Evaluation the Activity of Leptin and Oxyntomodulin in Obese, Overweight and Healthy Individuals

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Abstract—**Background and Objective: A high level of body fat is a chronic disorder known as obesity. It is unknown how gastrointestinal hormones and obesity are related. The human biological system has various neuroendocrine inputs for managing food intake, including effects on appetite regulation and satiety signals. One of the recent new parameters for evaluating obesity is serum Oxyntomodulin and Leptin which is thought to be due to a disruption in the levels of these hormones. The present study aimed to evaluate the gastrointestinal hormones and their impact in obese and non-obese individuals.**

Methods: This comparative study carried out at the Biochemistry Unit/ Basic Science College of Medicine-Hawler Medical University, from September 1st, 2021 to March 30th, 2022. A total number (76) participants Obese and non-Obese individuals (30-66 years) age ranged both males and females at (Hawler Cardiac Center, and Erbil's Court). Fasting blood specimens were collected from participants. The following parameters were measured (OXM, and Leptin) along with (T.C, TGs, HDL, LDL, and VLDL).

Results: In this study represented 39% Male, and 37% Female obese. Du to the BMI of participants, a significant association (P < 0.001) observed between OXM, Leptin, and BMI, Pearson correlation analysis showed that Leptin was positively correlated with TG and VLDL (p<0.05), a significant association of Leptin/OXM ratio, Leptin/BMI ratio and OXM/BMI ratio in obese Individuals.

Conclusion: Due to low levels of OXM with high Leptin levels in obese individuals and strong relationship between these hormones and BMI, the findings from this study clearly show that body weight gain and increased hunger are linked to the effects of these hormones in obesity.

Keywords: Obesity, Appetite, Gastrointestinal peptides, OXM, Leptin.

1.INTRODUCTION:

The growing epidemic of obesity is one of the main health problems of the twenty-first century. It is associated with a higher rate of morbidity and increases the risk of heart disease, type 2 diabetes, hypertension, dyslipidemia, and many cancers. There is still much to be discovered about the physiological factors behind food consumption behavior and overeating, especially in humans. (Hanssen et al., 2021, Abbas et al., 2020, Dizaye et al., 2011). Oxyntomodulin is a 37-amino-acid peptide enteroendocrine hormone derived from the pre-proglucagon gene family, is a gut peptide hormone released in a post-prandial state that plays a role in the activation of the glucagon-like peptide-1 receptor and the glucagon receptor, as well as meal termination ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"JDDLRhtQ","properties":{"formattedCitation":"(Pocai,2014a)","plainCitation":"(Pocai,2014a)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":1325,"uris":["http://zotero.org/users/9182839/items/2GLCGEJ7"],"itemData":{"id":1325,"type":"article-journal","abstract":"Oxyntomodulin (OXM) is a peptide hormone released from the gut in post-prandial state that activates both the glucagon-like peptide-1 receptor (GLP1R) and the glucagon receptor (GCGR) resulting in superior body weight lowering to selective GLP1R agonists. OXM reduces food intake and increases energy expenditure in humans. While activation of the GCGR increases glucose production posing a hyperglycemic risk, the simultaneous activation of the GLP1R counteracts this effect. Acute OXM infusion improves glucose tolerance in T2DM patients making dual agonists of the GCGR and GLP1R new promising treatments for diabetes and obesity with the potential for weight loss and glucose lowering superior to that of GLP1R agonists.","collection-title":"Metabolic Syndrome: Removing Road Blocks to Therapy","container-title":"Molecular Metabolism","DOI":"10.1016/j.molmet.2013.12.001","ISSN":"2212-8778","issue":"3","journalAbbreviation":"Molecular Metabolism","language":"en","page":"241251","source":"ScienceDirect","title":"Action and therapeutic potential of oxyntomodulin","volume":"3","author":[{"family":"Pocai","given":"Alessandro"}],"issued":{"dateparts":[["2014",6,1]]}}}],"schema":"https://github.com/citation-style language/schema/raw/master/csl-citation.json"} (Pocai, 2014). It regulates glucose metabolism, insulin secretion, food intake, energy expenditure, and appetite suppression, and lowers fasting ghrelin levels and weight loss in overweight and obese people with good tolerability (ADDIN ZOTERO_ITEM CSL_CITATION{"citationID":"lwiMwd5W","properties":{"formattedCitation":"(Taha and Abbas, 2023)","plainCitation":"(Taha and Abbas, 2023)","noteIndex":0},"citationItems":[{"id":305,"uris":["http://zotero.org/users/local/td9sNOXj/items/PWJ3UY36"],"item

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Oxyntomodulin levels peak about 30 minutes after consumption. Oxyntomodulin levels vary throughout the day, regardless of meal consumption, with the greatest concentrations in the evening and the lowest concentrations in the early morning ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a2hb5bvopn6","properties":{"formattedCitation":"(Jens J. Holst et al., 2018)","plainCitation":"(Jens J. Holst et al., 2018)","noteIndex":0},"citationItems":[{"id":3075,"uris":["http://zotero.org/users/9182839/items/GL9BTHW5"],"itemData":{"id":3075,"type":"article-journal","abstract":"Oxyntomodulin is a product of the glucagon precursor, proglucagon, produced and released from the endocrine L-cells of the gut after enzymatic processing by the precursor prohormone convertase 1/3. It corresponds to the proglucagon sequence 33–69 and thus contains the entire glucagon sequence plus a C-terminal octapeptide, comprising in total 37 amino acids. As might have been expected, it has glucagon-like bioactivity, but also and more surprisingly also activates the receptor for GLP-1. This has given the molecule an interesting status as a glucagon-GLP-1 co-agonist, which is currently attracting considerable interest for its potential in the treatment of diabetes and obesity. Here, we provide an update on oxyntomodulin with a focus on its potential role in metabolic diseases.","collection-title":"Newer peptide-based agents for treatment of patients with Type 2 diabetes","container-title":"Peptides","DOI":"10.1016/j.peptides.2017.09.018","ISSN":"0196-9781","journalAbbreviation":"Peptides","language":"en","page":"48-53","source":"ScienceDirect","title":"Oxyntomodulin: Actions and role in diabetes","title-short":"Oxyntomodulin","volume":"100","author":[{"family":"Holst","given":"Jens J."},{"family":"Albrechtsen","given":"Nicolai J. Wewer"},{"family":"Gabe","given":"Maria Buur Nordskov"},{"family":"Rosenkilde","given":"Mette Marie"}],"issued":{"date-parts":[["2018",2,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} (Holst et al., 2018).

Leptin (also known as OB protein), is a 16-kD protein. Leptin is a product of the cloned OB gene that is primarily generated by adipocytes (white adipose tissue) and is implicated in the regulation of energy intake and expenditure, and reduced food intake ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"1tpBjaql","properties":{"formattedCitation":"(Friedman, 2019a)","plainCitation":"(Friedman, 2019a)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":2693,"uris":["http://zotero.org/users/9182839/items/LM3XJVC5"],"itemData":{"id":2693,"type":"article-journal","abstract":"The discovery of leptin changed the view of adipose tissue from that of a passive vessel that stores fat to that of a dynamic endocrine organ that actively regulates behaviour and metabolism. Secreted by adipose tissue, leptin functions as an afferent signal in a negative feedback loop, acting primarily on neurons in the hypothalamus and regulating feeding and many other functions. The leptin endocrine system serves a critical evolutionary function by maintaining the relative constancy of adipose tissue mass, thereby protecting individuals from the risks associated with being too thin (starvation and infertility) or too obese (predation). In this Review, the biology of leptin is summarized, and a conceptual framework is established for studying the pathogenesis of obesity, which, analogously to diabetes, can result from either leptin hyposecretion or leptin resistance. Herein, these two states are distinguished with the terms 'type 1 obesity' and 'type 2 obesity': type 1 obesity describes a subset of obese individuals with low endogenous plasma leptin levels who respond to leptin therapy, whereas type 2 obesity describes most obese individuals, who are leptin resistant but might respond to leptin therapy in combination with other drugs, such as leptin sensitizers.","container-title":"Nature Metabolism","DOI":"10.1038/s42255-019-0095-y","ISSN":"2522-5812","issue":"8","journalAbbreviation":"Nat Metab","language":"en","license":"2019 Springer Nature Limited","note":"number: 8\npublisher: Nature Publishing Group","page":"754-764","source":"www.nature.com","title":"Leptin and the endocrine control of energy balance","volume":"1","author":[{"family":"Friedman","given":"Jeffrey M."}],"issued":{"date-parts":[["2019",8]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} (Friedman, 2019). The GI system's motility is influenced by leptin in a complicated way. Leptin is found in the afferent and efferent ends of the vagus nerve ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"mkWuwIIr","properties":{"formattedCitation":"(Yarandi et al., 2011)","plainCitation":"(Yarandi et al., 2011)","noteIndex":0},"citationItems":[{"id":1345,"uris":["http://zotero.org/users/9182839/items/EC5GVK8M"],"itemData":{"id":1345,"type":"article-journal","abstract":"Objective\nLeptin was discovered in 1994 as a hormone produced by adipose tissue with a modulatory effect on feeding behavior and weight control. Recently, the stomach has been identified as an important source of leptin and growing evidence has shown diverse functions for leptin in the gastrointestinal tract.\nMethods\nUsing leptin as a keyword in PubMed, more than 17 000 articles were identified, of which more than 500 articles were related to the role of leptin in the gastrointestinal tract. Available abstracts were reviewed and more than 200 original articles were reviewed in detail.\nResults\nThe available literature demonstrated that leptin can modulate several important functions of the gastrointestinal tract. Leptin interacts with the vagus nerve and cholecystokinin to delay gastric emptying and has a complex effect on motility of the small bowel. Leptin modulates

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absorption of macronutrients in the gastrointestinal tract differentially in physiologic and pathologic states. In physiologic states, exogenous leptin has been shown to decrease carbohydrate absorption and to increase the absorption of small peptides by the PepT1 di-/tripeptide transporter. In certain pathologic states, leptin has been shown to increase absorption of carbohydrates, proteins, and fat. Leptin has been shown to be upregulated in the colonic mucosa in patients with inflammatory bowel disease. Leptin stimulates gut mucosal cell proliferation and inhibits apoptosis. These functions have led to speculation about the role of leptin in tumorigenesis in the gastrointestinal tract, which is complicated by the multiple immunoregulatory effects of leptin.\nConclusion\nLeptin is an important modulator of major aspects of gastrointestinal tract functions, independent of its more well-described roles in appetite regulation and obesity.","container-title":"Nutrition","DOI":"10.1016/j.nut.2010.07.004","ISSN":"0899-9007","issue":"3","journalAbbreviation":"Nutrition","language":"en","page":"269-275","source":"ScienceDirect","title":"Diverse roles of leptin in the gastrointestinal tract: Modulation of motility, absorption, growth, and inflammation","title-short":"Diverse roles of leptin in the gastrointestinal tract","volume":"27","author":[{"family":"Yarandi","given":"Shadi S."},{"family":"Hebbar","given":"Gautam"},{"family":"Sauer","given":"Cary G."},{"family":"Cole","given":"Conrad R."},{"family":"Ziegler","given":"Thomas R."}],"issued":{"date-parts":[["2011",3,1]]}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} (Yarandi et al., 2011). Leptin regulates energy intake by interacting with multiple neural pathways both inside and outside the hypothalamus via orexigenic and anorexigenic neuropeptides ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"XlnTal3L","properties":{"formattedCitation":"(Dardeno et al., 2010)","plainCitation":"(Dardeno et al., 2010)","noteIndex":0},"citationItems":[{"id":1362,"uris":["http://zotero.org/users/9182839/items/SQ8Z8SXS"],"itemData":{"id":1362,"type":"article-journal","abstract":"Leptin regulates energy homeostasis and reproductive, neuroendocrine, immune, and metabolic functions. In this review, we describe the role of leptin in human physiology and review evidence from recent "proof of concept" clinical trials using recombinant human leptin in subjects with congenital leptin deficiency, hypoleptinemia associated with energy-deficient states, and hyperleptinemia associated with garden-variety obesity. Since most obese individuals are largely leptin-tolerant or -resistant, therapeutic uses of leptin are currently limited to patients with complete or partial leptin deficiency, including hypothalamic amenorrhea and lipoatrophy. Leptin administration in these energy-deficient states may help restore associated neuroendocrine, metabolic, and immune function and bone metabolism. Leptin treatment is currently available for individuals with congenital leptin deficiency and congenital lipoatrophy. The long-term efficacy and safety of leptin treatment in hypothalamic amenorrhea and acquired lipoatrophy are currently under investigation. Whether combination therapy with leptin and potential leptin sensitizers will prove effective in the treatment of garden-variety obesity and whether leptin may have a role in weight loss maintenance is being greatly anticipated.","container-title":"Frontiers in neuroendocrinology","DOI":"10.1016/j.yfrne.2010.06.002","ISSN":"0091-3022","issue":"3","journalAbbreviation":"Front Neuroendocrinol","note":"PMID: 20600241\nPMCID: PMC2916735","page":"377-393","source":"PubMed Central","title":"Leptin in Human Physiology and Therapeutics","volume":"31","author":[{"family":"Dardeno","given":"Tina A."},{"family":"Chou","given":"Sharon H."},{"family":"Moon","given":"Hyun-Seuk"},{"family":"Chamberland","given":"John P."},{"family":"Fiorenza","given":"Christina G."},{"family":"Mantzoros","given":"Christos S."}],"issued":{"date-parts":[["2010",7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} (Dardeno et al., 2010). The hypothalamic ARC is an important leptin action site ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Xnw8nVhe","properties":{"formattedCitation":"(van Swieten et al., 2014)","plainCitation":"(van Swieten et al., 2014)","noteIndex":0},"citationItems":[{"id":3077,"uris":["http://zotero.org/users/9182839/items/T9569PCC"],"itemData":{"id":3077,"type":"article-journal","abstract":"The anorexigenic hormone leptin plays an important role in the control of food intake and feeding-related behavior, for an important part through its action in the hypothalamus. The adipose-derived hormone modulates a complex network of several intercommunicating orexigenic and anorexigenic neuropeptides in the hypothalamus to reduce food intake and increase energy expenditure. In this review we present an updated overview of the functional role of leptin in respect to feeding and feeding-related behavior per distinct hypothalamic nuclei. In addition to the arcuate nucleus, which is a major leptin sensitive hub, leptin-responsive neurons in other hypothalamic nuclei, including the, dorsomedial-, ventromedial- and paraventricular nucleus and the lateral hypothalamic area, are direct targets of leptin. However, leptin also modulates hypothalamic neurons in an indirect manner, such as via the melanocortin system. The dissection of the complexity of leptin's action on the networks involved in energy balance is subject of recent and future studies. A full understanding of the role of hypothalamic leptin in the regulation of energy balance requires cell-specific manipulation using of conditional deletion and expression of leptin receptors. In addition, optogenetic and pharmacogenetic tools in combination with other pharmacological (such as the recent discovery of a leptin receptor antagonist) and neuronal tracing techniques to map the circuit, will be helpful to understand the role of leptin receptor expressing neurons. Better understanding of these circuits and the involvement of leptin could provide potential sites for therapeutic interventions in obesity and metabolic diseases characterized by dysregulation of energy balance.","container-title":"Journal of Chemical Neuroanatomy","DOI":"10.1016/j.jchemneu.2014.05.004","ISSN":"0891-0618","journalAbbreviation":"Journal of Chemical Neuroanatomy","language":"en","page":"207-220","source":"ScienceDirect","title":"The neuroanatomical function of leptin in the hypothalamus","volume":"61-

62","author":[{"family":"Swieten","given":"M. M. H.","non-dropping-particle":"van"},{"family":"Pandit","given":"R."},{"family":"Adan","given":"R. A. H."},{"family":"Plasse","given":"G.","non-dropping-particle":"van der"}],"issued":{"date-parts":[["2014",11,1]]}}},"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} (van Swieten et al., 2014).

2.MATERIALS AND METHODS:

Study population and design: A comparative study. There were 76 participants. The subjects of this study were divided into three categories: Normal group (Group I): 28 non-obese people were chosen as normal weight, with BMIs ranging from (18.5-24.9). Overweight group (Group II): 20 overweight individuals chose a BMI ranging from (25.0 - 29.9). Obese group (Group III): 28 obese participants chose BMIs ranging from (30.0-40.0). (BMI) For all samples, body mass index was determined as weight (kg) divided by height (metre2). Each participant had medical examinations.

Collection Of Blood Samples:

A total of 76 blood samples were obtained from 28 healthy individuals, 20 overweight, and 28 obese individuals. The materials were centrifuged at 3500 rpm for ten minutes. Leptin and OXM serums were analyzed for S.TC, S.TG, S.HDL, S.LDL, and S.VLDL levels. Hormone tests were maintained at -70°C until analysis, whereas kits were kept at 2-8°C.

Inclusion And Exclusion Criteria:

Inclusion criteria were: Both of genders, people aged 30-66 years, obese, normal weight, and overweight samples, ≥30 years old, with cardiovascular disease, hypertension, and diabetes. Exclusion criteria included being underweight, being under the age of 30, taking hormone replacement therapy, taking antioxidant supplements, having a history of endocrine diseases, being pregnant, having cancer, having chronic kidney disease, dieting, taking hormonal supplements, having hemolyzed blood samples, having gastric bypass surgery, and having a cholecystectomy.

Study Timeline:

The current study was conducted from September 1st, 2021 to March 30th, 2022, through a cooperation between the cardiac center and Erbil's court in Erbil, Iraq.

Questionnaire Form Design:

The data collection instrument was face-to-face questionnaire that is pretested with modifications access made before its use in the study, along with medical records which contain intimate personal information. The questionnaire includes the demographic variables (name, age, gender, address), the patient's clinical risk factors, their family history, and their smoking habits.

Ethical Considerations:

The study protocols were reviewed and approved by the scientific committee of the College of Medicine at Hawler Medical University, and the Ethical Committee of the General Directorate of Health in Erbil. Permission also was taken from participants in this study. In addition to assurances on the safety of the data and their anonymity, each participant received a thorough explanation of the nature and goals of the study.

Hormonal Assays:

The Enzyme-linked immunosorbent assay (ELIZA) technique was used to do the fasting serum hormone tests. The ELIZA Kit USA was provided by the company Al-Shkairate establishment for medical supplies, for determining the Leptin and OXM tests. The test was conducted in accordance with the manufacturer's specifications. Serums were separated using centrifugation at 3500 rpm for 10 minutes. Adult OXM levels range from 31.25 to 2000 pg/mL. Leptin ranges from 0.3 to 13.4 ng/mL.

Biochemical Assays

Using colorimetric-enzymatic techniques, the fasting serum lipid tests were conducted. Total cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol were measured using a fully automated biochemistry analyzer (Roche/Hitachi COBAS C-311, Germany). Following the manufacturer's instructions, the assay was carried out. Centrifugation at 3500 rpm for 10 minutes was used to separate the serums. Cholesterol levels below 200 mg/dL in adults (Greiling and Gressner, 1995). Triglyceride levels below 150 mg/dL in adults (Greiling and Gressner, 1995). HDL-C levels (45-65 mg/dL) in Female and (33-55 mg/dL) in male (Nauck et al.,1997).

LDL-C levels below 100 mg/dL in adults (Rifai et al., 1992). (VLDL-C) was determined indirectly using the (VLDL-C = triglycerides/5) equation. And (VLDL-C) levels in adults should be between (2-30) mg/dL.

Statically Analysis

The statistical package for social sciences (SPSS, version 26) was used to analyze the data. The findings were presented as mean ± SD and mean ± SE. It was established how different the group mean values were from one another. the chi-square test, and a one-way (ANOVA) ests were employed to look at the variation in the group mean values. The statistical measure of the degree of correlation between two numerical variables is the Pearson correlation coefficient (r). (p-value $\leq$ 0.05) was considered statistically significant.

RESULTS

There were 76 participants in all, split up into three groups: Group I consisted of 28 individuals (18% who were normal), Group II consisted of 20 overweight individuals (14%), and Group III consisted of 28 obese individuals (18%) who were obese out of the total study population. The age range covered the years 30-66. Of the participants, the majority (36.9%) were under 50 years old, and the majority (35.6%) were men. Table 1. Medical history is represented in Table 2. Table 3 displays the arithmetic means of the biochemical parameters in the study population. On the other hand, TG and VLDL serum levels were considerably greater ($p<0.025$ and $p<0.025$), respectively, whereas HDL serum levels were decreased ($p<0.023$), were calculated between patients who were obese and those who were not, and it was found that there was no significant

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correlation between the blood levels of T.C. (p=0.383) and LDL (p=0.645) in the obese people in Table 4. Table 5 makes it clear that higher BMIs are associated with higher leptin means ($p < 0.001$), but the opposite is also true for OXM: in obese people, higher BMIs are associated with lower OXM means ($p < 0.001$). As shown in (Figure 1), there was a clear positive strong correlation found between BMI and leptin ($r = 0.801$, $p < 0.001$). Figure 2 shows an inverse significant correlation ($r = -0.569$, $p < 0.001$) between Oxyntomodulin and BMI.

Additionally, the study's outcomes showed that the mean HDL levels in the obese group were lower than normal but higher than those in the overweight group. (19.36±0.99mg/dl), (p=0.023), (Table 4). Because there is a strong link between increased initial and recurrent CVD events in obese with low levels and high levels of HDL ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"a8tmou76m7","properties":{"formattedCitation":"(Asztalos et al., 2010)","plainCitation":"(Asztalos et al., 2010)","noteIndex":0},"citationItems":[{"id":3419,"uris":["http://zotero.org/users/9182839/items/AZPKXIGN"],"itemData":{"id":3419,"type":"article-journal","abstract":" Plasma lipoproteins and glucose homeostasis were evaluated after marked weight loss before and over 12 months following Roux-en-Y gastric-bypass (RYGBP) surgery in 19 morbidly obese women. Standard lipids, remnant-lipoprotein cholesterol (RLP-C); HDL-triglyceride (TG); apolipoproteins (apo) A-I, A-II, E, and A-I-containing HDL subpopulations; lecithin-cholesterol acyltransferase (LCAT) and cholesteryl ester transfer protein (CETP) mass and activity; plasma glucose and insulin levels were measured before and at 1, 3, 6, and 12 months after GBP surgery. Baseline concentrations of TG, RLP-C, glucose, and insulin were significantly higher in obese than in normal-weight, age-matched women, whereas HDL cholesterol (HDL-C), apoA-I, apoA-II, α-1 and α-2 levels were significantly lower. Over 1 year, significant decreases of body mass index, glucose, insulin, TG, RLP-C, HDL-TG, and preβ-1 levels were observed with significant increases of HDL-C and α-1 levels (all P < 0.05). Changes of fat mass were correlated with those of LDL cholesterol (P = 0.018) and LCAT mass (P = 0.011), but not with CETP mass (P = 0.265). Changes of fasting plasma glucose concentrations were inversely correlated with those of CETP mass (P = 0.005) and α-1 level (P = 0.004). Changes of fasting plasma insulin concentrations were positively correlated with those of LCAT mass (P = 0.043) and inversely with changes of α-1 (P = 0.03) and α-2 (P = 0.05) concentrations. These results demonstrate beneficial changes in HDL remodeling following substantial weight loss induced by RYGBP surgery and that these changes are associated with improvement of glucose homeostasis in these patients. ","container-title":"Journal of Lipid Research","DOI":"10.1194/jlr.P900015-JLR200","ISSN":"0022-2275, 1539-7262","issue":"8","journalAbbreviation":"Journal of Lipid Research","language":"English","note":"publisher: Elsevier","page":"2405-2412","source":"www.jlr.org","title":"Effects of weight loss, induced by gastric bypass surgery, on HDL remodeling in obese women","volume":"51","author":[{"family":"Asztalos","given":"Bela F."},{"family":"Swarbrick","given":"Michael M."},{"family":"Schaefer","given":"Ernst J."},{"family":"Dallal","given":"Gerard E."},{"family":"Horvath","given":"Katalin V."},{"family":"Ai","given":"Masumi"},{"family":"Stanhope","given":"Kimber L."},{"family":"Austrheim-Smith","given":"Iselin"},{"family":"Wolfe","given":"Bruce M."},{"family":"Ali","given":"Mohamed"},{"family":"Havel","given":"Peter J."}],"issued":{"date-parts":[["2010",8,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} (Asztalos et al., 2010). In this study leptin positively correlated with TG and VLDL TG (r=0.190, p=0.019), VLDL (r=0.189, p=0.019), (Table 6). ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"yjJL28L0","properties":{"formattedCitation":"(Guo et al., 2022)","plainCitation":"(Guo et al., 2022)","noteIndex":0},"citationItems":[{"id":3133,"uris":["http://zotero.org/users/9182839/items/AJ7VBHZE"],"itemData":{"id":3133,"type":"article-journal","abstract":"Aim To determine the antiobesity effect and safety of glucagon-like peptide-1 receptor agonist (GLP-1RA) including liraglutide, exenatide and semaglutide treatment in overweight/obese patients without diabetes. The random-effect model was used to pool data extracted from included literatures. The weighted mean difference (WMD), odds ratio and 95% confidence interval (CI) were used to present the meta-analysis results (PROSPERO registration number: CRD 42020173199). The sources of intertrial heterogeneity, bias and the robustness of results were evaluated by subgroup analysis, sensitivity analysis and regression analysis, respectively. A total of 24 RCTs were recruited in the present analysis which included 5867 patients. The results showed that the treatment of overweight/obese patients without diabetes with GLP-1RAs including liraglutide, exenatide and semaglutide significantly achieved greater weight loss than placebo [WMD=–5.39, 95% CI (–6.82, –3.96)] and metformin [WMD=–5.46, 95% CI (–5.87, –5.05)]. The subgroup analysis showed that semaglutide displayed the most obvious antiobesity effect in terms of weight loss, the reduction of body mass index (BMI) and waist circumference (WC). However, GLP-1RAs treatments had more gastrointestinal adverse events (such as nausea and vomiting) than placebo and Met. The subgroup analysis also represented that semaglutide displayed the lowest risk of gastrointestinal adverse events among three kinds of GLP-1RAs. Our meta-analysis demonstrated that GLP-1RA had a superior antiobesity effect than placebo/Met in overweight/obese patients without diabetes in terms of body weight, BMI, and WC, especially for semaglutide, which had more obvious antiobesity effect and lower GI adverse events than liraglutide and exenatide.","container-title":"Hormone and Metabolic Research","DOI":"10.1055/a-1844-1176","ISSN":"0018-5043, 1439-4286","issue":"7","journalAbbreviation":"Horm Metab Res","language":"en","license":"Georg Thieme Verlag Rüdigerstraße 14, 70469 Stuttgart, Germany","note":"publisher: Georg Thieme Verlag","page":"458-471","source":"www.thieme-connect.com","title":"The Antiobesity Effect and Safety of GLP-1 Receptor Agonist in Overweight/Obese Patients Without Diabetes: A Systematic Review and Meta-

Analysis","title-short":"The Antiobesity Effect and Safety of GLP-1 Receptor Agonist in Overweight/Obese Patients Without Diabetes","volume":"54","author":[{"family":"Guo","given":"Xiaonan"},{"family":"Zhou","given":"Zhibo"},{"family":"Lyu","given":"Xiaorui"},{"family":"Xu","given":"Hanyuan"},{"family":"Zhu","given":"Huijuan"},{"family":"Pan","given":"Hui"},{"family":"Wang","given":"Linjie"},{"family":"Yang","given":"Hongbo"},{"family":"Gong","given":"Fengying"}],"issued":{"date-parts":[["2022",7]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} (Guo et al., 2022). The results in this study showed a significant association of Leptin/OXM ratio, Leptin/BMI ratio and OXM/BMI ratio (Table 7). The findings of this study reinforce the data reported by ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"xw4B4CqP","properties":{"formattedCitation":"(Crujeiras et al., 2014b)","plainCitation":"(Crujeiras et al., 2014b)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":3201,"uris":["http://zotero.org/users/9182839/items/U38NJV9I"],"itemData":{"id":3201,"type":"article-journal","abstract":"Leptin and ghrelin appear to play a role in weight regain after a successful weight loss. The pre-treatment plasma levels of leptin/ghrelin ratio (L/G) could have power to predict this clinically relevant issue in the obesity treatment.","container-title":"Journal of Endocrinological Investigation","DOI":"10.1007/s40618-013-0004-2","ISSN":"1720-8386","issue":"2","journalAbbreviation":"J Endocrinol Invest","language":"en","page":"119-126","source":"Springer Link","title":"Pre-treatment circulating leptin/ghrelin ratio as a non-invasive marker to identify patients likely to regain the lost weight after an energy restriction treatment","volume":"37","author":[{"family":"Crujeiras","given":"A. B."},{"family":"Díaz-Lagares","given":"A."},{"family":"Abete","given":"I."},{"family":"Goyenechea","given":"E."},{"family":"Amil","given":"M."},{"family":"Martínez","given":"J. A."},{"family":"Casanueva","given":"F. F."}],"issued":{"date-parts":[["2014",2,1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} (Crujeiras et al., 2014), ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"Xo3xEjTY","properties":{"formattedCitation":"(Adamska-Patruno et al., 2018b)","plainCitation":"(Adamska-Patruno et al., 2018b)","dontUpdate":true,"noteIndex":0},"citationItems":[{"id":3206,"uris":["http://zotero.org/users/9182839/items/RHRMFE3Y"],"itemData":{"id":3206,"type":"article-journal","abstract":"Background: Hormones, which influence satiety and hunger, play a significant role in body energy balance regulation. Ghrelin is a peptide that plays an important role in short-term appetite regulation, whereas leptin is a factor that controls long-term energy balance and is considered as a satiety hormone. The aim of this study was to evaluate the leptin/ghrelin ratio in a fasting state and after the intake of meals with varying macronutrient contents and to assess the possible differences between normal body weight and overweight/obese men.\nMethods: We examined 46 healthy adult men (23 with normal body weight and 23 overweight/obese) aged 21–58, who were divided into two groups. In the crossover study, participants received isocaloric (450 kcal) meals with different macronutrient contents: men from the first group received high-carbohydrate (HC) and normo-carbohydrate (NC) meals, and in the second group, participants received high-carbohydrate and high-fat (HF) meals. The ratio of leptin/ghrelin levels was calculated from leptin and total ghrelin serum concentrations in a fasting state and 30, 60, 120, 180 and 240 min after meal intake. One-way ANOVA and Wilcoxon signed-rank tests were carried out. The normality of the variable distribution was checked with the Shapiro–Wilk test, the homogeneity of variances was verified with the Levene test, and the false discovery rate p-value adjustment method was used.\nResults: The leptin/ghrelin ratio was significantly higher in overweight/obese men than individuals with normal body weight in a fasting state, as well as postprandially. We observed trends towards a higher leptin/ghrelin ratio values from the 60 min after HC-meal intake compared to the NC- and HF-meals in normal body weight participants, while in overweight/obese men, we did not note any significant differences dependent on the meal type.\nConclusions: We have observed a significantly different postprandial leptin/ghrelin ratio in normal body weight and overweight/obese men, and our results suggest that in men with normal body weight, a greater feeling of satiety may occur after high-carbohydrate meal intake, which was not noted in the overweight/obese individuals.","container-title":"Nutrition Journal","DOI":"10.1186/s12937-018-0427-x","ISSN":"1475-2891","issue":"1","journalAbbreviation":"Nutr J","language":"en","page":"118","source":"DOI.org (Crossref)","title":"The relationship between the leptin/ghrelin ratio and meals with various macronutrient contents in men with different nutritional status: a randomized crossover study","title-short":"The relationship between the leptin/ghrelin ratio and meals with various macronutrient contents in men with different nutritional status","volume":"17","author":[{"family":"Adamska-Patruno","given":"Edyta"},{"family":"Ostrowska","given":"Lucyna"},{"family":"Goscik","given":"Joanna"},{"family":"Pietraszewska","given":"Barbara"},{"family":"Kretowski","given":"Adam"},{"family":"Gorska","given":"Maria"}],"issued":{"date-parts":[["2018",12]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} (Adamska-Patruno et al., 2018) and ADDIN ZOTERO_ITEM CSL_CITATION {"citationID":"lVCbFyf5","properties":{"formattedCitation":"(Arabi et al., 2020)","plainCitation":"(Arabi et al., 2020)","noteIndex":0},"citationItems":[{"id":3202,"uris":["http://zotero.org/users/9182839/items/UP5SCJ73"],"itemData":{"id":3202,"type":"article-journal","abstract":"The objective of this study was to evaluate leptin, ghrelin, and leptin/ghrelin ratio in critically ill patients and association of leptin/ghrelin ratio with outcomes. This is a sub-study of the PermiT trial (ISRCTN68144998). A subset of 72 patients who were expected to stay >14 days in the Intensive care unit were enrolled. Blood samples were collected on days 1, 3, 5, 7, and 14. Samples were analyzed for leptin and active ghrelin in addition to other hormones. Baseline leptin/ghrelin ratio was

calculated, and patients were stratified into low and high leptin/ghrelin ratio based on the median value of 236. There was a considerable variation in baseline leptin level: Median 5.22 ng/mL (Q1, Q3: 1.26, 17.60). Ghrelin level was generally low: 10.61 pg/mL (Q1, Q3: 8.62, 25.36). Patients with high leptin/ghrelin ratio compared to patients with low leptin/ghrelin ratio were older, had higher body mass index and more likely to be diabetic. There were no differences in leptin/ghrelin ratio between patients who received permissive underfeeding and standard feeding. Multivariable logistic regression analysis showed that age and body mass index were significant independent predictors of high leptin–ghrelin ratio. Leptin–ghrelin ratio was not associated with 90-day mortality or other outcomes. Age and body mass index are predictors of high leptin/ghrelin ratio. Leptin/ghrelin ratio is not affected by permissive underfeeding and is not associated with mortality.","container-title":"Nutrients","DOI":"10.3390/nu12010036","ISSN":"2072-6643","issue":"1","language":"en","license":"http://creativecommons.org/licenses/by/3.0/","note":"number: 1\npublisher: Multidisciplinary Digital Publishing Institute","page":"36","source":"www.mdpi.com","title":"Leptin, Ghrelin, and Leptin/Ghrelin Ratio in Critically Ill Patients","volume":"12","author":[{"family":"Arabi","given":"Yaseen M."},{"family":"Jawdat","given":"Dunia"},{"family":"Al-Dorzi","given":"Hasan M."},{"family":"Tamim","given":"Hani"},{"family":"Tamimi","given":"Waleed"},{"family":"Bouchama","given":"Abderrezak"},{"family":"Sadat","given":"Musharaf"},{"family":"Afesh","given":"Lara"},{"family":"Abdullah","given":"Mashan L."},{"family":"Mashaqbeh","given":"Walid"},{"family":"Sakhija","given":"Maram"},{"family":"Al-Dawood","given":"Abdulaziz"}],"issued":{"date-parts":[["2020",1]]}}}],"schema":"https://github.com/citation-style-language/schema/raw/master/csl-citation.json"} (Arabi et al., 2020). Significant and interesting associations might be a helpful marker for central obesity.

5. CONCLUSIONS:

According to our research, there were notable differences in the blood concentrations of peptide hormones between persons who were obese and those who were not. This study evaluates blood levels of oxyntomodulin and leptin in obese individuals. Since there is a significant correlation between these hormones and BMI, impacting both BMI markers and lipid profiles, obese people have higher levels of leptin and lower levels of OXM than non-obese people. Leptin was shown positively related to serum TC, TG HDL and VLDL, while Oxyntomodulin was negatively correlated with TG, HDL, VLDL, a significant association of Leptin/OXM ratio, Leptin/BMI ratio and OXM/BMI ratio in obese Individuals. The present study concluded that serum Leptin and OXM hormones significantly impacted controlling appetite in obesity.

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Conflict of Interest

The writers informed they had no competing interests.

TABLE 1. HABITS AND SOCIO-DEMOGRAPHIC CHARACTERISTICS

Variables	No. (%)
Age (years)	
30-39	33 (27.1 %)
40-49	23 (15.15 %)
50-59	14 (9.2 %)
≥ 60	6 (3.95 %)
Gender	
Male	54 (35.55 %)
Female	22 (14.45 %)
Smoking	
Never	39.5 (26 %)
Ex-smoker	10 (6.6 %)
Current smoker	26.5 (17.45 %)
Consumption of sweets, soft drinks and Junk foods	
Yes	62.5 (41.1 %)
No	13.5 (8.9 %)
Alcohol	
Never	69.5 (45.7 %)
Occasionally	1.5 (1 %)
Sometimes	5 (3.3 %)
Diet	
I eat meat	74 (48.7 %)
I don't love meat	2 (1.3 %)
Meals	
Once	4 (2.65 %)
Twice	15 (9.85 %)
Three times	51.5 (33.9 %)
More than three times	5.5 (3.6 %)
Total	76 (100%)

TABLE 2. MEDICAL HISTORY

Variables	No. (%)
Diabetes	
Type 2 DM	10 (6.6 %)
No DM	66 (43.4 %)
Chronic heart disease	
None	61.5 (40.45 %)
Cardiovascular disease (CVD)	6 (3.95 %)
Congestive heart failure (CHF)	3.5(2.3 %)
CVD and CHF	2.5 (1.65 %)
CVD and previous myocardial infarction	1.3 (3.3 %)
Hypertension	
Yes	12.5 (8.2 %)
No	31.75 (41.8 %)
Total	76 (100%)

TABLE 3. ARITHMETIC MEANS OF BIOCHEMICAL PARAMETERS IN THE STUDY POPULATION

Variables	Mean ±SD	p-value
FBS (mg/dl)	62.43± 21.85	<0.001
BMI (kg/m^2)	14.87± 3.75	<0.001
Total cholesterol (mg/dl)	82.69± 18.38	0.15
Triglycerides (mg/dl)	93.86± 59.52	0.004
HDL (mg/dl)	19.54± 4.65	0.37
LDL (mg/dl)	44.40± 15.34	0.83
VLDL (mg/dl)	18.78± 11.9	0.004

FBS: Fasting blood sugar, BMI: Body mass index, SD: Standard deviation, TC: Total Cholesterol, TG: Triglycerides, HDL: High-density lipoprotein, LDL: Low-density lipoprotein, VLDL: Very-low-density lipoprotein, p: p-value.

TABLE 4: ARITHMETIC MEANS OF BIOCHEMICAL PARAMETERS AMONG GROUPS

Metabolic parameters		Mean ± SE	95% CI* Lower-Upper	p-value
T.C (mg/dL)	Normal	80.55 ± 2.751	75.03-86.06	0.383
	Overweigh t	83 ±2.56	77.92-88.26	
	Obese	84.78±4.19	75.91-93.65	
TGs (mg/dL)	Normal	75.16 ± 8.80	57.52-92.79	0.025
	Overweigh t	94.57 ± 6.41	81.64-107.51	
	Obese	112.67±14.71	81.54-143.79	
HDL (mg/dL)	Normal	20.65 ± 0.75	19.16-22.15	0.023
	Overweigh t	18.41 ± 0.53	17.34-19.48	
	Obese	19.36±0.99	17.25-21.47	
LDL (mg/dL)	Normal	44.86± 1.85	41.16-48.56	0.645
	Overweigh t	45.76± 2.48	40.76-50.76	
	Obese	42.93±3.962	34.55-51.32	
VLDL (mg/dL)	Normal	15.03 ± 1.759	11.50-18.56	0.025
	Overweigh t	18.92± 1.28	16.33-21.51	
	Obese	22.53±2.94	16.31-28.76	

TABLE 5. DESCRIPTIVE STATISTICS OF THE STUDIED PARAMETERS BY BMI CATEGORIES

	BMI	Mean ± SE		95% CI** Lower - Upper	p-value
Leptin (ng/ml)	Normal	2.72±0.26		2.19-3.24	<0.001
	Overweight	6.42±0.53		5.36-7.49	
	Obese	18.26± 1.85		14.36-22.16	
Oxyntomodulin (OXM) (pg/ml)	Normal	1.09±0.06		0.99-1.2	<0.001
	Overweight	0.75±0.07		0.61-0.89	
	Obese	0.44±0.07		0.29-0.58	

*CI: Confidence interval. By ANOVA, p: p- value, SE: Standard Error.

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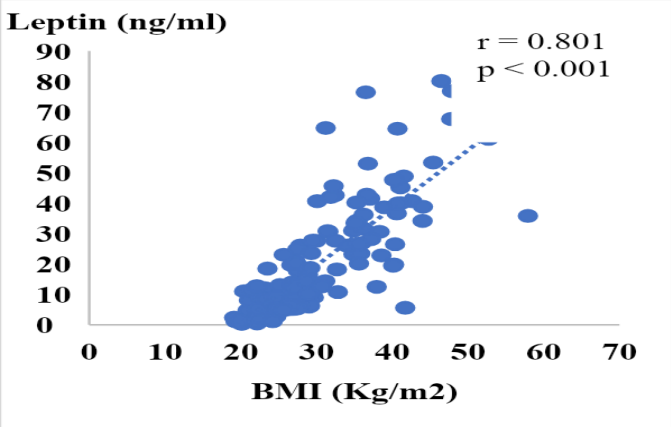

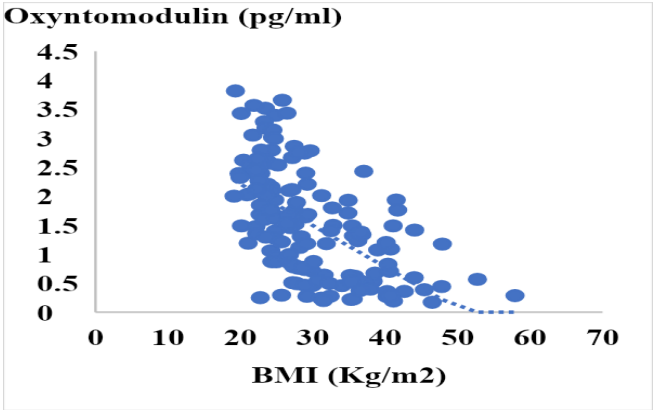

Figure 1: Correlation Coefficient Between BMI and Leptin, Figure 2: Correlation Coefficient Between BMI and Oxyntomodulin

TABLE 6: CORRELATION BETWEEN HORMONE PARAMETERS WITH LIPID PARAMETERS IN OBESITY

Hormone parameters	Pearson correlation and p-value	T.C mg/dl	TGs mg/dl	HDL mg/dl	LDL mg/dl	VLDL mg/dl
OXM (pg/mL)	r	0.016	-0.130	-0.004	0.121	-0.130
	p-value	0.844	0.109	0.960	0.136	0.109
Leptin (ng/mL)	r	0.121	0.190	0.096	-0.029	0.189
	p-value	0.137	0.019	0.238	0.714	0.019

OXM: Oxyntomodulin

TABLE 7: THE RELATIONSHIP BETWEEN HORMONES RATIO AND BMI IN OBESE

		Mean ±SE	95% CI Lower- Upper	p-value
L/BMI ratio	Normal	11.51±1.14	9.23-13.79	<0.001
	Overweight	22.83±1.87	19.06-26.61	
	Obese	48.13±4.92	37.73-58.54	
O/BMI ratio	Normal	4.58±0.25	4.08-5.08	<0.001
	Overweight	2.42±0.26	1.88-2.95	
	Obese	0.92±0.20	0.51-1.34	
L/O ratio	Normal	1.26±0.18	0.89-1.62	<0.001
	Overweight	6.99±1.27	4.43-9.55	
	Obese	35.74±7.77	19.38-52.10	

O: Oxyntomodulin, L: Leptin, BMI: Body mass index

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