

Pharmacological methods for weight reduction and their connection with the human gut microbiota

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Abstract

In the beginning of the twenty-first century, obesity has become a concerning world-wide issue due to its high prevalence in modern society. It is a metabolic disorder, caused by excessive accumulation of adipose tissue in the human organism – the main reason for which is increased caloric intake and decreased caloric expenditure in combination with dysregulation of hunger. It is a chronic systematic disease that leads to the development of a large number of health complications, the most common of which are: diabetes mellitus type 2, arterial hypertension, atherosclerosis, sleep apnea, different types of cancer and more.

During the last decade, significant advancements have been made in regard to treatment of many endocrine and metabolic conditions, using pharmacological means, and some of these novel medications have proven to be an effective therapy for obesity. There is emerging evidence that such drugs can exhibit an effect over the human gut microbiota – the complex system of commensal bacteria located in the gastrointestinal tract, which could affect appetite, mucosal integrity, nutrient absorption, and that interaction can be the key to understanding the pathogenesis of obesity and its treatment.

Keywords

antiobesity drugs, GI tract microorganisms, obesity, weight reduction

Introduction

Obesity and its closely related condition metabolic syndrome are becoming more and more relevant problems for our modern society with every passing year – they represent a serious threat to the health of people, especially in developed and developing countries, and there is a clear tendency for progressively increasing numbers of affected patients – both in the adult population and also in children (Nuttall 2015; Lustig et al. 2022; Yang et al. 2022; Masood and Moorthy 2023). Obesity is a systematic chronic disease, which is characterized by excessive fat deposition in the human body,

resulted from an increased energy intake (the modern diet consists of calorie-dense foods containing high amounts of easily digestible simple carbohydrates /monosaccharides/ and saturated fats), impaired regulation of appetite and furthermore – due to decreased energy expenditure (low levels of physical activity and stationary lifestyle) (Nuttall 2015; Lustig et al. 2022; Yang et al. 2022; Masood and Moorthy 2023). Obesity has a very complex pathogenesis and some of the reasons that contribute to the development of the disease can be social, economic, environmental, genetic factors, underlying endocrine and metabolic disruptions (Lustig et al. 2022; Yang et al. 2022; Masood and Moorthy

2023). Some additional factors are the dysregulation in production and secretion of some hormones and other regulatory molecules in the central nervous system which affect hunger and appetite, for example – ghrelin, leptin, proopiomelanocortin (POMC), cocaine-amphetamine-regulated transcript (CART) and other similar compounds (Lustig et al. 2022; Yang et al. 2022; Masood and Moorthy 2023).

Obesity can lead to significant long-term damage to several organs and increase the risk for developing of: cardiovascular system conditions (endothelial dysfunction, atherosclerosis, myocardial infarction, brain stroke), chronic kidney disease (glomerular damage), liver steatosis (non-alcoholic fatty liver disease – NAFLD), malignant tumors (including hepatocellular and pancreatic cancer), metabolic and endocrine system conditions (diabetes mellitus type 2) (Gonzalo-Encabo et al. 2021; Lustig et al. 2022; Masood and Moorthy 2023). Obesity is directly responsible for the condition known as low-grade systematic inflammation, characterized by permanently elevated blood plasma levels of pro-inflammatory molecules – cytokines like interleukin IL-1 and IL-6, tumor-necrosis factor-alpha TNF- α , C-reactive protein CRP and other similar compounds (Gonzalo-Encabo et al. 2021; Lustig et al. 2022; Masood and Moorthy 2023). This state of inflammation is a major pathogenic feature of obesity and is responsible for the increased activation of immune cells (leukocytes, macrophages), increased vascular permeability and immune cell infiltration of tissues (adipose tissue, skeletal muscles, liver, pancreas), leading to formation of free radicals, oxidative stress and subsequent cellular damage (Gonzalo-Encabo et al. 2021; Lustig et al. 2022; Masood and Moorthy 2023). These molecular processes are manifested as organ dysfunctions at the macroorganism level.

Conventional methods for treatment of obesity

Due to the significant impact that obesity has on society, it is important to take into consideration different strategies and approaches for prevention of weight gain and treatment of obese patients. The successful management of obesity should start with a plan that identifies the patient's individual profile and needs – the potential contributory

factors to weight gain, dietary habits, physical activity, genetic predisposition and family history of obesity, previous attempts at weight loss and other medical underlying conditions or medications that may lead to increase in body weight – such information can provide useful insight about the origins of obesity in the specific patient's case (Wirth et al. 2014; Shukla et al. 2015).

Lifestyle interventions form the basis for initial therapy for obesity and include diet modification, increased physical activity and cognitive behavioral therapy (Wirth et al. 2014; Shukla et al. 2015). An individual patient's body weight is directly proportional to the caloric intake and energy expenditure over a certain period of time, and it follows the principle that weight is lost when a fewer amount of calories is being consumed than expended (Wirth et al. 2014; Shukla et al. 2015). Diet-induced weight loss can be achieved through negative energy balance (it is recommended for obese individuals to consume a diet with an energy deficit of approximately 500–750 kcal per day), and such caloric restriction can be accomplished through adjusting the macronutrient composition of a diet by alteration in the consumption of certain food products – amongst the most effective approaches which have shown practical efficiency are low-fat, low-carbohydrate, protein-rich, and fiber-rich diets (Wirth et al. 2014; Shukla et al. 2015). Physical activity and frequent exercise can produce meaningful weight reduction if used in addition to the previously mentioned approaches as part of the intervention, and are an important part of maintaining weight loss (Wirth et al. 2014; Shukla et al. 2015). Cognitive behavioral therapy as a component of lifestyle therapy for obesity is designed to assist with the patient's adherence to the diet modifications and physical exercises, but it requires a greater level of commitment from the patient (Wirth et al. 2014; Shukla et al. 2015). Combining the three previously mentioned approaches leads to more successful results in achieving and maintaining a reduced body weight in obese patients (Table 1).

If this first line of multidisciplinary treatment does not prove effective, the patient may require additional pharmacological therapy in order to meet the required weight loss goals and health goals (usually such approach is reserved for cases of persistent obesity, not influenced by the use of previously mentioned methods, and showing signs of early development of obesity-related health complications).

Table 1. Step-wise approach in the treatment of obesity.

	Normal weight BMI = 20–24.9	Overweight BMI = 25–29.9	Class I Obesity BMI = 30–34.9	Class II Obesity BMI = 35–39.9	Class III Obesity BMI > 40
Balanced diet Physical activity	+	+	+	+	+
Cognitive Behavioral Therapy		+	+	+	+
Pharmacological Therapy		* In the presence of obesity-related complications; comorbidities	+	+	+
Surgical therapy			* If pharmacological and cognitive behavioral therapy proves ineffective; comorbidities	* In the presence of obesity-related complications; comorbidities	+

Legend: Body Mass Index /BMI/ represented in kg/m² shown according to Nuttall (2015). Therapeutical strategies represented according to Wirth et al. (2014), Shukla et al. (2015).

Novel pharmacological approaches for treatment of obesity

Recent research has shown that improper interaction between hormones and the central nervous system (CNS) satiety centers is responsible for excessive food consumption – specifically, a dysregulation of the orexigenic hormones (increased levels of ghrelin) and anorexigenic hormones (decreased levels of leptin, cholecystokinin, peptide YY /PYY/, glucagon-like peptide-1 /GLP-1/) – the impaired interaction between these regulatory molecules and the hypothalamic satiety centers is a significant component of the pathophysiology of obesity (Sharma et al. 2018; Popoviciu et al. 2023).

In recent years the incretin system has been identified as a promising therapeutic target – incretins are small peptide molecules (secreted from the enteroendocrine L-type cells of the small intestines in the presence of glucose), that include the glucagon-like peptide-1 /GLP-1/ and glucose-dependent insulinotropic polypeptide /GIP/ (Sharma et al. 2018; Popoviciu et al. 2023). They function as metabolic regulators (by increasing insulin secretion from the pancreas and also inhibiting glucagon secretion) and can also act on both peripheral tissues and on brain structures involved in food intake, appetite, satiety and hunger (Sharma et al. 2018; Popoviciu et al. 2023). As a result of their effect on different target receptors in the central nervous system, GI tract, liver, pancreas, skeletal muscles and adipose tissue, they regulate energy homeostasis, glucose metabolism and insulin sensitivity, thus promoting reduction of food intake, decreased hunger, slowing down of gastric emptying, and furthermore, it has been shown that GLP-1 secretion from the gut epithelium is impaired in patients with diabetes mellitus type 2 and obesity, suggesting an important role in the pathophysiology of these metabolic-endocrine conditions (Sharma et al. 2018; Popoviciu et al. 2023).

It has been established that the naturally occurring incretin GLP-1 has a severely limited use as a medication because of its extremely short half-life (~2 min) due to being susceptible to quick degradation from the plasma enzyme

DiPeptidylPeptidase-4 (DPP-4) (Sharma et al. 2018; Popoviciu et al. 2023). In order to overcome these drawbacks of GLP-1 and to achieve therapeutic advantages, new drugs called GLP-1 receptor agonists were introduced – while they retain the same effects as the endogenous molecule (the main pharmacological action being – stimulating the secretion of insulin from the beta-cells of the pancreas), they are resistant to being metabolized from DPP-4 (Sharma et al. 2018; Popoviciu et al. 2023). Examples of GLP-1 receptor agonists used in modern clinical practice are the medications: Exenatide, Liraglutide, Semaglutide, Dulaglutide, and Lixisenatide (Table 2) – their main clinical use in the last decade has been for treatment of patients with diabetes mellitus type 2, however in addition to consistently providing efficient lowering of blood glucose levels, drugs from this class also retain another property of the endogenous incretins – by acting on both the central and peripheral mechanisms, they result in decreased appetite, reduced food intake and long-term weight loss (Sharma et al. 2018; Popoviciu et al. 2023).

GLP-1 receptor agonists appear to be generally safe and very well tolerated. The side effects include: gastrointestinal tract disturbances – commonly nausea, vomiting, diarrhea (in severe cases that could be a reason for discontinuation of therapy), very rare instances of hypoglycemia (usually in higher doses when combined with other antidiabetic drugs from the sulfonylurea class; extremely uncommon when used independently) and local inflammatory skin reaction near the site of injection (for the ones applied subcutaneously) (Ryder 2013; Consoli and Formoso 2014; Popoviciu et al. 2023). There is data indicating that long-term GLP-1 receptor agonist used may be associated with an increased risk of acute pancreatitis and developing pancreatic cancer, however these potential hazards have not been confirmed yet in thorough large scale clinical trials, so at the moment increased caution is advised (observing levels of pancreatic enzymes – amylase and lipase – in patients on long-term GLP-1 receptor agonist therapy) (Ryder 2013; Consoli and Formoso 2014; Popoviciu et al. 2023).

In addition to all previously mentioned therapeutic effects there is also emerging evidence that these medications may also interact with and influence the complex system of bac-

Table 2. Glucagon-like peptide-1 receptor agonist drugs.

GLP-1 Receptor Agonist Generic name	GLP-1 Receptor Agonist Trademark name (Authorized for use in the EU)	Method of administration	Pharmacological effects (identical for all medications in the group)	Side effects (identical for all medications in the group)
Exenatide	Byetta *	subcutaneous	↑ insulin	GI disturbance
	Bydureon *	subcutaneous	secretion	- nausea
Liraglutide	Victoza *	subcutaneous	↓ glucagon	- vomiting
	Saxenda *	subcutaneous	secretion	- diarrhea
Semaglutide	Ozempic *	subcutaneous	↓ blood glucose	Hypoglycemia
	Wegovy *	subcutaneous	levels	/rare/
	Rybelsus *	oral tablets	↓ weight	(?) ↑ risk of
Dulaglutide	Trulicity *	subcutaneous	↓ hunger	pancreatitis
Lixisenatide	Lyxumia *	subcutaneous	↓ appetite ↓ food intake	pancreatic cancer

Legend: Glucagon-like peptide-1 receptor agonist drugs shown with their generic names, trademark names (of drugs approved by the European Medicines Agency /EMA/), and other relevant data concerning their clinical use, presented according to Ryder 2013; Consoli and Formoso 2014; Sharma et al. 2018; Popoviciu et al. 2023.

terial microorganisms in the gastrointestinal tract, known as the human gut microbiota, which by itself is proving to be a fundamental target for treatment of endocrine and metabolic disorders like obesity and diabetes mellitus type 2.

Human gut microbiota – physiological functions and composition

The gut microbiota is a complex system formed by all commensal bacteria that inhabit the human gastrointestinal system, mainly – the intestines (and the colon in particular). Due to extensive research in this area in the last couple of decades, we have gained valuable information about the physiological function and composition of the gut microbiota, but also about its relation to the pathogenesis of different health conditions (Cani and Delzenne 2009, 2011). The human GI tract contains more than 100 trillion bacterial cells, and the main representatives of these microorganisms are several groups, including: phylum Bacteroidetes (containing genus *Bacteroides*, *Prevotella*), phylum Firmicutes (containing genus *Clostridium*, *Enterococcus*, *Lactobacillus*) and in relatively small amount phylum Actinobacteria (containing genus *Bifidobacterium*), genus Proteobacteria (containing genus *Helicobacter*, *Escherichia*) (Cani and Delzenne 2009, 2011).

These bacteria play an important role in the regulation of processes both locally in the GI tract but also systemically in the entire human organism – research shows that some of their physiological effects include: inhibition of growth of pathogenic intestinal bacteria, promoting normal barrier function of the epithelial layer of intestinal mucosa, contribution to normal digestion, fermentation of food products in the colon, regulating energy balance through modifying nutrient absorption, supporting human macroorganism homeostasis by affecting endocrine and metabolic functions (Cani and Delzenne 2009, 2011). All of the previously mentioned facts show that the gut microbiota has a strong influence over a variety of physiological processes in the human macroorganism, and due to this, it has been suggested that there is a connection between the gut microorganisms and diseases like obesity – experimental models and human patients evaluation has confirmed this hypothesis: obese individuals show pathological deviation in the microbiota composition (Cani and Delzenne 2009, 2011).

For example, in normal weight patients, the gut microbiota consists mainly of the two large phyla Firmicutes and Bacteroidetes, which together compose up to 90% of all GI tract bacteria (Ley et al. 2006; Turnbaugh et al. 2006). Research shows that in obese patients, the ratio between these two large groups is shifted – high-calorie diets (rich in saturated fats and easily digestible carbohydrates) lead to clear increase in the abundance of phylum Firmicutes and a significant decrease of phylum Bacteroidetes (Ley et al. 2006; Turnbaugh et al. 2006). Due to the important role of gut bacteria in regulating nutrient absorption, such a

shift can lead to disruption of energy homeostasis and affect the pathogenesis of endocrine and metabolic diseases like obesity.

There has been an increasing scientific interest during the last decade in regard to the interaction between commensal bacterial cells and human host cells from the intestinal epithelium, especially the regulatory enteroendocrine cells, due to their innate ability to interact with chemical compounds inside of the lumen and correspond by secreting peptide molecules that regulate homeostasis in the organism (Cani et al. 2013). One specific subtype – the L-type enteroendocrine cells – possess certain membrane-bound G-protein coupled receptors like GPR41 and GPR43 that can be activated by different bacterial metabolites, after which these cells will respond with secreting regulatory molecules, including GLP-1 and peptide YY (both of which are part of the anorexigenic peptides) – that represents the fine mechanisms of endocrine regulation for energy homeostasis carried out by the interaction between the human host cells and bacteria from the gut microbiota (Cani et al. 2013).

GLP-1 receptor agonists and gut microbiota

The GLP-1 receptor agonists have proven themselves as highly effective drugs for therapy of both diabetes mellitus type 2 and obesity in the past decade (Montandon and Jornayvaz 2017; Xourgia et al. 2019). Due to their extensive use in that area of endocrinology, many authors have started to suggest a possible link between the weight reducing effects of these medications and modulation in the composition and function of GI tract bacteria – there is emerging evidence that the presence of such a connection is not only plausible but also very probable and it may give researchers insight into the pathogenesis of such metabolic diseases (Montandon and Jornayvaz 2017; Xourgia et al. 2019). Our current knowledge about the effects of these drugs on gut dysbiosis is provided by studies based mainly on PCR techniques like 16S rDNA and 16S rRNA sequencing methods to identify bacterial operational taxonomic unit (OTUs) in experimental subject's fecal samples, and more recently – on metagenomic sequencing due to a decrease in sequencing costs (Montandon and Jornayvaz 2017; Xourgia et al. 2019). However, it is important to consider the main variation amongst studies – use of different models (even though the gut microbiota shows similarities between human and rodent subjects /rats, mice/ there are certain differences that can influence the results), also the gut microbiota is not homogenous along the digestive tract (ileum/caecum/colon), thus, different stool samples will generate different results (Montandon and Jornayvaz 2017; Xourgia et al. 2019).

All of the above-mentioned variations as well as the individual peculiarities, dietary habits, age, comorbidities, ethnicity, genetic predisposition exhibit an influence on gut dysbiosis associated with obesity and related diseases

and it is interesting to look into how these novel medications could lead to reduction of weight through modifications of gut microbiota composition (Montandon and Jornayvaz 2017; Xourgia et al. 2019).

Wang et al. (2016) conducted an experiment in a mice model using subcutaneous injections of the GLP-1 receptor agonist liraglutide to determine whether the medication associated reduction of body weight is associated with alterations in gut microbiota. After the treatment fecal sample analysis from the experimental subjects showed the subsequent results: there was a substantial change of the bacterial structure in liraglutide-treated mice compared to the control group. The following data was established: liraglutide had a prominent impact on the abundance of weight-related phylotypes – the relative abundance of all obesity-related phylotypes was substantially decreased under liraglutide administration (genera associated with an increase in weight are *Roseburia*, *Parabacteroides*, *Marvinbryantia*, *Candidatus*, *Erysipelotrichaceae*), while also increasing the relative abundance of lean-related genera *Blautia* and *Coproccoccus*. The medication showed a more prominent impact on the overall microbial architecture in the hyperglycemic mice relative to normoglycemic mice. This study demonstrates that the application of this drug could shift the gut microbiota to a more lean-related composition by regulating the abundance of weight-relevant phylotypes and such a structural rearrangement could contribute to weight loss.

Zhang et al. (2017) conducted an experiment in a rat model using subcutaneous injections of the GLP-1 receptor agonist liraglutide. After treatment with the medication the following data was uncovered, showing the differences in gut microbiota diversity among the groups of experimental animals: the rat microbiome was mainly dominated by the phyla Firmicutes and Bacteroides however the Firmicutes/Bacteroidetes ratio in the diabetic rats was greatly increased in comparison to the liraglutide-treated group which had a significantly reduced Firmicutes/Bacteroidetes ratio. Moreover, the liraglutide-treated group also had a significant increase in relative abundance of genera *Bacteroides*, *Bifidobacterium*, *Lachnospiraceae*, *Lachnoclostridium*, *Tenericutes*, *Flavonifractor* (all of which positively correlate with weight reduction) compared to the diabetic rats group. The data also shows that genus *Prevotella* was much reduced in liraglutide-treated rats (there is observed increase in *Prevotella* in subjects with diabetes mellitus type 2 and obesity compared to healthy control group). The authors propose that such a structural change in the microbiota composition could be associated with enhanced weight reduction effects.

Zhao et al. (2018) conducted an experiment in a rat model using subcutaneous injections of the GLP-1 receptor agonist liraglutide, and they established that treatment with the medication decreased obesity-related microbial phenotypes and increased lean-related microbial phenotypes in both simple obese rats and diabetic obese rats. At the phylum level, the microflora of experimental animals was dominated by species of the phyla Firmicutes

(positively associated with obesity), Bacteroidetes (negatively associated with obesity), Tenericutes, and Proteobacteria. Liraglutide intervention decreased the Firmicutes and increased the Bacteroidetes and in both simple obese rats and diabetic obese rats and that resulted in a lower Firmicutes/Bacteroidetes ratio in the treated groups in comparison to the control groups. High-fat diet caused a lower percentage of class Bacteroidia (phylum Bacteroidetes) and a higher percentage of class Clostridia (phylum Firmicutes) in both simple obese rats and diabetic obese rats however these changes were reverted by liraglutide treatment. The authors suggest that one possible mechanism for gut microbiota modulation by liraglutide is that direct activation of endogenous incretin receptors leads to delayed gastric emptying, slower transit time through the GI tract and potentially affects the gut lumen internal environment – pH level and nutrient composition – all these factors could be contributing to the effect over the microbiota. An important conclusion reached by the authors is that very similar shifts in microbial composition were established in all animal groups during liraglutide treatment regardless of blood glucose levels – the effects of the drug were analogous in both simple obese subjects and diabetic obese subjects.

Moreira et al. (2018) conducted an experiment in two mice models using subcutaneous injections of the GLP-1 receptor agonist liraglutide and the results show that liraglutide modifies gut microbiota diversity in both high-fat diet obese mice and genetically obese mice – the data reveals that liraglutide treatment leads to reduction of the Proteobacteria phylum in both obese animal models, and that also correlates with an increase in *Akkermansia muciniphila*, genus *Parabacteroides* and genus *Oscillospira* – changes which are associated with weight loss, improved glycemic parameters, and reduction in inflammatory cell response in both models of obese mice.

Zhang et al. (2020) conducted an experiment in a rat model using subcutaneous injections of the GLP-1 receptor agonist liraglutide – analysis of experimental data revealed that liraglutide significantly altered the composition of the GI tract microbiota in high fat diet rats – bacteria of phylum Bacteroidetes, Tenericutes, Cyanobacteria, Elusimicrobia and Fusobacteria were significantly increased, while those of phylum Firmicutes, Actinobacteria, Proteobacteria were significantly decreased in the high-fat diet group treated with liraglutide. Together, the results indicate that the drug can modulate the microbiota in such a manner that results in a composition very similar to that of control lean rats.

Zhao et al. (2022) conducted an experiment in a mice model using subcutaneous injections of the GLP-1 receptor agonist liraglutide – after the end of the experiment data analysis revealed that liraglutide application significantly reduced the relative abundance of Firmicutes and increased that of Bacteroidetes, with a corresponding decrease in the Firmicutes/Bacteroidetes ratio. A change to the overall microbiota composition can be observed – the medication promoted the growth of beneficial microbes

(of genus *Akkermansia*, *Lactobacillus*, *Parabacteroides*, *Oscillospira*, *Sutterella*, *Allobaculum*) and inhibited the growth of harmful microbes (of genus *Shigella*, *Proteobacteria*). The authors suggest that regulation of the composition of the gut microbiota, especially the previously mentioned representatives associated with lipid metabolism, might be a potential mechanism for affecting dyslipidemia and lipid accumulation in adipose tissue using the aforementioned pharmacological therapy.

Ying et al. (2023) conducted an experiment in a group of 15 patients with diabetes mellitus type 2 that were treated with a daily subcutaneous injection of liraglutide. Fecal samples were collected from the patients in the group and the structure and function of the intestinal bacterial community was analyzed and compared before and after treatment using bacterial rRNA 16S sequencing technology. Liraglutide treatment significantly increased the diversity and richness of the intestinal bacterial community and it led to a significant increase in the relative abundances of phylum Bacteroidetes and phylum Proteobacteria, and also – of genus *Bacillus*. Such a change in the bacterial representatives shifted the microbiota into a composition with very similar characteristics to that of healthy controls.

Conclusion

In conclusion, emerging data from recent studies supports a growing body of evidence showing that novel anti-diabetic drugs – GLP-1 receptor agonists like liraglutide – have the capability to modulate the gut microbiome and that topic is a promising direction for researching the pathogenesis of obesity. The changes in the GI tract bacterial composition include: improving the diversity and richness of the intestinal bacterial community, increasing the relative abundance of lean-related microbial phenotypes and decreasing obesity-related microbial phenotypes, normalizing the Firmicutes/Bacteroidetes ratio – and all of these effects were observed in both subjects with obesity and/or diabetes mellitus type 2. However, at the current moment the evidence about this fine interplay between the antiobesity drugs and microorganisms is still severely limited, it comes mainly from animal experimental models and further and much more in-depth clinical studies in patients are required to explore the specific mechanism by which liraglutide affects intestinal microbiota and to what extent the weight-controlling effects of liraglutide are dependent on that modulation.

References

- Cani PD, Delzenne NM (2009) Interplay between obesity and associated metabolic disorders: new insights into the gut microbiota. *Current Opinion in Pharmacology* 9(6): 737–743. <https://doi.org/10.1016/j.coph.2009.06.016>
- Cani PD, Delzenne NM (2011) The gut microbiome as therapeutic target. *Pharmacology and Therapeutics* 130(2): 202–212. <https://doi.org/10.1016/j.pharmthera.2011.01.012>
- Cani PD, Everard A, Duparc T (2013) Gut microbiota, enteroendocrine functions and metabolism. *Current Opinion in Pharmacology* 13(6): 935–940. <https://doi.org/10.1016/j.coph.2013.09.008>
- Consoli A, Formoso G (2014) Potential side effects to GLP-1 agonists: understanding their safety and tolerability. *Expert Opinion on Drug Safety* 14(2): 207–218. <https://doi.org/10.1517/14740338.2015.987122>
- Gonzalo-Encabo P, Maldonado G, Valadés D, Ferragut C, Pérez-López A (2021) The role of exercise training on low-grade systemic inflammation in adults with overweight and obesity: A systematic review. *International Journal of Environmental Research and Public Health* 18(24): 13258. <https://doi.org/10.3390/ijerph182413258>
- Ley RE, Turnbaugh PJ, Klein S, Gordon JI (2006) Human gut microbes associated with obesity. *Nature* 444(7122): 1022–1023. <https://doi.org/10.1038/4441022a>
- Lustig R, Collier D, Kassotis C, Roepke T, Kim M, Blanc E, Barouki R, Bansal A, Cave M, Chatterjee S, Choudhury M, Gilbertson M, Lagadic-Gossmann D, Howard S, Lind L, Tolinson C, Vondracek J, Heindel J (2022) Obesity I: Overview and molecular and biochemical mechanisms. *Biochemical Pharmacology* 199(115012): 1–22. <https://doi.org/10.1016/j.bcp.2022.115012>
- Masood B, Moorthy M (2023) Causes of obesity: a review. *Clinical Medicine* 23(4): 284–291. <https://doi.org/10.7861/clinmed.2023-0168>
- Montandon SA, Jornayvaz FR (2017) Effects of antidiabetic drugs on gut microbiota composition. *Genes* 8(10): 250. <https://doi.org/10.3390/genes8100250>
- Moreira GV, Azevedo FF, Ribeiro LM, Santos A, Guadagnini D, Gama P, Liberti EA, Saad MJ, Carvalho CR (2018) Liraglutide modulates gut microbiota and reduces NAFLD in obese mice. *The Journal of Nutritional Biochemistry* 62(1): 143–154. <https://doi.org/10.1016/j.jnutbio.2018.07.009>
- Nuttall F (2015) Body Mass Index - Obesity, BMI, and Health: A Critical Review. *Nutrition Today* 50(3): 117–128. <https://doi.org/10.1097/NT.0000000000000092>
- Popoviciu MS, Păduraru L, Yahya G, Metwally K, Cavalu S (2023) Emerging role of GLP-1 agonists in obesity: A Comprehensive review of randomised controlled trials. *International Journal of Molecular Sciences* 24(13): 10449. <https://doi.org/10.3390/ijms241310449>
- Ryder R (2013) The potential risks of pancreatitis and pancreatic cancer with GLP-1-based therapies are far outweighed by the proven and potential (cardiovascular) benefits. *Diabetic Medicine: a Journal of the British Diabetic Association* 30(10): 1148–1155. <https://doi.org/10.1111/dme.12301>
- Sharma D, Verma S, Vaidya S, Kalia K, Tiwari V (2018) Recent updates on GLP-1 agonists: Current advancements & challenges. *Biomedicine and Pharmacotherapy* 108(1): 952–962. <https://doi.org/10.1016/j.biopha.2018.08.088>
- Shukla AP, Buniak WL, Aronne LJ (2015) Treatment of Obesity in 2015. *Journal of Cardiopulmonary Rehabilitation and Prevention* 35(2): 81–92. <https://doi.org/10.1097/HCR.0000000000000112>
- Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI (2006) An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature* 444(7122): 1027–1031. <https://doi.org/10.1038/nature05414>

- Wang L, Li P, Tang Z, Yan X, Feng B (2016) Structural modulation of the gut microbiota and the relationship with body weight: compared evaluation of liraglutide and saxagliptin treatment. *Scientific Reports* 6(1): 33251. <https://doi.org/10.1038/srep33251>
- Wirth A, Wabitsch M, Hauner H (2014) The prevention and treatment of obesity. *Deutsches Ärzteblatt International* 111(42): 705–713. <https://doi.org/10.3238/arztebl.2014.0705>
- Xourgia E, Papazafropoulou A, Papanas N, Melidonis A (2019) Anti-diabetic treatment leads to changes in gut microbiome. *Frontiers in Bioscience* 24(4): 688–699. <https://doi.org/10.2741/4743>
- Yang M, Liu S, Zhang C (2022) The related metabolic diseases and treatments of obesity. *Healthcare* 10(9): 1616. <https://doi.org/10.3390/healthcare10091616>
- Ying X, Rongjiong Z, Kahaer M, Chunhui J, Wulasihan M (2023) Therapeutic efficacy of liraglutide versus metformin in modulating the gut microbiota for treating type 2 diabetes mellitus complicated with nonalcoholic fatty liver disease. *Frontiers in Microbiology* 14(1088187): 1–14. <https://doi.org/10.3389/fmicb.2023.1088187>
- Zhang Q, Xiao X, Zheng J, Li M, Yu M, Ping F, Wang T, Wang X (2017) Structure moderation of gut microbiota in liraglutide-treated diabetic male rats. *Society for Experimental Biology and Medicine* 243(1): 34–44. <https://doi.org/10.1177/1535370217743765>
- Zhang N, Tao J, Gao L, Bi Y, Ping L, Wang H, Zhu D, Feng W (2020) Liraglutide attenuates nonalcoholic fatty liver disease by modulating gut microbiota in rats administered a high-fat diet. *BioMed Research International* 2020(1): 1–10. <https://doi.org/10.1155/2020/2947549>
- Zhao L, Chen Y, Xia F, Abudukerimu B, Zhang W, Guo Y, Wang N, Lu Y (2018) A glucagon-like peptide-1 receptor agonist lowers weight by modulating the structure of gut microbiota. *Frontiers in Endocrinology* 9(233): 1–13. <https://doi.org/10.3389/fendo.2018.00233>
- Zhao L, Qiu Y, Zhang P, Wu X, Zhao Z, Deng X, Yang L, Wang D, Yuan G (2022) Gut microbiota mediates positive effects of liraglutide on dyslipidemia in mice fed a high-fat diet. *Frontiers in nutrition* 9(1048693): 1–11. <https://doi.org/10.3389/fnut.2022.1048693>