Etiopathogenic Factors for Obesity

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Obesity is an abnormal or excessive accumulation of fat that represents a health risk, and it is characterized by reaching a body mass index (BMI) equal to or greater than 30 kg/m^2. Obesity is a chronic disease of multifactorial etiology that involves an energy imbalance, genetic and epigenetic factors, alterations in glucose and lipid metabolism, disorders of adipose tissue functioning, neuroendocrine dysregulation, and alterations in the intestinal microbiota, among others.

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1. Introduction

Obesity is defined as an abnormal or excessive accumulation of fat that represents a health risk, and it is characterized by reaching a body mass index (BMI) equal to or greater than 30 kg/m^2 [1]. Its prevalence continues to increase in all age groups in Europe and some American countries [2], and it is estimated that more than 60% of the population is obese or overweight [1][2]. Ischemic heart disease, the leading cause of death worldwide, is tightly linked to obesity [3], which is also related to ischemic or hemorrhagic strokes [4], representing the second global cause of death, as well as high blood pressure, type 2 diabetes mellitus (DM2), metabolic syndrome, and cancer [3][5]. Furthermore, obesity is correlated with significant causes of work disability, such as low back pain and osteoarticular diseases, which significantly impact the financial resources of healthcare systems [5]. Despite this, the general population still fails to fully grasp the severity of this metabolic disorder [2].

Obesity has a complex origin. In addition to the energy imbalance, some foods promote the pro-inflammatory pathway of eicosanoids, such as arachidonic acid and linoleic acid, among others, related to obesity and other chronic non-communicable diseases. However, obesity involves multiple etiopathogenic factors.

2. Genetic Factors

It is estimated that the genetic load may be responsible for the development of obesity by 40 to 70% [6]. So far, researchers have identified 227 gene variants and over 300 single nucleotide polymorphisms (SNPs) linked to obesity [7]. In genome-wide association studies, more than 1100 independent obesity-associated loci have been identified. Although monogenic obesity can happen, polygenic alterations are more frequently observed.

Some of the most studied alterations include the mutation of the leptin (*LEP*) and leptin receptor (*LEPR*) genes, which causes a deficiency of the LEP protein and, therefore, alterations in the satiety stimulus with increased appetite. Some rearrangements in the sequence of the proprotein convertase subtilisin/kexin type 1 (*PCSK1*), proopiomelanocortin (*POMC*), and melanocortin-4 receptor (*MC4R*) genes have also been studied, which cause the expression of the Agouti-related protein that, when binding to the melanocortin-2 receptor accessory protein (MRAP) 4, increases the appetite. Changes in the Ras2 suppressor protein kinase gene (KSR2) affect energy consumption and expenditure by interacting with adenosine monophosphate-activated protein kinase (AMPK) and the cyclic-adenosine monophosphate response-element-binding protein 3-regulatory factor (CREBRF), which participates in the storage and use of cellular energy [6].

Other widely studied alterations include loss-of-function variants of the gene that encodes adenylate cyclase 3, which is widely distributed, predominantly in adipose and subcutaneous tissue, but also participates in the correct functioning of the *MC4R* gene [8] and in the synthesis of cyclic adenosine monophosphate (cAMP), which functions as a second messenger in the glucagon-like peptide-1 (GLP-1) signaling pathway, the hormone ghrelin and the melanocortin-stimulating hormone [8], *POMC*, Fat Mass and Obesity (*FTO*) [9], interleukin 6 (*IL-6*) [10], perilipin (*PLIN*) [11], adiponectin (*ADIPOQ*) [12], *LEP* [13], *LEPR* [14], *POMC* [15] genes, the family of peroxisome proliferator-activated receptors (PPAR) [16] and the uncoupling proteins (UCPs) [17], which are related to the activation of thermogenesis. These genes and their metabolic and signaling pathways have a close relationship with systemic oxidative stress and inflammation, both linked to the development of obesity and the appearance of many associated comorbidities [6][18].

3. Epigenetic Factors

Epigenetics plays a fundamental role in the expression of the obesity phenotype. Epigenetic modifications are modulations in gene expression without changes in the deoxyribonucleic acid (DNA) [19]. This modulation can be induced through DNA modifications, histone alterations, non-coding ribonucleic acids (RNAs), or adenosine triphosphate (ATP)-dependent chromatin remodeling complexes [20].

Histone methylation and DNA methylation are common modifications through which some environmental factors can prevent the expression of specific genes or DNA segments [18][19]. Histone methylation consists of adding a methyl group to lysine and arginine of histones, which are DNA packaging proteins. Methylated histones adhere strongly to the DNA, keeping the chain condensed, and, in this way, do not allow the integration of transcription factors, which means that the information from that section of DNA cannot be expressed. This process is also known as transcriptional gene silencing (TGS). DNA methylation occurs because DNA-methyltransferase adds a methyl group to cytokines, generally in regions rich in guanine and cytosine. These regions are called “CpG islands” and are part of the non-coding DNA, but their importance lies in the fact that they are usually located in the promoter region of most genes [20][21]. DNA methylation of CpG islands, in addition to maintaining the compact configuration of chromatin, prevents the integration of transcription factors and thus also produces gene silencing. Other modifications include acetylation, which favors gene expression; deacetylation, which inhibits gene expression; or modulation of the expression of some non-coding RNAs, such as microRNAs (miRNAs) [18][20][22].

The main importance of epigenetics is that unlike genotype and genetic changes, epigenetic changes are modifiable and, in many cases, reversible [22]. However, epigenetic modifications that persist can be replicated and conserved in mitosis or meiosis [20][22][23] so they can be transmitted to subsequent generations [24][25]. Epigenetic modifications can be induced by external factors such as diet, physical activity, inflammatory processes, stress, etc., and they can occur during pregnancy or throughout life [19][23], with critical moments of greater susceptibility in the fetal and neonatal stages. Although some prenatal epigenetic modifications are unstable, others remain in adulthood but can be corrected with interventions, such as exercise or favorable dietary changes [19][23][26].

Maternal malnutrition or obesity can cause intrauterine modifications that affect DNA methylation [19][24]. Similarly, obesity prior to pregnancy or overnutrition during pregnancy favors a pro-inflammatory state or insulin resistance that stimulates the release of pro-inflammatory molecules such as interleukins (IL) and tumor necrosis factor (TNF-α), and the expression of adipogenic factors in the mother and the fetus [24]. Exposure to these alterations can cause histone modification and DNA methylation, with a consequent increase in the expression of adipogenic and lipogenic genes that favor obesity in other stages of extrauterine life [24][25][27]. One of the genes studied is *POMC*, which, in cases of hypermethylation, can disrupt the regulation of food intake even in the presence of leptin and insulin [19]. Maternal obesity also promotes methylation and increases leptin expression, leading to hypersecretion and functional resistance to leptin from infancy or later in life [24]. Likewise, a high-fat diet during pregnancy produces more acetylation of histone H3K14 and lower sirtuin-1 (*SIRT1*) gene expression in the liver and heart. This decrease in *SIRT1* expression favors the presence of fatty liver, obesity, DM2, and diabetic cardiomyopathy [28][29].

The diet throughout the lives is crucial in epigenetics. Consuming high levels of saturated fat leads to DNA methylation in adipose tissue and alters the expression of 28 messenger RNAs. A diet with polyunsaturated fats induces multiple methylations, but these do not generate changes in gene expression, although both diets have a similar effect on weight gain [19]. High concentrations of palmitate increase histone acetyltransferase activity [25]. On the contrary, calorie restriction for more than eight weeks reduces hypermethylation in some genes affected by a high-fat diet. However, the adverse effects of insufficient overfeeding are quickly noticeable, while the positive effects of a calorie-restricted diet take longer to impact DNA methylation changes [19][25]. The above partly explains the benefits produced by metabolic surgery (restrictive, malabsorptive or combined technique) [30], which causes a sudden and sustained reduction in caloric intake, contributing to energy balance. After six to 12 months, it induces favorable effects on promoter methylation of the pyruvate dehydrogenase kinase 4 (*PDK4*) gene and proliferator-activated receptor coactivator g-1 alpha (*PGC-1a*), among other genes [19][31]. Dietary folate deficiency has been related to a more significant volume of fat mass, insulin resistance, increased risk of DM2, decreased DNA methylation of lymphocytes, and changes in DNA methylation of 236 CpG sites and genes associated with obesity [25].

A sedentary lifestyle, exercise, and moderate or intense physical activity have also been recognized as epigenetic modifiers. In individuals with a history of low physical activity, exercise for six months produced changes in the DNA methylation of 7663 genes, including some related to obesity, such as the cAMP response element-binding protein 4 (*CREB4*), elongation of very long-chain fatty acid proteins (*ELOV*), glucose transporter 4 (*GLUT4*), and

hormone-sensitive lipase (*HSL*) [21][25]. Furthermore, a relationship has been reported between exercise and the expression of proinflammatory cytokines such as IL-6 and TNF-α [21][32]. Subjects who exercise periodically have lower expression of proinflammatory cytokines and are better adapted when they are released. Although exercise-induced methylation changes can be observed from the first session, the duration of this epigenetic modification is longer with chronic exercise exposure [21].

4. Energy Imbalance

Excessive caloric intake, compared to individual requirements, contributes to the development of obesity [33]. This explains the growing incidence of obesity, since food consumption high in fat and sugar has increased globally, coupled with decreased physical activity [33][34][35]. The state of positive energy balance is characterized by caloric intake greater than energy expenditure. This originates from a complex interaction of behavioral, environmental, physiological, genetic, and social factors influenced by interactions between individuals, families, institutions, organizations, and communities [36].

A fundamental element in the regulation of energy balance is physical activity, which regularly requires 60 minutes per day for children and 150 minutes per week for adults [33]. Insufficient physical activity is favored by societal changes, leading to a significant decrease in total energy expenditure. Furthermore, when obesity occurs during childhood, it predisposes the individual to develop obesity in later stages of life [33].

5. Neuroendocrine Dysregulation

The regulation of energy expenditure and intake involves several body systems, such as the nervous system, digestive system (including the liver and pancreas), and adipose tissue cells, which play a crucial role [37]. Obesity is correlated with the dysregulation of many signaling pathways, including hormones, cytokines, neurotransmitters, neuropeptides, adipokines, chemokines, growth factors, proliferation molecules, differentiation factors, antioxidant enzymatic systems, non-enzymatic antioxidants, and the overexpression or underexpression of many genes [38]. These alterations can begin gradually and progressively, activating other neuroendocrine responses and promoting dysfunction. The principal occurrences of this pathophysiology are summarized below.

The foods consumed are digested into macronutrients (carbohydrates, lipids, and proteins) to be used in the body, and the excess nutrients are stored for later use. In the presence of insulin, excess of glucose is polymerized into glycogen in the liver and striated muscle. The excess of macronutrients can only be stored in adipose tissue, which requires being transformed into triglycerides in the liver. In its catabolic process, glucose generates acetyl coenzyme A (Acetyl-CoA) that can pass into the anabolic pathway for the synthesis of fatty acids (lipogenesis), mainly in adipose tissue and the liver [39]. Amino acids are catabolized to generate intermediates of the Krebs cycle, from where they can leave the mitochondria as citrate and be metabolized to form Acetyl CoA for lipogenesis [40][41]. These fatty acids are re-esterified and linked to glycerol-3-phosphate to form triglycerides, which are transported from the liver in very low-density lipoprotein (VLDL) molecules and stored in adipose tissue [42]. Mature

adipocytes can store a large number of triglycerides, increasing their volume up to 20 times through hypertrophy [39]. Furthermore, this excessive growth favors adipocyte hypoxia, the release of reactive oxygen species (ROS), and inflammatory cytokines that activates adipogenesis (adipocyte hyperplasia), another mechanism to increase storage capacity [43].

Adipogenesis develops from multipotent mesenchymal stem cells related to preadipocytes, which remain available in the vascular stroma of adipose tissue and undergo mitotic clonal expansion and differentiation of adipocytes to white adipose tissue that has triglyceride storage functions, or to brown adipose tissue with thermogenesis functions [44]. The CCAAT/enhancer-binding protein β (C/EBP)β and C/EBP δ, which are highly sensitive to adipogenic stimuli, increase from the initial stages [43][45][46] and stimulate the expression of the C/EBPα, sterol regulatory element-binding binding protein 1 (SREBP-1) and the expression of the peroxisome proliferator-activated receptor γ (*PPARγ*), which has an essential role in the final phases of adipogenesis [46] and regulates the increase in adipogenic factors, including *C/EBPα* expression itself, in a positive feedback mechanism [43]. Because adipose tissue is not a passive storage space but rather a tissue with endocrine, paracrine, and autocrine functions, new mature adipocytes are capable of not only increasing storage capacity but also releasing adipocytokines, some of which function as neurotransmitters and participate in the neuroendocrine regulatory complex [47].

In healthy individuals, leptin, an adipocytokine, is typically present at 5 to 15 ng/mL [48]. However, its expression is influenced by various factors, including diet, insulin secretion, glucocorticoids, cytokines, and the amount of adipose tissue [48][49]. Under normal conditions, it can cross the blood–brain barrier by facilitated diffusion and induce satiety and energy consumption by stimulating POMC and inhibiting neuropeptide Y. However, high concentrations induce a state of leptin resistance that favors the presence of obesity and other metabolic alterations by limiting the stimulation of extracellular signal-regulated kinases (ERK) 1 and 2, mitogen-activated protein kinase (MAPK), and other downstream factors [50].

Adiponectin is secreted mainly by adipose tissue and has multiple functions, including (a) its participation as a promoter of the substrate of the insulin receptor IRS 1 and 2, which promotes insulin sensitivity; (b) activator of AMPK, which also promotes insulin sensitivity and the oxidation of fatty acids, and (c) MAPK activator, which stimulates glucose uptake [51][52]. However, obesity decreases serum adiponectin concentrations, with a consequent decrease in insulin sensitivity [12][51]. By reducing insulin sensitivity, insulin-dependent glucose transport decreases, which favors the presence of high plasma glucose concentrations and the consequent glucotoxicity that increases insulin resistance, creating positive feedback with glucose concentrations. Because insulin performs other functions, a series of metabolic pathways are triggered, including increased adipogenesis and lipogenesis [39].

6. Neuropsychological Factors

Multiple neurophysiological and psychological mechanisms related to adipose dysfunction or some food consumption participate in the regulation of appetite, hunger, satiety, and the psychological state, developing a

bidirectional axis [53].

Many pathways are involved in this process, e.g., the dopaminergic system, which widely influences mood, addictions, motivation, and hunger regulation [54][55][56]. Dopamine acts on the nigrostriatal, mesolimbic, and mesocortical systems of the central nervous system by binding to the RD-1, 2, 3, and 4 receptors, resulting in appetite diminution. In obesity, these receptors decrease in number, affinity, and capacity to activate second messengers, thus inducing orexigenic effects [56].

The serotonergic system also plays an important role. Serotonin is produced from the amino acid L-tryptophan, present in some protein foods, and sweet foods facilitate the crossing of L-tryptophan through the blood–brain barrier, as well as its 5-HT metabolite [57]. Various serotonin reuptake inhibitors have been used to treat obesity. The serotonergic system also plays an important role in regulating hunger, acting on the raphe nucleus and stimulating the neurotransmitter Gamma-Aminobutyric Acid (GABA) [57].

The GABA-mediated GABAergic system also can regulate satiety [58]. GABA is related to pleasurable sensations and the feeling of reward, like dopamine. There are two receptors for GABA, type A and type B, whose activation stimulates the Agouti-related peptide (AgRP), which, through negative feedback, inhibits GABA, generating greater food consumption. Subjects with depressive and anxiety disorders frequently present alterations in the regulation of this system [57][58].

The neural system also influences energy intake, which branches into two pathways, cannabinoids and opioids. This system controls enkephalins, nociceptins, and endorphins, which influence hunger and the consumption of palatable foods [58]. Obesity patients regularly have a deregulation of this neurophysiological system, thus increasing their energy intake. The receptors involved in this system are R-CB1 and R-CB2 in the cannabinoid pathway, and R-δ, R-κ, and R-μ in the opioid pathway [58]. Stress represents another important factor in the etiology of obesity [54][55]. Acute stress inhibits appetite; however, under continued stress, adrenal glands release cortisol, which increases appetite, particularly for foods high in fat, sugar, or both, with inhibition of the limbic system [54].

Stress is also related to sleep deprivation, which contributes to weight gain [54]. The “emotional ingestion” is another risk factor for obesity. It is characterized by food intake as a way to suppress or attenuate negative emotions [53][54]. All of these feelings, emotions, and psychological states interact directly with neurophysiological systems and food, forming a multidirectional axis of emotions–neurotransmitters–food where each of these variables influences the others.

7. Gut Microbiota

Another important factor in the etiopathogenesis of obesity is the intestinal microbiota. This is the set of communities of living microorganisms colonizing the intestine and plays a critical role in the health–disease balance in the individual. The composition of the human microbiome results from millions of years of coevolution

and selective pressure, selecting a specialized community to live in the intestinal environment and achieving a mutualistic relationship and a state of balance with the host that is beneficial, both for humans and for the microorganisms they harbor [59]. Among all of the ecological niches found in the human body, the gastrointestinal tract (GIT) is the one with the greatest diversity and abundance of microbial taxa. In the proximal regions of the GIT, there is a low concentration of microorganisms due to the acidic pH and the rapid transit of the bolus; meanwhile, in the distal region (colon), the most significant number of microbes is found [60].

The intestinal microbiota has a vital role in energy balance since these microorganisms can metabolize an enormous amount of compounds from the diet, produce metabolites related to the hunger–satiety process, as well as a large number of hormones and neurotransmitters such as serotonin, which induces satiety [61][62][63]. In humans, the gut microbiota mainly comprises five distinct phyla: *Actinobacteria*, *Bacteroidetes*, *Verrucomicrobia*, *Firmicutes*, and *Proteobacteria*. *Bacteroidetes* and *Firmicutes* represent up to 90% of all intestinal bacteria [64]. The microbiota's impact on host physiology is supported by a growing body of evidence that highlights multiple pathways, including improved energy utilization, immune system changes, metabolic signaling, and inflammatory pathways [59].

Dysbiosis, an alteration in the composition of the microbiota, has been linked to three distinct mechanisms that can occur at the same time: (a) the loss of "beneficial" bacteria, (b) an overgrowth of potentially dangerous bacteria, and (c) a reduction in microbial diversity [65]. It can also lead to an increase in caloric intake to the detriment of basal and total energy expenditure, but a correlation has also been identified between the existing intestinal microbiota and metabolic and nutritional status. In this way, healthy individuals have a greater amount of *Bacteroidetes* than *Firmicutes*, but industrialized diets low in dietary fiber cause a decrease in *Bacteroidetes* and an increase in *Firmicutes* [63][65]. In addition to bacteria, intestinal archaea, fungi, and viruses participate in the etiopathogenesis of obesity [63].

The microbiota can contribute significantly to the promotion of weight gain and fat storage and the generation of insulin resistance [66]. DM2, a pathology associated with obesity, also involves dysbiosis, which can also favor infections due to changes in the regulation of receptors in immune cells. An example is infection by fungal species of the genus *Rhizopus*, which is the causal agent of the severe infection called rhinocerebral mucormycosis [67]. The correlation between obesity and the bacterial composition of the human microbiome has been established through previous investigations, with particular attention given to members of the *Christensenellaceae* family and the *Methanobacteriales*, *Lactobacillus*, Bifidobacteria, and *Akkermansia* genera [68].

More recently, it has been identified that the *Christensenellaceae* family is linked to weight loss, showing an inverse correlation between its relative presence and an individual's body mass index (BMI) [69]. In particular, it has been shown that *Akkermansia muciniphila* plays a crucial role in regulating body weight, and supplementation with this bacterium significantly improves the metabolic parameters of overweight and obese individuals [70].

The *Lactobacillus* and *Bifidobacterium* genera are recognized for promoting intestinal health. They have been used as traditional probiotics that significantly affect the balance of the intestinal microecology in humans, but the effects

on body weight in overweight individuals vary depending on the species of *Lactobacillus*; specifically, a negative correlation was found between the abundance of *Lactobacillus paracasei* and obesity, while the abundance of *Lactobacillus reuteri* and *Lactobacillus gasseri* showed significant correlations with obesity development [71]. Therefore, it can be summarized that the participation of the intestinal microbiota in weight control focuses on bacterial diversity, some specific species found, the metabolites that bacteria produce and are absorbed intestinally, the relationship between the microbiota, the immune system, inflammation, and oxidative stress, the participation of metabolites in gene expression, acting as transcription factors, and the capacity of the microbiota to degrade, biotransform and metabolize compounds from the diet [72].

8. Other Etiopathogenic Factors

There are medications associated with the development of obesity, known as obesogenic drugs, which include mineralocorticoids, glucocorticoids, insulin, and some antidiabetic or antihypertensive drugs, among many others. On the other hand, there are obesogenic molecules known as endocrine disruptors, mainly in foods (due to agrochemicals) and plastic containers, which interfere with the function and/or signaling of various hormones, neurotransmitters and neuropeptides, including androgenic and progestin sex hormones and peptides related to satiety and hunger, such as LEP, ghrelin, peptide YY, neuropeptide Y, GLP-1, and serotonin [73].

Circadian rhythms related to sleep–wake also play an important role in controlling energy balance, whose deregulation can cause greater hunger and lower basal energy expenditure. Several mediators regulate this system; however, the most important are cortisol, melatonin, growth hormone, and *CLOCK* genes [74]. There are viruses related to the obesity process, known as obesogenic viruses, among which is *Adenovirus* 36, which increases insulin sensitivity in adipocytes, generating more significant lipogenesis while reducing the expression and secretion of leptin, thus increasing hunger [75]. Likewise, many psychological, cultural, social, economic, climatic, political, and geographical factors determine eating patterns, the type of food available, the amount of physical exercise performed, as well as the quantity and quality of the nourishment consumed [76].

References

1. Tutor, A.W.; Lavie, C.J.; Kachur, S.; Milani, R.V.; Ventura, H.O. Updates on obesity and the obesity paradox in cardiovascular diseases. Prog. Cardiovasc. Dis. 2023, 78, 2.
2. Boutari, C.; Mantzoros, C.S. A 2022 update on the epidemiology of obesity and a call to action: As its twin COVID-19 pandemic appears to be receding, the obesity and dysmetabolism pandemic continues to rage on. Metabolism 2022, 133, 155217.
3. McPherson, R. Obesity and ischemic heart disease. Circ. Res. 2015, 116, 570.
4. Shiozawa, M.; Kaneko, H.; Itoh, H.; Morita, K.; Okada, A.; Matsuoka, S.; Kiriyama, H.; Kamon, T.; Fujiu, K.; Michihata, N.; et al. Association of body mass index with ischemic and hemorrhagic

stroke. Nutrients 2021, 13, 2343.

5. Smith, K.B.; Smith, M.S. Obesity statistics. Prim. Care 2016, 43, 121.
6. Loos, R.J.F.; Yeo, G.S.H. The genetics of obesity: From discovery to biology. Nat. Rev. Genet. 2022, 23, 120.
7. Wen, X.; Zhang, B.; Wu, B.; Xiao, H.; Li, Z.; Li, R.; Xu, X.; Li, T. Signaling pathways in obesity: Mechanisms and therapeutic interventions. Sig. Transduct. Target Ther. 2022, 7, 1.
8. Grarup, N.; Moltke, I.; Andersen, M.K.; Dalby, M.; Vitting-Seerup, K.; Kern, T.; Mahendran, Y.; Jørsboe, E.; Larsen, C.V.L.; Dahl-Petersen, I.K.; et al. Loss-of-function variants in ADCY3 increase risk of obesity and type 2 diabetes. Nat. Genet. 2018, 50, 172.
9. Yin, D.; Li, Y.; Liao, X.; Tian, D.; Xu, Y.; Zhou, C.; Liu, J.; Li, S.; Zhou, J.; Nie, Y.; et al. FTO: A critical role in obesity and obesity-related diseases. Br. J. Nutr. 2023, 130, 1657–1664.
10. Wu, O.; Yuan, C.; Leng, J.; Zhang, X.; Liu, W.; Yang, F. Colorable role of interleukin (IL)-6 in obesity hypertension: A hint from a Chinese adult case-control study. Cytokine 2023, 168, 156226.
11. Bombarda-Rocha, V.; Silva, D.; Badr-Eddine, A.; Nogueira, P.; Gonçalves, J.; Fresco, P. Challenges in pharmacological intervention in perilipins (PLINs) to modulate lipid droplet dynamics in obesity and cancer. Cancers 2023, 15, 4013.
12. Ramakrishnan, N.; Auger, K.; Rahimi, N.; Jialal, I. Biochemistry, Adiponectin; StatPearls Publishing: St. Petersburg, FL, USA, 2023. Available online: http://www.ncbi.nlm.nih.gov/books/NBK537041/ (accessed on 29 September 2023).
13. Ayed, K.; Nabi, L.; Akrout, R.; Mrizak, H.; Gorrab, A.; Bacha, D.; Boussen, H.; Gati, A. Obesity and cancer: Focus on leptin. Mol. Biol. Rep. 2023, 50, 6177.
14. Wang, Y.; Wan, R.; Hu, C. Leptin/obR signaling exacerbates obesity-related neutrophilic airway inflammation through inflammatory M1 macrophages. Mol. Med. 2023, 29, 100.
15. Lechner, L.; Opitz, R.; Silver, M.J.; Krabusch, P.M.; Prentice, A.M.; Field, M.S.; Stachelscheid, H.; Leitão, E.; Schröder, C.; Fernandez Vallone, V.; et al. Early-set POMC methylation variability is accompanied by increased risk for obesity and is addressable by MC4R agonist treatment. Sci. Transl. Med. 2023, 15, 1659.
16. Shaji, A.; Jayasri, M.A. A review of the role of liposome-encapsulated phytochemicals targeting PPAR ɣ and associated pathways to combat obesity. 3 Biotech 2023, 13, 313.
17. Kim, D.S.; Lee, H.Y.; Kim, H.J.; Lee, G.H.; Lim, Y.J.; Ko, B.M.; Kim, J.H.; Kim, T.W.; Kim, H.K.; Kim, T.Y.; et al. Combined treatment of mori folium and mori cortex radicis ameliorate obesity in mice via UCP-1 in brown adipocytes. Nutrients 2023, 15, 3713.

18. Rohde, K.; Keller, M.; la Cour-Poulsen, L.; Blüher, M.; Kovacs, P.; Böttcher, Y. Genetics and epigenetics in obesity. Metabolism 2019, 92, 37.
19. Ouni, M.; Schürmann, A. Epigenetic contribution to obesity. Mamm. Genom. 2020, 31, 134.
20. Pagiatakis, C.; Musolino, E.; Gornati, R.; Bernardini, G.; Papait, R. Epigenetics of aging and disease: A brief overview. Aging Clin. Exp. Res. 2021, 33, 737.
21. Plaza-Diaz, J.; Izquierdo, D.; Torres-Martos, Á.; Baig, A.T.; Aguilera, C.M.; Ruiz-Ojeda, F.J. Impact of physical activity and exercise on the epigenome in skeletal muscle and effects on systemic metabolism. Biomedicines 2022, 10, 126.
22. Zhang, L.; Lu, Q.; Chang, C. Epigenetics in Health and Disease. In Epigenetics in Allergy and Autoimmunity; Chang, C., Lu, Q., Eds.; Springer: Singapore, 2020; pp. 3–55.
23. Wu, F.Y.; Yin, R.X. Recent progress in epigenetics of obesity. Diabetol. Metab. Syndr. 2022, 14, 171.
24. Şanlı, E.; Kabaran, S. Maternal obesity, maternal overnutrition and fetal programming: Effects of epigenetic mechanisms on the development of metabolic disorders. Curr. Genom. 2019, 20, 419.
25. Ling, C.; Rönn, T. Epigenetics in human obesity and type 2 diabetes. Cell Metab. 2019, 29, 1028.
26. Grijalva-Avila, J.; Villanueva-Fierro, I.; Lares-Asseff, I.; Chairez-Hernández, I.; Rivera-Sanchez, G.; Martínez-Estrada, S.; Martínez-Rivera, I.; Quiñones, L.A.; Loera-Castañeda, V. Milk intake and IGF-1 rs6214 polymorphism as protective factors to obesity. Int. J. Food Sci. Nutr. 2020, 71, 388.
27. Chiu, Y.; Fadadu, R.P.; Gaskins, A.J.; Rifas-Shiman, S.L.; Laue, H.E.; Moley, K.H.; Hivert, M.F.; Baccarelli, A.; Oken, E.; Chavarro, J.E.; et al. Dietary fat intake during early pregnancy is associated with cord blood DNA methylation at IGF2 and H19 genes in newborns. Environ. Mol. Mutagen. 2021, 62, 388.
28. Kim, J.Y.; Mondaca-Ruff, D.; Singh, S.; Wang, Y. SIRT1 and autophagy: Implications in endocrine disorders. Front. Endocrinol. 2022, 13, 930919.
29. Hernández-Bedolla, M.; Barajas, A.; Cortés, F.; Alonso, D.; Hernández, A.; Ostoa, Z.; Salguero, I. Papel pleiotrópico y homeostático de las sirtuinas en la función biológica humana. Cienc. Huasteca Boletín Científico Esc. Super. Huejutla 2020, 8, 6.
30. Lahsen, M.R.; Kuzmanic, V.A. Cirugía metabólica 10 años después: Una mirada desde la diabetología. Rev. Med. Clin. Condes. 2016, 27, 188.
31. Nicoletti, C.F.; Cortes-Oliveira, C.; Pinhel, M.A.S.; Nonino, C.B. Bariatric surgery and precision nutrition. Nutrients 2017, 9, 974.

32. Hunter, D.J.; James, L.S.; Hussey, B.; Ferguson, R.A.; Lindley, M.R.; Mastana, S.S. Impacts of eccentric resistance exercise on DNA methylation of candidate genes for inflammatory cytokines in skeletal muscle and leukocytes of healthy males. Genes 2023, 14, 478.
33. Blüher, M. Obesity: Global epidemiology and pathogenesis. Nat. Rev. Endocrinol. 2019, 15, 288.
34. Milton, K.; Gomersall, S.R.; Schipperijn, J. Let's get moving: The Global Status Report on Physical Activity 2022 calls for urgent action. J. Sport Health Sci. 2023, 12, 5.
35. Sung, H.; Siegel, R.L.; Torre, L.A.; Pearson-Stuttard, J.; Islami, F.; Fedewa, S.A.; Goding Sauer, A.; Shuval, K.; Gapstur, S.M.; Jacobs, E.J.; et al. Global patterns in excess body weight and the associated cancer burden. CA Cancer J. Clin. 2019, 69, 88.
36. Kaufer-Horwitz, M.; Pérez-Hernández, J.F.; Kaufer-Horwitz, M.; Pérez-Hernández, J.F. La obesidad: Aspectos fisiopatológicos y clínicos. Inter. Discip. 2022, 10, 147.
37. González-Jiménez, E. Obesidad: Análisis etiopatogénico y fisiopatológico. Endocrinol. Nutr. 2013, 60, 17.
38. Santos, A.L.; Sinha, S. Obesity and aging: Molecular mechanisms and therapeutic approaches. Ageing Res. Rev. 2021, 67, 101268.
39. Hafidi, M.E.; Buelna-Chontal, M.; Sánchez-Muñoz, F.; Carbó, R. Adipogenesis: A necessary but harmful strategy. Int. J. Mol. Sci. 2019, 20, 3657.
40. Zolla, L. On the need to distinguish between insulin-normal and insulin-resistant patients in testosterone therapy. Int. J. Mol. Sci. 2022, 23, 12730.
41. Malfacini, D.; Pfeifer, A. GPCR in adipose tissue function-focus on lipolysis. Biomedicines 2023, 11, 588.
42. Lytle, K.A.; Bush, N.C.; Triay, J.M.; Kellogg, T.A.; Kendrick, M.L.; Swain, J.M.; Gathaiya, N.W.; Hames, K.C.; Jensen, M.D. Adipocyte proteins and storage of endogenous fatty acids in visceral and subcutaneous adipose tissue in severe obesity. Obesity 2021, 29, 1014.
43. Horwitz, A.; Birk, R. Adipose tissue hyperplasia and hypertrophy in common and syndromic obesity—The case of BBS obesity. Nutrients 2023, 15, 3445.
44. Gupta, A.; Efthymiou, V.; Kodani, S.D.; Shamsi, F.; Patti, M.E.; Tseng, Y.H.; Streets, A. Mapping the transcriptional landscape of human white and brown adipogenesis using single-nuclei RNA-seq. Mol. Metab. 2023, 74, 101746.
45. Lee, E.O.; Joo, H.K.; Lee, Y.R.; Kim, S.; Lee, K.H.; Lee, S.D.; Jeon, B. APE1/Ref-1 inhibits adipogenic transcription factors during adipocyte differentiation in 3T3-L1 cells. Int. J. Mol. Sci. 2023, 24, 3251.

46. Guo, L.; Li, X.; Tang, Q.Q. Transcriptional regulation of adipocyte differentiation: A central role for CCAAT/Enhancer-binding Protein (C/EBP) β. J. Biol. Chem. 2015, 290, 755.
47. Kahn, C.R.; Wang, G.; Lee, K.Y. Altered adipose tissue and adipocyte function in the pathogenesis of metabolic syndrome. J. Clin. Investig. 2019, 129, 3990.
48. Yang, R.; Barouch, L.A. Leptin signaling and obesity. Circ. Res. 2007, 101, 545.
49. Gjermeni, E.; Kirstein, A.S.; Kolbig, F.; Kirchhof, M.; Bundalian, L.; Katzmann, J.L.; Laufs, U.; Blüher, M.; Garten, A.; Le Duc, D. Obesity—An update on the basic pathophysiology and review of recent therapeutic advances. Biomolecules 2021, 11, 1426.
50. Gruzdeva, O.; Borodkina, D.; Uchasova, E.; Dyleva, Y.; Barbarash, O. Leptin resistance: Underlying mechanisms and diagnosis. Diabetes Metab. Syndr. Obes. 2019, 12, 191.
51. Achari, A.E.; Jain, S.K. Adiponectin, a therapeutic target for obesity, diabetes, and endothelial dysfunction. Int. J. Mol. Sci. 2017, 18, 1321.
52. Ruan, H.; Dong, L.Q. Adiponectin signaling and function in insulin target tissues. J. Mol. Cell Biol. 2016, 8, 101.
53. Kalra, S.; Chawla, K.L.; Kapoor, N. Motivation and obesity care. J. Pak. Med. Assoc. 2023, 74, 182–184.
54. Lopera, D.T.; Restrepo, M. Aspectos psicológicos de la obesidad en adultos. Rev. Psicol. Univ. Antioq. 2014, 6, 91.
55. Sarwer, D.B.; Polonsky, H.M. The psychosocial burden of obesity. Endocrinol. Metab. Clin. N. Am. 2016, 45, 677–688.
56. Schmidt, R.; Sebert, C.; Kösling, C.; Grünwald, M.; Hilbert, A.; Hübner, C.; Schäfer, L. Neuropsychological and Neurophysiological Indicators of General and Food-Specific Impulsivity in Children with Overweight and Obesity: A Pilot Study. Nutrients 2018, 10, 1983.
57. Cohen, D.A. Neurophysiological pathways to obesity: Below awareness and beyond individual control. Diabetes 2008, 57, 1768–1773.
58. López-Espinoza, A.; Moreno, M. La Educación en Alimentación y Nutrición, 1st ed.; McGraw-Hill/Interamericana Editores: New York, NY, USA, 2016; ISBN 978-607-15-1371-7.
59. Puljiz, Z.; Kumric, M.; Vrdoljak, J.; Martinovic, D.; Ticinovic, K.T.; Krnic, M.O. Obesity, gut microbiota, and metabolome: From pathophysiology to nutritional interventions. Nutrients 2023, 15, 2236.
60. Lee, J.Y.; Tsolis, R.M.; Bäumler, A.J. The microbiome and gut homeostasis. Science 2022, 377, eabp9960.

61. Cheng, Z.; Zhang, L.; Yang, L.; Chu, H. The critical role of gut microbiota in obesity. Front. Endocrinol. 2022, 13, 1025706.
62. Fontané, L.; Benaiges, D.; Goday, A.; Llauradó, G.; Pedro-Botet, J. Influencia de la microbiota y de los probióticos en la obesidad. Clin. Investig. Arterioscler. 2018, 30, 271.
63. Amabebe, E.; Robert, F.O.; Agbalalah, T.; Orubu, E.S.F. Microbial dysbiosis-induced obesity: Role of gut microbiota in homoeostasis of energy metabolism. Br. J. Nutr. 2020, 123, 1127.
64. Milani, C.; Duranti, S.; Bottacini, F.; Casey, E.; Turroni, F.; Mahony, J. The first microbial colonizers of the human gut: Composition, activities, and health implications of the infant gut microbiota. Microbiol. Mol. Biol. Rev. 2017, 81, e00036-17.
65. DeGruttola, A.K.; Low, D.; Mizoguchi, A.; Mizoguchi, E. Current understanding of dysbiosis in disease in human and animal models. Inflamm. Bowel Dis. 2016, 22, 1137.
66. Cardinelli, C.S.; Sala, P.C.; Alves, C.C.; Torrinhas, R.S.; Waitzberg, D.L. Influence of intestinal microbiota on body weight gain: A narrative review of the literature. Obes. Surg. 2015, 25, 346.
67. Morales-Franco, B.; Nava-Villalba, M.; Medina-Guerrero, E.O.; Sánchez-Nuño, Y.A.; Davila-Villa, P.; Anaya-Ambriz, E.J. Host-pathogen molecular factors contribute to the pathogenesis of Rhizopus spp. in diabetes mellitus. Curr. Trop. Med. Rep. 2021, 8, 6.
68. Liu, B.N.; Liu, X.T.; Liang, Z.H.; Wang, J.H. Gut microbiota in obesity. World J. Gastroenterol. 2021, 27, 3837.
69. Waters, J.L.; Ley, R.E. The human gut bacteria Christensenellaceae are widespread, heritable, and associated with health. BMC Biol. 2019, 17, 83.
70. Depommier, C.; Vitale, R.M.; Iannotti, F.A.; Silvestri, C.; Flamand, N.; Druart, C.; Everard, A.; Pelicaen, R.; Maiter, D.; Thissen, J.P.; et al. Beneficial Effects of Akkermansia muciniphila Are Not Associated with Major Changes in the Circulating Endocannabinoidome but Linked to Higher Mono-Palmitoyl-Glycerol Levels as New PPARα Agonists. Cells 2021, 10, 185.
71. Crovesy, L.; Ostrowski, M.; Ferreira, D.M.T.P.; Rosado, E.L.; Soares-Mota, M. Effect of Lactobacillus on body weight and body fat in overweight subjects: A systematic review of randomized controlled clinical trials. Int. J. Obes. 2017, 41, 1607.
72. Moore, S.C.; Matthews, C.E.; Sampson, J.N.; Stolzenberg-Solomon, R.Z.; Zheng, W.; Cai, Q. Human metabolic correlates of body mass index. Metabolomics 2014, 10, 259.
73. Miller, G.D. Appetite regulation: Hormones, peptides, and neurotransmitters and their role in obesity. Am. J. Lifestyle Med. 2019, 13, 586.
74. Albrecht, U. The circadian clock, metabolism and obesity. Obes. Rev. 2017, 18, 25.

75. Marjani, A.; Khatami, A.; Saadati, H.; Asghari, M.; Razizadeh, M.H.; Abbasi, A. Association of adenovirus 36 infection and obesity: An updated meta-analysis of community-based studies. Rev. Med. Virol. 2022, 32, e2255.
76. Calloway, E.E.; Parks, C.A.; Bowen, D.J.; Yaroch, A.L. Environmental, social, and economic factors related to the intersection of food security, dietary quality, and obesity: An introduction to a special issue of the Translational Behavioral Medicine journal. Transl. Behav. Med. 2019, 9, 823.