high insulin levels ghrelin is downregulated in the obese population[16]. Administration of ghrelin in obese individuals lowers insulin concentrations and worsens glucose tolerance by lowering insulin sensitivity[16]. This indicates that ghrelin can have a diabetogenic effect in individuals with obesity. The varied effects of ghrelin create a potential to improve obesity and diabetes by blocking the functions of ghrelin to improve glucose tolerance.

Insulin stimulates the production of leptin when adipocytes are exposed to glucose to encourage satiety; while leptin, via negative feedback, decreases the secretion of insulin and enhances tissue sensitivity to it, leading to glucose uptake for energy utilization or storage[39].

Insulin resistance and leptin resistance are both implicated in obesity. In obese individuals, when insulin resistance is observed there is also, frequently, leptin resistance[39]. Rising leptin levels may lead to increased food intake which then causes increases in insulin[40]. As the insulin fails to suppress glucose production in the liver, insulin levels rise which leads to lipogenesis. This would indicate that insulin and leptin affect each other and further contribute to obesity. Strategies that reduce leptin may also reduce insulin resistance and show a reduction in obesity.

Insulin has a satiety effect on the central nervous system[40]. The gut hormone GLP-1 stimulates the pancreas to release insulin which is stimulated by nutrients in the gut[41]. GLP-1 is known to slow the effects of gastric emptying and is an accepted way to potentially control glycemia[43]. Gastric emptying is a homeostatic mechanism to control blood glucose.

Studies have shown that insulin and GLP-1 increase in the presence of glucose overload[40]. This creates possibilities to develop treatment strategies utilizing GLP-1 that can positively control the postprandial rate of glucose levels.

Natural Ways to Reduce Insulin and Improve Insulin Resistance

Insulin is the major hormone that influences weight gain[42]. Strategies that are intended to reduce insulin can have an effect on obesity and reduce insulin resistance such as:

- Limit Processed foods[43]
  - These often contain added sugars, are devoid of fiber, and are high in calories especially carbohydrates
- Limit Sugar-Sweetened Beverages[44]
  - Soft drinks, fruit juices, energy drinks, drinks that contain artificial sweeteners
- Limit Snacking
  - This creates constant insulin levels. Consistent insulin levels can lead to insulin resistance and obesity[45]
- Eat More Healthy Fat[46]
  - Omega 3 fatty acids in the form of wild-caught fish, walnuts, chia seeds, flax seeds.
  - Avoid vegetable oils and use olive oil, coconut oil, grass-fed butter or ghee
- Eat Protein[47]
  - A higher dietary protein intake reduces hunger, improves satiety, increases thermogenesis, and limits lean muscle mass loss during weight reduction using a reduced calorie diet and increased physical activity.
  - Lean high-protein foods, such as organic chicken, wild fish, free-range eggs, yogurt, and almonds, help regulate your blood sugar levels.

Supplements That Have Been Shown to Help Maintain Normal Blood Sugar Levels

Berberine has been shown to induce the secretion of insulin in the body, reduce insulin resistance, and improve the sensitivity of the liver, muscle tissues, and fat to insulin[48].

Alpha Lipoic Acid has been shown to prevent beta cell destruction, enhances glucose uptake, and its antioxidant effects may be particularly useful in slowing the development of diabetic complications such as diabetic neuropathy[49].

Chromium can enhance the metabolic action of insulin[50]. Chromium 500 µg/day Research suggests favorable effects of chromium supplementation on glycemic control in patients with blood sugar dysregulation[56].

Green Tea may help inhibit glucose absorption from the small intestine and increase insulin secretion from the pancreas[51].

Forskolin was found to predominantly decrease basal glucose in healthy rats and support healthy blood sugars in rats with insulin dysregulation[52].

Carnitine supplementation may help remodel fatty acid metabolism, insulin action, and mitochondrial function and is positively indicated for those with blood sugar dysregulation[53].

Vanadium has possible insulinotropic effects[54].

Vitamin E and Selenium may be highly beneficial to the diabetic patient due to complications associated with diabetes and excess free radical activity[55].

Biotin improved postprandial glucose levels in subjects with blood sugar dysregulation due to its effect on key enzymes in glucose metabolism such as GCK and phosphoenolpyruvate carboxykinase 1 (PCK1)[57].

Butyrate can also regulate the cAMP signaling for insulin secretion via glucagon-like peptide-1 receptors (GLP-1R)[58].

STRESS LEVELS

Cortisol

Cortisol is a class of hormones called glucocorticoids that are synthesized from cholesterol. Known as the body's stress hormone, it is regulated by the hypothalamus-pituitary-adrenal axis (HPA). Cortisol influences the liver, muscle, adipose tissue, and pancreas to increase the availability of blood glucose[59].

Cortisol can be considered the opposite of insulin. When insulin levels are high cortisol levels are low. Cortisol prepares the body for action to maintain awareness and high alertness in response to a threat stimulus. In response to a short-term stressor, for example, vigorous exercise produces a temporary increase in cortisol and glucose levels. After the stressful event is over cortisol levels and glucose levels are reduced back to normal[59].

Cortisol levels can increase up to 9 times during stressful periods[60]. Long-term psychological stress, consumption of high glycemic index foods, and reduced sleep can cause increases in cortisol production[61]. Glucocorticoids stimulate the need to eat specific foods that are rich in fat and sucrose. It is well established that high glycemic index foods result in increases in insulin. Cortisol, therefore, can contribute to higher insulin levels, and reduced insulin sensitivity which can eventually lead to obesity[62].

The HPA axis is involved in mediating stress responses. Recent evidence suggests that GLP-1 is also released in the CNS and may play a part in the regulation of the HPA axis mediated stress[63]. Increases in GLP-1 seem to play an excitatory role in glucocorticoid secretion and parallels its role in body weight regulation[63]. Therefore GLP-1 may play a role in reducing stress mediated cortisol responses, and improved glycemic response by stimulating a reduction in food intake and drive to eat which may contribute to a reduction in body weight and in type 2 diabetes[64].

Reducing cortisol levels is important to reducing weight since high cortisol levels raise insulin levels. Natural ways to reduce cortisol levels include but are not limited to:

- Omega-3 fatty acids have been shown to reduce morning cortisol levels[65].
- Ashwagandha has been shown to reduce stress and anxiety levels[66].
- Rhodiola has also been shown to reduce stress and anxiety levels[67].
- Prebiotic and Probiotics decrease urinary cortisol[68].
- Regular high intensity exercise can reduce cortisol levels[69].
- Getting adequate sleep can reduce cortisol levels[70].

THE POTENTIAL ROLE OF GLP-1

GLP-1 influences the release of hormones such as insulin and glucagon. GLP-1 slows down digestion and is secreted by the intestines in response to food intake[71]. Therefore, it seems that nutritional strategies that enhance GLP-1 can help with weight management by improving blood glucose regulation. Maximizing the production of GLP-1 in the management of the hormonal response to food intake could prove to be an effective strategy in reducing the rate of obesity and type 2 diabetes.

Some foods that may increase GLP-1 secretion[72]

- High Fiber foods like vegetables and whole grains
- Foods rich in healthy fats such as avocado oil, olive oil, coconut oil, and grass-fed butter
- Healthy proteins such as grass-fed beef, wild caught salmon, and free range chicken

Some supplements that may increase GLP-1 Secretion[73]

- Berberine
- Resveratrol
- Curcumin
- Cinnamon

CONCLUSION

The common link between the hormones discussed in this literature review is insulin. Lowering insulin appears to positively affect weight management and insulin resistance. Elevated blood glucose is the result of insulin resistance and not the cause. Excess glucose is removed from the bloodstream and is stored as adipose tissue. It is well established that in an environment of excess glucose, we see a concomitant rise in insulin. We also know that more insulin eventually leads to insulin resistance which is a major factor in obesity and type 2 diabetes.

Outdated theories of calories in and out and low-fat diets are still prevalent in diet culture. We continue to have a prevalence of convenience foods, high carbohydrate (mainly fructose), and low fiber foods as the predominant food source in our society. Dietary guidelines should therefore be directed not at "eat this or eat that" type of thinking but rather focus on ways to reduce the hormonal imbalance of insulin levels. The effects of hormones on obesity have been widely researched and are well documented. Obesity is a multifactorial disease that cannot be relegated to one single cause.

The recent popularity of GLP-1 receptor agonists as a therapeutic agent for obesity and type 2 diabetes presents a unique approach in treating these two diseases. There is ample evidence that GLP-1 can have an effect on appetite reduction, reduced ghrelin secretion, reduction in leptin resistance, improvements in insulin resistance, and balance stress-mediated responses in the CNS.

GLP-1 receptor agonist pharmaceuticals were only recently approved by the FDA in January of 2023. The long-term effects are unknown, and the author has observed that weight gain and hunger return soon after the discontinuation of the medication. Natural remedies can also have a positive effect on GLP-1 and have the potential therapeutic benefit without the risks associated with prescription medications.

Hormones are important regulatory mechanisms used by the human body and their interaction with each other can be influenced by two factors, the type of foods we eat and when we eat. Eating the right foods prevents high levels of insulin. Meal timing, such as intermittent fasting, is important as this helps regulate insulin response, glucose levels, and modulates our signal to eat.

Human obesity is a complicated problem with many causative factors. Ultimately the goal should be to adopt strategies that reduce insulin. Successful weight reduction requires that patients pay attention to a host of causative factors and it is critical to address each patient individually.

COMPETING INTEREST

The author declares that they have no competing interests.

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REFERENCES

1. https://www.cdc.gov/obesity/data/prevalence-maps.html
2. Ward ZJ, Bleich SN, Long MW, Gortmaker SL (2021) Association of body mass index with health care expenditures in the United States by age and sex. PLoS ONE 16(3): e0247307.
3. 4. Temple NJ. The Origins of the Obesity Epidemic in the USA-Lessons for Today. *Nutrients.* 2022;14(20):4253. Published 2022 Oct 12. doi:10.3390/nu14204253
4. Ludwig DS. Carbohydrate-insulin model: does the conventional view of obesity reverse cause and effect?. *Philos Trans R Soc Lond B Biol Sci.* 2023;378(1888):20220211. doi:10.1098/rstb.2022.0211
5. Masood B, Moorthy M. Causes of obesity: a review. *Clin Med (Lond).* 2023;23(4):284-291. doi:10.7861/clinmed.2023-0168
6. Marghoub S, Sanaie S, Sullman MJM, Nejadghaderi SA, Safiri S, Mohammadinasab R. Obesity from a sign of being rich to a disease of the new age: A historical review. *Health Sci Rep.* 2023; 6(11):e1670. Published 2023 Nov 1. doi:10.1002/hsr2.1670
7. Sarkar D, Walker-Swaney J, Shetty K. Food Diversity and Indigenous Food Systems to Combat Diet-Linked Chronic Diseases. *Curr Dev Nutr.* 2019;4(Suppl 1):3-11. Published 2019 Sep 2. doi:10.1093/cdn/nzz099
8. Popkin BM, Adair LS, Ng SW. Global nutrition transition and the pandemic of obesity in developing countries. *Nutr Rev.* 2012; 70(1):3-21. doi:10.1111/j.1753-4887.2011.00456.x
9. Thompson FE, McNeel TS, Dowling EC, Midthune D, Morrissette M, Zeruto CA. Interrelationships of added sugars intake, socioeconomic status, and race/ethnicity in adults in the United States: National Health Interview Survey, 2005. *J Am Diet Assoc.* 2009; 109(8):1376-1383. doi:10.1016/j.jada.2009.05.002
10. Li M, Gong W, Wang S, Li Z. Trends in body mass index, overweight and obesity among adults in the USA, the NHANES from 2003 to 2018: a repeat cross-sectional survey. *BMJ Open.* 2022;12(12):e065425. Published 2022 Dec 16. doi:10.1136/bmjopen-2022-065425
11. Stárka L, Dušková M. What is a hormone?. *Physiol Res.* 2020; 69(Suppl 2):S183-S185. doi:10.33549
12. Anderwald C, Brabant G, Bernroider E, et al. Insulin-dependent modulation of plasma ghrelin and leptin concentrations is less pronounced in type 2 diabetic patients. *Diabetes.* 2003;52(7): 1792-1798.
13. Chabot F, Caron A, Laplante M, St-Pierre DH. Interrelationships between ghrelin, insulin and glucose homeostasis: Physiological relevance. *World J Diabetes.* 2014;5(3):328-341. doi:10.4239/wjd.v5.i3.328
14. Campbell M, Jialal I. Physiology, Endocrine Hormones. [Updated 2022 Sep 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from:
15. Yeung AY, Tadi P. Physiology, Obesity Neurohormonal Appetite And Satiety Control. [Updated 2023 Jan 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan
16. Pulkkinen L, Ukkola O, Kolehmainen M, Uusitupa M. Ghrelin in diabetes and metabolic syndrome. *Int J Pept.* 2010;2010:248948. doi:10.1155/2010/248948
17. Decarie-Spain L, Kanoski SE. Ghrelin and Glucagon-Like Peptide-1: A Gut-Brain Axis Battle for Food Reward. *Nutrients.* 2021;13(3):977. Published 2021 Mar 17. doi:10.3390/nu13030977
18. Holst JJ. The physiology of glucagon-like peptide 1. *Physiol Rev.* 2007;87(4):1409-1439. doi:10.1152/physrev.00034.2006
19. Decarie-Spain L, Kanoski SE. Ghrelin and Glucagon-Like Peptide-1: A Gut-Brain Axis Battle for Food Reward. *Nutrients.* 2021;13(3):977. Published 2021 Mar 17. doi:10.3390/nu13030977
20. Blom WA, Lluch A, Stafleu A, et al. Effect of a high-protein breakfast on the postprandial ghrelin response. *Am J Clin Nutr.* 2006; 83(2):211-220. doi:10.1093/ajcn/83.2.211
21. Lin J, Jiang Y, Wang G, et al. Associations of short sleep duration with appetite-regulating hormones and adipokines: A systematic review and meta-analysis. *Obes Rev.* 2020;21(11):e13051. doi: 10.1111/obr.13051
22. Ouerghi N, Feki M, Bragazzi NL, et al. Ghrelin Response to Acute and Chronic Exercise: Insights and Implications from a Systematic Review of the Literature. *Sports Med.* 2021;51(11):2389-2410. doi:10.1007/s40279-021-01518-6Liu D, Li S. LEAP2: Next game-changer of pharmacotherapy for overweight and obesity?. *Cell Rep Med.* 2022;3(4):100612. Published 2022 Apr 19. doi:10.1016/j.xcrm.2022.100612
23. Dornbush S, Aeddula NR. Physiology, Leptin. [Updated 2023 Apr 10]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from:
24. Izquierdo AG, Crujeiras AB, Casanueva FF, Carreira MC. Leptin, Obesity, and Leptin Resistance: Where Are We 25 Years Later?. *Nutrients.* 2019;11(11):2704. Published 2019 Nov 8. doi:10.3390/nu11112704
25. Gruzdeva O, Borodkina D, Uchasova E, Dyleva Y, Barbarash O. Leptin resistance: underlying mechanisms and diagnosis. *Diabetes Metab Syndr Obes*. 2019;12:191-198. Published 2019 Jan 25. doi:10.2147/DMSO.S182406
26. Shangang Zhao, Christine M. Kusminski, Joel K. Elmquist, Philipp E. Scherer; Leptin: Less Is More. *Diabetes* 1 May 2020; 69 (5): 823–829.
27. Roujeau C, Jockers R, Dam J. New pharmacological perspectives for the leptin receptor in the treatment of obesity. *Front Endocrinol (Lausanne).* 2014;5:167. Published 2014 Oct 13. doi:10.3389/fendo.2014.00167
28. Anini Y, Brubaker PL. Role of leptin in the regulation of glucagon-like peptide-1 secretion. *Diabetes.* 2003;52(2):252-259. doi:10.2337/diabetes.52.2.252
29. Iepsen EW, Lundgren J, Dirksen C, et al. Treatment with a GLP-1 receptor agonist diminishes the decrease in free plasma leptin during maintenance of weight loss. *Int J Obes (Lond)*. 2015;39(5):834-841. doi:10.1038/ijo.2014.177
30. Figlewicz DP. Modulation of Food Reward by Endocrine and Environmental Factors: Update and Perspective. *Psychosom Med.* 2015;77(6):664-670. doi:10.1097/PSY.0000000000000146
31. Moro T, Tinsley G, Bianco A, et al. Effects of eight weeks of time-restricted feeding (16/8) on basal metabolism, maximal strength,

body composition, inflammation, and cardiovascular risk factors in resistance-trained males. *J Transl Med.* 2016;14(1):290. Published 2016 Oct 13. doi:10.1186/s12967-016-1044-0
32. Buchheit M, Laursen PB. High-intensity interval training, solutions to the programming puzzle: Part I: cardiopulmonary emphasis. *Sports Med.* 2013;43(5):313-338. doi:10.1007/s40279-013-0029-x
33. Ardid-Ruiz A, Ibars M, Mena P, et al. Resveratrol Treatment Enhances the Cellular Response to Leptin by Increasing OBRb Content in Palmitate-Induced Steatotic HepG2 Cells. *Int J Mol Sci.* 2019;20(24):6282. Published 2019 Dec 12. doi:10.3390/ijms20246282
34. Kim HJ, Kim S, Lee AY, et al. The Effects of Gymnema sylvestre in High-Fat Diet-Induced Metabolic Disorders. *Am J Chin Med.* 2017;45(4):813-832. doi:10.1142/S0192415X17500434
35. Wilcox G. Insulin and insulin resistance. *Clin Biochem Rev.* 2005;26(2):19-39.
36. Kahn BB, Flier JS. Obesity and insulin resistance. *J Clin Invest.* 2000;106(4):473-481. doi:10.1172/JCI10842
37. Roder PV, Wu B, Liu Y, Han W: Pancreatic regulation of glucose homeostasis. Exp Mol Med. 2016, 48:219. 10.1038/emm.2016.6
38. Tambascia MA, Malerbi DA, Eliaschewitz FG. Influence of gastric emptying on the control of postprandial glycemia: physiology and therapeutic implications. *Einstein (Sao Paulo).* 2014;12(2):251-253. doi:10.1590/s1679-45082014rb2862
39. Osegbe I, Okpara H, Azinge E. Relationship between serum leptin and insulin resistance among obese Nigerian women. *Ann Afr Med.* 2016;15(1):14-19. doi:10.4103/1596-3519.158524
40. Kahn BB, Flier JS. Obesity and insulin resistance. *J Clin Invest.* 2000;106(4):473-481. doi:10.1172/JCI10842
41. Maselli DB, Camilleri M. Effects of GLP-1 and Its Analogs on Gastric Physiology in Diabetes Mellitus and Obesity. *Adv Exp Med Biol.* 2021;1307:171-192. doi:10.1007/5584_2020_496
42. Amalia Gastaldelli, Melania Gaggini, Ralph A. DeFronzo; Role of Adipose Tissue Insulin Resistance in the Natural History of Type 2 Diabetes: Results From the San Antonio Metabolism Study. *Diabetes* 1 April 2017; 66 (4): 815–822.
43. Almarshad MI, Algonaiman R, Alharbi HF, Almujaydil MS, Barakat H. Relationship between Ultra-Processed Food Consumption and Risk of Diabetes Mellitus: A Mini-Review. *Nutrients.* 2022; 14(12):2366. Published 2022 Jun 7. doi:10.3390/nu14122366
44. Tseng TS, Lin WT, Gonzalez GV, Kao YH, Chen LS, Lin HY. Sugar intake from sweetened beverages and diabetes: A narrative review. World J *Diabetes.* 2021;12(9):1530-1538. doi:10.4239/wjd.v12.i9.1530
45. Clawson RC, Dela Cruz LN, Allen S, et al. Continuous access to snacks from weaning onwards in female rats causes weight gain, insulin insensitivity, and sustained leptin resistance in adulthood. *Physiol Behav.* 2019;201:165-174. doi:10.1016/j.physbeh.2018.11.026
46. Riccardi G, Giacco R, Rivellese AA. Dietary fat, insulin sensitivity and the metabolic syndrome. *Clin Nutr.* 2004;23(4):447-456. doi:10.1016/j.clnu.2004.02.006
47. Foster-Schubert KE, Overduin J, Prudom CE, et al. Acyl and total ghrelin are suppressed strongly by ingested proteins, weakly by lipids, and biphasically by carbohydrates. *J Clin Endocrinol Metab.* 2008;93(5):1971-1979. doi:10.1210/jc.2007-2289
48. Cao C, Su M. Effects of berberine on glucose-lipid metabolism, inflammatory factors and insulin resistance in patients with metabolic syndrome. *Exp Ther Med.* 2019;17(4):3009-3014. doi:10.3892/etm.2019.7295
49. Ansar H, Mazloom Z, Kazemi F, Hejazi N. Effect of alpha-lipoic acid on blood glucose, insulin resistance and glutathione peroxidase of type 2 diabetic patients. *Saudi Med J.* 2011;32(6):584-588.
50. Zhao F, Pan D, Wang N, et al. Effect of Chromium Supplementation on Blood Glucose and Lipid Levels in Patients with Type 2 Diabetes Mellitus: a Systematic Review and Meta-analysis. *Biol Trace Elem Res.* 2022;200(2):516-525. doi:10.1007/s12011-021-02693-3
51. Hanhineva K, Törrönen R, Bondia-Pons I, et al. Impact of dietary polyphenols on carbohydrate metabolism. *Int J Mol Sci.* 2010;11(4):1365-1402. Published 2010 Mar 31. doi:10.3390/ijms11041365
52. Ríos-Silva M, Trujillo X, Trujillo-Hernández B, et al. Effect of chronic administration of forskolin on glycemia and oxidative stress in rats with and without experimental diabetes. *Int J Med Sci.* 2014;11(5):448-452. Published 2014 Mar 11. doi:10.7150/ijms.8034
53. Fathizadeh H, Milajerdi A, Reiner Ž, Kolahdooz F, Asemi Z. The effects of L-carnitine supplementation on glycemic control: a systematic review and meta-analysis of randomized controlled trials. *EXCLI J.* 2019;18:631-643. Published 2019 Aug 19. doi:10.17179/excli2019-1447
54. Wang J, Yuen VG, McNeill JH. Effect of vanadium on insulin sensitivity and appetite. *Metabolism.* 2001;50(6):667-673. doi:10.1053/meta.2001.23294
55. Ghaffari T, Nouri M, Irannejad E, Rashidi MR. Effect of vitamin e and selenium supplement on paraoxonase-1 activity, oxidized low density lipoprotein and antioxidant defense in diabetic rats. *Bioimpacts.* 2011;1(2):121-128. doi:10.5681/bi.2011.016
56. Suksomboon N, Poolsup N, Yuwanakorn A. Systematic review and meta-analysis of the efficacy and safety of chromium supplementation in diabetes. *J Clin Pharm Ther.* 2014 Jun;39(3):292-306.
57. Zhang Y, Ding Y, Fan Y, et al. Influence of biotin intervention on glycemic control and lipid profile in patients with type 2 diabetes mellitus: A systematic review and meta-analysis. *Front Nutr.* 2022;9:1046800. Published 2022 Oct 31. doi:10.3389/ fnut.2022.1046800
58. Mayorga-Ramos A, Barba-Ostria C, Simancas-Racines D, Guamán LP. Protective role of butyrate in obesity and diabetes: New insights. *Front Nutr.* 2022;9:1067647. Published 2022 Nov 24. doi:10.3389/fnut.2022.1067647
59. Thau L, Gandhi J, Sharma S. Physiology, Cortisol. [Updated 2023 Aug 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538239/
60. Cay M, Ucar C, Senol D, et al. Effect of increase in cortisol level due to stress in healthy young individuals on dynamic and static balance scores. *North Clin Istanb.* 2018;5(4):295-301. Published 2018 May 29. doi:10.14744/nci.2017.42103
61. van der Valk ES, Savas M, van Rossum EFC. Stress and Obesity: Are There More Susceptible Individuals?. *Curr Obes Rep.* 2018;7(2):193-203. doi:10.1007/s13679-018-0306-y
62. Adam TC, Hasson RE, Ventura EE, et al. Cortisol is negatively associated with insulin sensitivity in overweight Latino youth. *J Clin Endocrinol Metab.* 2010;95(10):4729-4735. doi:10.1210/jc.2010-0322
63. Ghosal S, Myers B, Herman JP. Role of central glucagon-like peptide-1 in stress regulation. *Physiol Behav.* 2013;122:201-207. doi:10.1016/j.physbeh.2013.04.003

64. Korsatko S, Jensen L, Brunner M, et al. Effect of once-weekly semaglutide on the counterregulatory response to hypoglycaemia in people with type 2 diabetes: A randomized, placebo-controlled, double-blind, crossover trial. *Diabetes Obes Metab.* 2018;20(11): 2565-2573. doi:10.1111/dom.13422
65. Jahangard L, Hedayati M, Abbasalipourkabir R, et al. Omega-3-polyunsatured fatty acids (O3PUFAs), compared to placebo, reduced symptoms of occupational burnout and lowered morning cortisol secretion. *Psychoneuroendocrinology.* 2019;109:104384. doi:10.1016/j.psyneuen.2019.104384
66. Pratte MA, Nanavati KB, Young V, Morley CP. An alternative treatment for anxiety: a systematic review of human trial results reported for the Ayurvedic herb ashwagandha (Withania somnifera). *J Altern Complement Med.* 2014;20(12):901-908. doi:10.1089/acm.2014.0177
67. Anghelescu, I. G., Edwards, D., Seifritz, E., & Kasper, S. (2018). Stress management and the role of *Rhodiola rosea:* a review. *International Journal of Psychiatry in Clinical Practice,* 22(4), 242–252. https://doi.org/10.1080/13651501.2017.1417442
68. Kazemi A, Noorbala AA, Azam K, Eskandari MH, Djafarian K. Effect of probiotic and prebiotic vs placebo on psychological outcomes in patients with major depressive disorder: A randomized clinical trial. *Clin Nutr.* 2019;38(2):522-528. doi:10.1016/j.clnu.2018.04.010
69. Wood CJ, Clow A, Hucklebridge F, Law R, Smyth N. Physical fitness and prior physical activity are both associated with less cortisol secretion during psychosocial stress. *Anxiety Stress Coping*. 2018;31(2):135-145. doi:10.1080/10615806.2017.1390083
70. Hirotsu C, Tufik S, Andersen ML. Interactions between sleep, stress, and metabolism: From physiological to pathological conditions. *Sleep Sci.* 2015;8(3):143-152. doi:10.1016/j.slsci.2015.09.002
71. Nadkarni P, Chepurny OG, Holz GG. Regulation of glucose homeostasis by GLP-1. *Prog Mol Biol Transl Sci.* 2014;121:23-65. doi:10.1016/B978-0-12-800101-1.00002-8
72. Hira T, Trakooncharoenvit A, Taguchi H, Hara H. Improvement of Glucose Tolerance by Food Factors Having Glucagon-Like Peptide-1 Releasing Activity. *Int J Mol Sci.* 2021;22(12):6623. Published 2021 Jun 21. doi:10.3390/ijms22126623
73. Yang WL, Zhang CY, Ji WY, et al. Berberine Metabolites Stimulate GLP-1 Secretion by Alleviating Oxidative Stress and Mitochondrial Dysfunction. *Am J Chin Med.* 2024;52(1):253-274. doi:10.1142/S0192415X24500113