Metabolic hormones and ethnic aspects in obesity

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CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE

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1. Epidemiology of obesity

1.1. Definition of obesity

Obesity results from a positive energy balance (i.e., energy intake exceeds energy expenditure), and is defined by the World Health Organization (WHO) as a chronic complex disease defined by excessive fat deposits that can impair health (1). A person is considered to be living with overweight or obesity when body mass index (BMI), calculated by weight divided by height squared, is ≥ 25 kg/m^2 or ≥ 30 kg/m^2, respectively (1). Obesity is further categorized into either class I (BMI ≥ 30 and < 35 kg/m^2), class II (BMI ≥ 35 and < 40 kg/m^2), and class III (BMI ≥ 40 kg/m^2) (2). Classifications of obesity based on BMI are supplemented by an increased waist circumference (≥ 102 cm for males and ≥ 88 cm for females). The presence of comorbidities, such as cardiometabolic diseases, respiratory diseases, fertility issues, and psychological issues, is also included in the assessment (2).

1.2. Obesity throughout history

The first representation of obesity dates to at least 30,000 years Before Common Era (B.C.E.), with statuettes depicting women with obesity. These have been found throughout Europe, with the Venus of Willendorf among the most famous (3, 4). For years, obesity was viewed as a symbol of beauty, prosperity, and fertility, celebrated in the artworks of renowned painters like Rubens and Renoir (5, 6). Hippocrates noted the potential causes and detrimental consequences of obesity as early as the 5th century B.C.E. He linked obesity to infertility and attributed the sedentary lifestyle to excess fat mass in the tribe of Scythians. He recommended lifestyle modifications such as dietary adjustments and increased physical activity to maintain a healthy weight (7, 8). While people with obesity have been described throughout history, the incidence of obesity has always been rare (9). By the 20th century, particularly between 1960 and 1980, the obesity rate surged (10), as linked to economic growth, the growing availability of inexpensive nutrient-poor food, industrialization, urbanization, and mechanized transportation, resulting in reduced physical activity (9). This shift prompted the WHO in 1997 to declare an obesity pandemic (11).

1.3. Obesity is a worldwide problem

Since the declaration of obesity as a pandemic by the WHO, the prevalence of people living with obesity has kept on rising. In the Netherlands, 16% of adults aged 20 and above are currently living with obesity, which is triple the amount compared to the early

1980s, though it remains among the lowest in Europe (12). Worldwide, it is expected that 51% of the global population will be living with obesity by 2035 (13).

These increasing rates are alarming, as obesity impairs body health and is associated with the risk of developing various obesity-related diseases, like type 2 diabetes mellitus (T2DM), cardiovascular diseases, and even 13 types of cancer (1). This results in a reduced life expectancy of 3 years for people living with obesity and up to even 10 years for people with obesity class III (14). Combined, these factors have led to an economic impact of 2.4% of global gross domestic product in 2020, consisting of healthcare costs of treating obesity and its related diseases, as well as the effect of high BMI on economic productivity (13). This impact is expected to rise to 2.9% in 2035, which corresponds to 4.3 trillion dollars annually (13, 15).

1.4. Obesity stigma

Alongside the rising prevalence of obesity, in the twentieth century, the attitude towards people living with obesity shifted from a positive to a negative connotation (4). Currently, approximately 56-61% of people living with obesity have encountered weight stigma at some point in their lives, defined by discriminatory acts and ideologies towards individuals because of their weight and size (16, 17). The stigma often manifests in the belief that people who are living with obesity are responsible for their health solely due to laziness and overeating, suggesting a lack of motivation and willpower to lose weight (16, 17). Moreover, it coincides with beliefs that people with obesity are less intelligent and less capable of fulfilling leading positions at work (18). Encounters with the stigma result in diminished mental health, the development of unhealthy eating behavior, reduced physical activity, and increased stress, potentially exacerbating obesity development and the risk of comorbidities (16, 17, 19). Unfortunately, stigmatization not only occur in the general population. Two-thirds of people living with obesity report being stigmatized by their healthcare professionals (16, 20). Stigmatization can cause healthcare professionals to spend less time with individuals with obesity, reduce screening for underlying health conditions, and decrease their willingness to help them (20). Consequently, people with obesity may delay seeking help or avoid it altogether (16, 21). Addressing this issue requires training and education of healthcare professionals on the complex mechanisms of obesity and how to address weight-related concerns adequately (19).

2. Underlying causes and sustaining factors in obesity

According to the new Dutch guideline Overweight and obesity in adults, launched in 2023, the mechanisms driving obesity development and the factors that maintain it can be divided into seven categories: lifestyle, socioeconomic, psychological, medication

use, hormonal, hypothalamic, and genetic (i.e., monogenetic or syndromic) (22). Identifying the underlying cause(s) and sustaining factors in individuals living with obesity is an important first step for determining appropriate intervention options (2).

2.1. Lifestyle

Lifestyle factors play a significant role in the development of obesity. The intake of ultra-processed and excessive amounts of foods combined with a sedentary lifestyle can disrupt the energy balance within the body, leading to a positive energy balance. Consequently, excess nutrients (i.e., glucose and fatty acids) are stored as triglycerides in subcutaneous and visceral white adipose tissue (WAT) depots (23-25). Inadequate sleep is also linked to the development of obesity, as night shift workers are known to have an increased risk of developing obesity compared to day shift workers (26, 27). This may well be because changes in melatonin levels, as occurs in the case of night shifts, disrupt metabolic homeostasis and alter the regulation of hunger hormones, as will be further discussed in section 3.4. Next to disturbed sleep rhythmicity, shorter sleep duration and decreased sleep quality result in increased levels of the hunger hormone ghrelin and decreased levels of the satiety hormone leptin, leading to increased feelings of hunger, nutrient intake, and weight gain (28). In addition, individuals with sleep quality-impairing obstructive sleep apnea (OSA), characterized by recurrent episodes of upper airway collapse leading to apnea and hypopnea, are reported to gain weight (28). OSA-induced hypoxia and its associated complications, including inflammation and endothelial dysfunction, increase the risk of developing obesity and related complications in the long term, resulting in a vicious cycle (28).

2.2. Social economic position

Social economic position, determined by education, income, and occupation, has been linked to obesity (2, 29, 30). Financial instability, unemployment, and unfavorable work conditions contribute to psychological stress and limit access to healthy food options and safe exercise environments, thereby increasing the risk of obesity (30). In addition, children born in families with lower socioeconomic positions are more prone to develop obesity, often influenced by parental factors such as parental obesity and smoking during pregnancy (31, 32).

2.3. Psychological factors

Psychological factors play a significant role in the development of obesity, exhibiting a bidirectional relationship with weight gain. Childhood traumas, sexual abuse, depression, chronic stress, and eating disorders are all linked to the development of obesity (2, 33-35). Conversely, people living with obesity are more prone to developing depression, chronic stress, and eating disorders (2, 35). Depression development is

linked to hormonal changes, microbiota shifts, and inflammation, suggesting a shared biological pathway with obesity development (36). Chronic stress exacerbates obesity by increasing cortisol levels, leading to more appetite and abdominal obesity (34).

2.4. Medication use

Weight gain is a common side effect of various medications, including certain antihypertensives (e.g., beta-blockers), pain relievers, diabetes medication (e.g., insulin), antidepressants, anti-epileptics, and corticosteroids (37, 38). Various mechanisms, such as appetite stimulation, reduced energy expenditure, and disruption of the hypothalamic-pituitary axis, have all been linked to these medications and may facilitate weight gain (39).

2.5. Hormonal

In addition to the endocrine changes that occur in obesity, as discussed below, various common endocrine disorders are linked to the development of obesity. Hypothyroidism, polycystic ovary syndrome (PCOS), male hypogonadism, and menopause can all contribute to decreased resting energy expenditure, leading to weight gain (40-42). Rare forms of endocrine disorders associated with obesity development include Cushing's syndrome, insulinoma, and growth hormone deficiency (43).

2.6. Hypothalamic obesity

Hypothalamic obesity refers to abnormal weight gain resulting from the physical destruction of the hypothalamus, the center in which satiety and energy expenditure are regulated (44). Hypothalamic obesity is a rare underlying cause of obesity, and the most common causes include suprasellar tumors, cranial radiation, vasculitis, or head trauma (44). Weight gain typically occurs rapidly, within weeks to months, and is associated with massively increased appetite (i.e., hyperphagia) and reduced satiety. Additionally, affected individuals may experience disturbed sleep patterns and reduced energy expenditure, further contributing to obesity development (44).

2.7. Monogenetic/syndromic

On rare occasions, obesity is caused by mutations in either a single gene (monogenic obesity) or a part of a chromosome (syndromic obesity) (45, 46). Monogenic obesity typically involves genes involved in the melanocortin 4 receptor (MC4R)/pro-opiomelanocortin deficiency (POMC) pathway, resulting in disturbances in satiety (45). Key indicators of a genetic basis for obesity include severe obesity, early onset, hyperphagia, and a distinct familiar pattern (45). Other symptoms vary depending on the affected gene. Syndromal forms of obesity, such as 16p11.2 deletion syndrome and Bardet-Biedl syndrome, are additionally characterized by cognitive deficits and

behavioral alteration (45). While screening for genetic obesity is not routine, it is indicated for individuals exhibiting high clinical suspicion as more specific treatment options are being developed (2).

3. Physiology of adipose tissue and energy metabolism

Obesity is a complex chronic disease with intricate mechanisms affecting various physiological systems in the body. During the development of obesity, tissue function of different organs is negatively affected by metabolic disturbances due to a positive energy balance in addition to the impairment of the total body by its excess weight.

3.1. Physiology of white adipose tissue in healthy and obesity

WAT is the predominant type of adipose tissue in the human body. It is primarily located beneath the skin (subcutaneous adipose tissue; SAT) and around organs (visceral adipose tissue; VAT) (47). WAT consists of large adipocytes that contain a single lipid droplet. Its primary function is to store energy in the form of triglycerides during energy surplus, from which fatty acids can be released via intracellular lipolysis into the circulation for uptake and beta-oxidation by metabolically active organs such as skeletal muscles and heart during times of energy demand (25, 48).

In addition to storage, WAT is receptive to signals from other tissues, including several hormones (e.g., cortisol and insulin) and the central nervous system (via catecholamines). Furthermore, WAT also functions as an endocrine organ itself via the secretion of adipokines (49, 50). These adipokines can influence almost every other organ within our body in an autocrine, paracrine, and/or endocrine manner (50). Two well-known adipokines are leptin and adiponectin, which are involved in inducing satiety and regulating insulin sensitivity, as will be further discussed below.

During the development of obesity, a prolonged positive energy balance results in enhanced energy storage (contained in glucose and fatty acids) as triglycerides and subsequent expansion of lipid droplets in adipocytes, primarily in the SAT depot (50, 51). However, there is a limit to how much adipocytes within SAT can expand, constrained by the extracellular matrix and vascularization. Once these limits are reached, hypoxia and dysfunction of the tissue occur (50, 52). This dysfunction triggers stress in the adipocytes, promoting the secretion of inflammatory cytokines and the recruitment of immune cells, resulting in low-grade inflammation in the adipose tissue. Cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-alpha) impair adipocyte differentiation, reduce lipid accumulation, and increase intracellular lipolysis within adipocytes (50, 51, 53). Moreover, these cytokines can directly impair insulin sensitivity, resulting in insulin resistance within WAT. Due to the occurring insulin resistance, the

physiological inhibition of insulin on lipolysis is diminished, resulting in an increase in intracellular lipolysis in WAT. Consequently, the release of fatty acids into the circulation is enhanced, directing lipids towards VAT and other tissues such as skeletal muscle, liver, pancreas, and heart, a process known as ectopic fat deposition (53). Ectopic fat accumulation can impair the function of these metabolic organs, contributing to insulin resistance of these tissues and further enhancing insulin resistance and metabolic disturbances (50, 53).

3.2. Lipid metabolism and its implications for obesity

Triglyceride-derived fatty acids are an important energy source in our body. After a meal, triglycerides are broken down within the stomach and intestine into 2-monoacylglycerol and free fatty acids (FFA) by gastric lipase and pancreatic lipase and then absorbed by the epithelial cells of the gut (i.e., enterocytes) (54, 55). Here, 2-monoacylglycerol and fatty acids are re-esterified into triglycerides and packed with dietary cholesterol to form chylomicrons, which are then released into the lymphatic system and subsequently enter the circulation (54, 56). At the endothelial surface of the capillaries of metabolically active tissues, including the heart, skeletal muscles, and various adipose tissues, chylomicrons bind to lipoprotein lipase (LPL) that hydrolyses its triglycerides into glycerol and fatty acids. The liberated fatty acids are taken up by the parenchymal cells of the LPL-expressing tissues, and used for storage (WAT), or for beta-oxidation to produce ATP (skeletal muscle and heart) or heat (brown adipose tissue (BAT); see section 3.5.1. (57). This process results in the formation of partially delipidated and ApoE-enriched chylomicron remnants that hepatocytes recognize and take up via the LDL receptor (LDLR) and LDLR-related protein-1 (LRP1) (58).

The liver can also synthesize triglyceride-rich lipoproteins, called very low-density lipoproteins (VLDL), which are especially important in the fasted state. Just like chylomicrons, VLDL provides triglyceride-derived fatty acids to metabolically active tissues such as the heart, skeletal muscle, and BAT as fuel through the action of LPL (59). Like chylomicron remnants, resulting VLDL remnants are recognized and taken up via ApoE by the LDLR and LRP1 on hepatocytes. Alternatively, VLDL can be converted into low-density lipoproteins (LDL), the lipolytic end product of VLDL, which are primarily recognized and taken up by the liver through the interaction of their ApoB100 with the LDLR on hepatocytes (54).

ApoA1, the high-density lipoproteins (HDL) precursor, is synthesized and secreted by the intestine and liver. During LPL-mediated lipolysis, liberated phospholipids from chylomicrons and VLDL are acquired by circulating lipid-poor ApoA1. These newly formed pre-HDL particles can take up cholesterol from peripheral organs, forming

cholesterol-enriched pre-HDL. Finally, the enzyme lecithin cholesterol acyltransferase (LCAT) residing on HDL converts the acquired free cholesterol into cholesteryl esters, resulting in mature HDL. As such, HDL particles are involved in reverse cholesterol transport, i.e., translocating cholesterol from peripheral tissues to the liver for excretion into the feces primarily as bile acids (60).

Insulin plays a major role in triglyceride metabolism by increasing LPL activity, thereby enhancing triglyceride storage in adipose tissue. This process reduces the availability of FFA in the circulation that could be used by the liver to synthesize VLDL (61). Additionally, insulin inhibits the breakdown of intracellular triglycerides by inhibiting adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) (61, 62). The glucose-dependent insulinotropic polypeptide (GIP), produced by K-cells of the small intestine after a meal, also influences lipid metabolism by promoting postprandial lipid storage in adipose tissue by activating LPL and increasing blood flow through vasodilation (63). Conversely, catecholamines reduce lipid storage by stimulating intracellular lipolysis in adipose tissue, increasing circulating FFA and enhancing fatty acid-driven VLDL production by the liver (56, 64).

People living with obesity frequently develop dyslipidemia, defined as increased levels of circulating total cholesterol, LDL-cholesterol, and triglycerides in combination with decreased HDL-cholesterol (65). In obesity, dyslipidemia generally develops due to increased nutrient intake and adipose tissue insulin resistance, resulting in high circulating FFA levels both postprandially and during fasting (56, 66). The increased FFAs are taken up by the liver, where they are converted into triglycerides to drive the production of VLDL, ultimately resulting in increased LDL-cholesterol levels. Increased (V)LDL increases the exchange of VLDL-triglycerides with HDL-cholesteryl esters as mediated by the cholesteryl ester transfer protein (CETP), thereby decreasing HDL-cholesterol levels (60). Concomitantly, this leads to the accumulation of smaller dense LDL particles that are slowly catabolized and more easily oxidized when exposed to oxidative stressors, such as smoking and unhealthy diet (67, 68). The increase in LDL-cholesterol, probably in combination with increased oxidative stress, is causal to the formation of atherosclerosis, which can result in atherosclerotic cardiovascular diseases, including myocardial infarction and stroke (67, 69).

3.3. Regulation of glucose homeostasis and its disruption in obesity

While fatty acids are a prominent energy source for many tissues in the body like skeletal muscle and the heart, the brain relies primarily on glucose and cannot use fatty acids as an energy source (70). As the body's demand for glucose fluctuates throughout the day, various glucoregulatory hormones maintain stable circulating glucose levels.

Glucose is derived from three sources: via food, the breakdown of glycogen stored in the liver (glycogenolysis), and *de novo* generation by the liver (gluconeogenesis) (71). Glycogenolysis and gluconeogenesis are predominantly stimulated by glucagon, a hormone released from the alpha cells in the pancreas during fasting to ensure glucose availability in the body (71, 72).

After a meal, when glucose is abundant, glucose levels are lowered via different mechanisms. The hormones insulin and amylin, released by the pancreatic beta cells, and glucagon-like peptide 1 (GLP-1) and GIP, released by the intestinal L-cells and K-cells, respectively, all work to lower postprandial glucose levels.

Insulin lowers circulating glucose levels by binding insulin receptors on insulin-sensitive tissues, such as skeletal muscle and WAT, to increase glucose uptake. This is achieved by translocation and fusion of the glucose transporter GLUT4 to the cell membrane (73). Additionally, insulin inhibits glucagon secretion, thereby inhibiting glycogenolysis and gluconeogenesis (71, 72, 74, 75). Furthermore, as mentioned in section 3.2., insulin increases LPL activity and inhibits intracellular lipolysis, thereby enhancing triglyceride storage in adipocytes. Amylin complements the effects of insulin by suppressing glucagon secretion via efferent vagal signals, decreasing gastric emptying, and decreasing satiety by binding to its receptor in the area postrema in the hindbrain (71, 76).

The incretin hormones GLP-1 and GIP are responsible for the 'incretin effect', which refers to a 2-3 fold increase in insulin secretion when glucose is administered enterally compared to intravenously (77). GLP-1 and GIP both stimulate insulin release in a glucose-dependent manner. This means they only stimulate insulin when circulating glucose levels are above the normal range, preventing hypoglycemic episodes (72). GIP and GLP-1 are secreted within minutes after food ingestion (78), and rapidly degraded by dipeptidyl peptide IV (DPP4) (79). GLP-1 receptors (GLP-1R) and GIP receptors (GIPR) are expressed throughout the body in different tissues, especially the pancreas, heart, and brain (80). As mentioned in section 3.2., the interaction of GIP with GIPR on white adipocytes postprandially increases LPL-medicated uptake of fatty acids in adipocytes (81). GLP-1 also inhibits glucagon secretion, further contributing to glucose level reduction. Additionally, GLP-1 and GIP play roles in inducing satiety, as further described in section 3.4.2.

In addition to hyperinsulinemia, obesity-associated insulin resistance is characterized by basal hyperglucagonemia and reduced suppression of glucagon after a meal (82, 83). The higher levels of basal and post-prandial glucagon contribute to hyperglycemia

by increasing gluconeogenesis in the liver (83). The liver uses amino acids to increase gluconeogenesis, causing protein loss in skeletal muscles and thereby wasting muscle mass (83). This can contribute to the development of so-called 'sarcopenic obesity'.

The role of amylin in obesity and its connection to the development of insulin resistance is not yet fully elucidated. Until now, evidence points to no clear effect of dysfunction in the amylin system (both levels and receptor function) in obesity (84).

In obesity, the secretion of GLP-1 and GIP is often altered, resulting in higher levels of GIP and possibly lower levels of GLP-1 during fasting and postprandial; however, higher GLP-1 levels have also been described (85-87). The decreased GLP-1 levels together with reduced responsiveness of pancreatic islets to GIP result in a diminished incretin effect in people living with obesity. This leads, in the initial stages of obesity, to lower insulin release and higher glucose levels (88, 89). When the disease progresses, insulin levels increase due to the development of insulin resistance.

3.4. Hunger and satiety hormones and their role in energy balance

Various hunger and satiety hormones regulate the energy intake aspect of the energy balance. Among the most prominent are the previously discussed leptin, GLP-1, and GIP for satiety and ghrelin for hunger. However, there are several others, such as cholecystokinin (CKK), peptide YY (PYY), and growth differentiation factor 15 (GDF15) all inducing satiety.

3.4.1. Leptin

Leptin, the first discovered adipokine, is key in maintaining energy balance by regulating food intake and energy expenditure (49). It works by signaling through leptin receptors in the hypothalamus and brainstem, promoting satiety and increasing energy expenditure (90, 91). The importance of leptin is evident from patients who suffer from leptin deficiency, which leads to extreme hunger and severe obesity from a young age (92).

In common multifactorial obesity, leptin regulation also becomes disrupted. Circulating leptin levels are directly linked to the size of adipocytes, especially those located subcutaneously (93). Therefore, people living with obesity generally have higher circulating leptin levels. Leptin levels further fluctuate based on the nutritional status, decreasing during fasting and increasing during feeding (90, 93). However, despite the high leptin levels in people with obesity, they generally experience less satiety compared to individuals who are lean, suggesting that obesity is a state of leptin resistance (94). This may, at least in part, be a consequence of the development of hypothalamic inflammation in obesity (95).

3.4.2. Incretin hormones

While GLP-1 and GIP play an important role in glucose metabolism (see section 3.3), they also induce satiety by signaling via afferent neurons of the vagus nerve from the intestine to the GLP-1R and GIPR in the hypothalamus and hindbrain (88, 96, 97). Recent research has shown that GIP has an additive effect on GLP-1 in satiety induction, although the precise mechanisms are still largely unknown (98, 99).

People living with obesity often experience persistent increases in hunger and lower satiety compared to lean people, which can contribute to overconsumption and difficulty in reducing food intake (100, 101). Besides leptin resistance as described above, this disturbed function of other hunger and satiety hormones in people living with obesity contributes to this phenomenon. For example, the lower postprandial GLP-1 release as mentioned above can lead to a diminished satiety response but potentially also increase gut emptying (102). This results in overall less suppression of hunger and increased return after a meal (100, 102).

3.4.3. Ghrelin

Ghrelin is a key modulator of food intake, energy metabolism, gastric acid secretion, and motility (103, 104). When the body demands nutrients, ghrelin is secreted from the stomach and small intestine, preparing the body for a meal. Acting via vagal afferent neurons, ghrelin signals via the vagal nerve to its GH secretagogues receptor 1a (GHS-R1a) located in the hypothalamus, stimulating appetite (104). Beyond its role in appetite regulation, ghrelin influences glucose homeostasis by promoting glucose production in the liver by activating gluconeogenesis pathways. It also stimulates gastric secretion and motility (105). Furthermore, ghrelin plays a role in lipid metabolism by promoting lipid storage in adipocytes by upregulating several fat storage-related proteins, including fatty acid synthase (FAS), LPL, and perilipin (106, 107).

Although the exact underlying mechanism is not well known, it is reported that postprandial suppression of ghrelin in people living with obesity is often reduced, contributing to persistent feelings of hunger after a meal (108).

3.4.4. Growth Differentiation Factor 15

Growth Differentiation Factor 15 (GDF15) is a stress-regulated hormone secreted by various body organs, including the kidneys, placenta, prostate, and gastrointestinal tract. Recent reports suggest that it is also a potent appetite-suppressing hormone that signals via binding to the glial cell line-derived neurotrophic factor (GDNF) family receptor alpha-like (GFRAL) located in the area postrema and solitary tract of the hindbrain (109-112). GDF15 is a stress-responsive hormone and in people living

with obesity, GDF15 levels are increased, especially in males (113, 114). However, the mechanism causing the increase in GDF15 during obesity and the consequences of obesity-induced GDF15 remains unclear (115).

3.5. Physiology of energy expenditure in health and obesity

Energy expenditure (EE) refers to the energy that an individual expends to maintain bodily functions, and consists of different components: resting energy expenditure (REE), food or diet-induced EE, adaptive thermogenesis, and activity-induced EE (116, 117). REE accounts for approximately two-thirds of the total EE (118). Many factors, like age, sex, body composition, genetics, and hormones influence REE (119). Environmental temperature can affect EE through adaptive thermogenesis; during colder temperatures, the body increases EE to maintain a stable core body temperature. Adaptive thermogenesis occurs in two forms: shivering thermogenesis, primarily caused by skeletal muscle contractions, and non-shivering thermogenesis, primarily driven by BAT but involving skeletal muscles (120-123).

As obesity results from an imbalance between energy intake and EE, people living with obesity might be expected to have decreased EE. However, REE is often increased compared to lean individuals (124). This is likely due to the increase in fat-free mass, which consists of highly active metabolic organs such as skeletal muscle, needed to support the excess body weight. When correcting for the increased fat-free mass, people living with obesity generally have similar REE compared to lean individuals (124).

3.5.1. Role of brown adipose tissue in thermogenesis and its detection in obesity

BAT contributes to adaptive thermogenesis by oxidizing glucose and triglyceride-derived fatty acids, thereby generating heat instead of adenosine triphosphate (ATP) (125). In adults, BAT is mainly located in the supraclavicular, cervical, and axial regions. BAT contains small multilocular brown adipocytes with mitochondria that contain uncoupling protein 1 (UCP1) (126). Long-chain fatty acids activate UCP1 and facilitates proton leak over the mitochondrial inner membrane, resulting in dissipation of energy as heat (121). Cold exposure is the main physiological activator of BAT, leading to the release of norepinephrine from the sympathetic nervous system, which binds to beta-adrenergic receptors on the cell membrane of brown adipocytes and triggers BAT thermogenesis (127). In addition, BAT has an autocrine, paracrine, and endocrine function, as it secretes several signaling molecules known as batokines that play a role in the homeostasis of different tissues, such as WAT, skeletal muscle, and liver (128, 129). While in mice the beta-adrenergic 3 receptor is the main receptor that stimulates BAT thermogenesis, the responsible beta-adrenergic receptor stimulating BAT thermogenesis in humans is less clear.

In humans, the uptake of glucose by BAT is used as a measure of BAT activity, often assessed via a [^{18}F]fluoro-D-deoxyglucose positron emission tomography/computed tomography ([^{18}F]FDG PET/CT) scan. This scan uses the tracer [^{18}F]FDG to quantify glucose uptake in BAT after an individualized cooling protocol. In people with obesity, the uptake of glucose by BAT often is lower or even absent (130). This is due to the visualization method of BAT. Both glucose and [^{18}F]FDG uptake by BAT are mediated via the GLUT4 and GLUT1 but GLUT4 is stimulated by insulin, so in case of reduced insulin sensitivity, less glucose, and [^{18}F]FDG are taken up by cells (131, 132). A large study using [^{18}F]FDG PET/CT scans showed that those people with obesity who had detectable BAT (i.e., with [^{18}F]DFG uptake above a certain threshold) have a healthier metabolic phenotype (lower VAT, insulin resistance, inflammation, odd to develop T2DM, dyslipidemia, and congestive heart failure) compared to those without detectable BAT, suggesting a contribution of BAT in whole-body metabolism (133-135).

3.5.2. Fibroblast growth factor 21

Fibroblast Growth Factor 21 (FGF21) is a stress-inducible hormone secreted by various organs. Following prolonged fasting (7-10 days), the liver mainly contributes to total FGF21 secretion (136). In hepatocytes, FGF21 secretion is controlled by the activation of peroxisome proliferator-activated receptor α (PPARα) which is, in turn, activated by non-esterified fatty acids released from adipocytes (137).

Other stressors that induce FGF21 release include cold exposure (FGF21 release by BAT, WAT, and liver) and exercise (FGF21 release by skeletal muscle). FGF21 is important in regulating lipid and glucose metabolism, enhancing insulin sensitivity, enhancing REE, and modulating mainly anti-inflammatory immune responses (138-140). FGF21 exerts its actions by binding to the isoforms of FGF 1,2,3, and 4 receptors, which forms a heterodimer with the co-receptor β-Klotho. Since β-Klotho is primarily expressed in the liver and in both white and brown adipose tissues, these are the main target tissues of FGF21. In adipose tissues, FGF21 enhances insulin sensitivity and glucose uptake. In the liver, FGF21 reduces lipogenesis and enhances fatty acid oxidation, lowering hepatic triglyceride content. However, during nutrient surplus, FGF21 suppresses lipolysis to lower triglyceride levels and prevent excessive hepatic lipid deposition (141, 142). Additionally, FGF21 reduces the expression of pro-inflammatory cytokines and inhibits inflammatory pathways in various tissues like the liver (138, 139).

Despite that FGF21 increases insulin sensitivity, reduces inflammation, and prevents excessive hepatic lipid depositions, circulating FGF21 levels are actually elevated in people living with obesity and positively correlate with BMI (143). This seeming discrepancy suggests that obesity is a state of FGF21 resistance, possibly with

downregulation of the FGF21 receptors. Indeed, different isoforms of the FGF receptor are downregulated in WAT in obese mice (144, 145). In obesity, higher FGF21 levels are positively associated with impaired glucose tolerance and lipid accumulation in the liver (145).

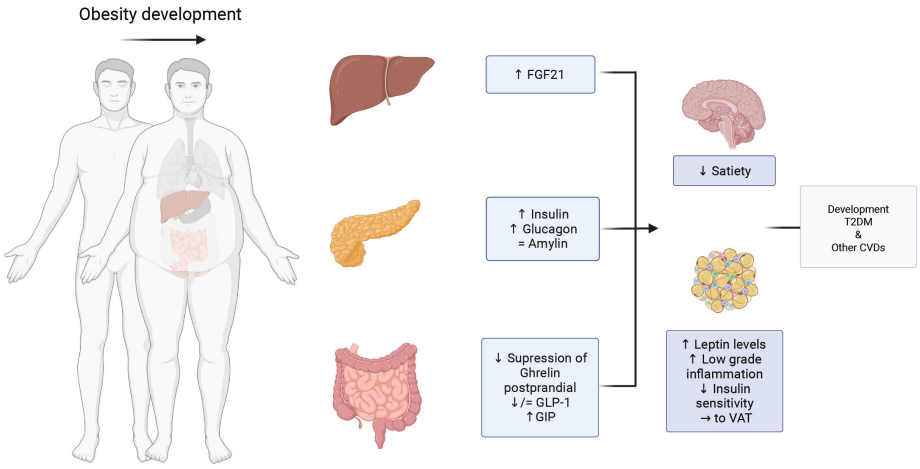

Figure 1. Dysregulation of various hormones during obesity development contributes to the development of obesity-related diseases. Obesity leads to dysregulation of hormones in the liver, pancreas, and gut, resulting in reduced satiety induction and alterations in white adipose tissue, all of which contribute to the development of obesity-related diseases. See sections 3.4 and 3.5.2. FGF21, fibroblast growth factor 21; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide 1; T2DM, type 2 diabetes mellitus; VAT, visceral adipose tissue.

4. Increased risk of South Asians to develop obesity and cardiometabolic diseases

4.1. Etiology of South Asians

Certain populations, such as the South Asian population, are more prone to develop obesity and obesity-related diseases as compared to e.g. Europids (146). South Asians (originally descended from Surinam, Bangladesh, India, Nepal, Pakistan, Afghanistan, Bhutan, and Sri Lanka) are predisposed to developing obesity and obesity-related diseases at a significantly younger age and lower BMI than other ethnic groups (146). The South Asian population constitutes approximately 25% of the world's population (147). In the Netherlands, there are about 240,000 people of South Asian descent (approximately 1.4% of the Dutch population), particularly concentrated in and around The Hague (148).

4.1.1. South Asians and migration towards the Netherlands

The large number of South Asians in the Netherlands is primarily due to the historical ties of the Netherlands with Surinam (148). In 1667, the Dutch defeated the British and occupied Surinam, establishing plantations for cotton, sugar, cocoa, and coffee. The labor-intensive work on these plantations was initially performed by enslaved Africans. However, after slavery was abolished in 1863 by the Emancipation Act, the Dutch recruited people from British India and the Dutch East Indies to replace the freed slaves as contract workers (149). Approximately 34,000 people migrated from Asia to Surinam. After the embellishment of contract work, supported by Mahatma Gandhi, about 25,000 people from South Asia remained in Surinam (150-152). Following Surinam's independence in 1975, around 40,000 individuals of South Asian descent migrated to the Netherlands (153). Therefore, many South Asians living in the Netherlands are of Surinam descent.

4.2. Underlying factors contributing to the high cardiometabolic disease risk in South Asians

An unfavorable metabolic phenotype in South Asians compared to Europids, consisting of central obesity, dyslipidemia, and insulin resistance, is an important factor that contributes to their high risk of developing cardiometabolic diseases, which will be discussed below.

4.2.1. Unfavorable metabolic phenotype of South Asians

South Asians have a higher body fat percentage, especially due to an increased abdominal visceral fat mass, and lower lean muscle mass than Europids (154, 155). These differences are already apparent in infancy, with South Asian neonates showing higher fat mass and lower fat free mass than Europid neonates (156). The higher fat mass in South Asians, especially in VAT and ectopic locations, may be explained by the adipose tissue overflow hypothesis (157). This hypothesis states that South Asians have less developed SAT than Europids, with a reduced capacity to store fatty acids. As a result, they utilize VAT for storage earlier than Europids (157). This theory is based on findings of higher VAT components in South Asian males and females, even though BMI and waist circumference differ slightly between South Asians and Europids (157). Another study showed that in healthy South Asians, adipocyte cell size was larger in subcutaneous fat biopsies compared to Europids with similar body fat content, and this was negatively correlated with insulin resistance and plasma adiponectin concentration (158).

Higher circulating insulin and glucose levels are already present in the cord blood of South Asian neonates compared to Europids neonates, suggesting that an unfavorable metabolic phenotype is already present from birth (159). This trend continues

throughout life, as young South Asians exhibit higher insulin responses to an oral glucose tolerance test (OGTT) than Europids (160). Increased insulin resistance in South Asians is likely partly explained by their increased VAT, ectopic fat, and lower muscle mass (161). As a result, South Asians are more prone to develop insulin resistance and T2DM at a younger age and lower BMI than Europids (162, 163). Moreover, an earlier decline in pancreatic beta cell function may also contribute to this increased risk (162).

Another pillar of the classical unfavorable metabolic phenotype in South Asians is dyslipidemia. This is characterized by high levels of triglycerides, low levels of HDL-C, and smaller, dysfunctional HDL particles despite having similar LDL-C levels (164). Dyslipidemia is a contributing factor to the increased risk of cardiovascular disease in the South Asian population (164). However, unfavorable fat distribution, dyslipidemia, and insulin resistance do not fully explain the increased risk of obesity-related diseases in South Asians. Other factors, such as lifestyle, inflammation, hormonal dysregulation, and energy expenditure changes, may also contribute (165). Additionally, there may be other yet unidentified factors that play a role.

4.2.2. Lifestyle of South Asians

As mentioned, unhealthy lifestyle factors can contribute to the development of obesity (2). Various unfavorable lifestyle factors are particularly prevalent in the South Asian population and may further aggravate their metabolic phenotype.

Food plays a main role in South Asian culture, especially during social gatherings. Offering abundant, flavorful, and nutrient-rich foods is seen as part of hospitality (166). In addition, the typical diet consists mainly of carbohydrates and saturated fats, with a low protein content, which is high in calories and can contribute to weight gain (154, 167).

Furthermore, South Asians tend to have lower levels of physical activity than other ethnic groups (166, 167). Different priorities, such as family and education, often take precedence, contributing to a more sedentary lifestyle (166). Moreover, the unfamiliarity with exercise, combined with cultural beliefs about appropriate clothing for exercise and concerns about the safety of women exercising alone, can discourage physical activity (166, 168).

Contributing to an unfavorable lifestyle is tobacco use in South Asians. Especially in males, the prevalence of smoking is much higher compared to the Europids (169). Alcohol use, on the other hand, is much lower in the South Asian population compared to Europids (170).

Finally, the quality and quantity of sleep among the South Asian population are lower compared to other ethnicities. Poor sleep quality is associated with greater VAT (171). Many South Asians sleep less than seven hours per night and have lower sleep quality, with a higher prevalence of obstructive sleep apnea. Poor sleep quality and quantity not only underlies obesity and increased VAT but also aggravates it (172).

4.2.3. Inflammation in South Asians

Inflammation has been increasingly acknowledged as a contributor to the development of obesity-related diseases (173). This is particularly evident in the South Asian population, who exhibit a more pro-inflammatory phenotype than Europids. C-reactive protein (CRP), an acute phase protein indicative of inflammation, is already elevated in the cord blood of South Asian neonates (174). These elevated CRP levels persist throughout life, with South Asians consistently showing higher CRP levels than Europids (175). Furthermore, South Asians with T2DM have a more activated interferon (IFN)-signaling pathway and higher B cell markers than Europids (176). These findings show the pro-inflammatory state of South Asians, which may contribute to their increased risk of obesity-related diseases (162). Indeed, IFN has been shown to accelerate insulin resistance in myocytes *in vitro* (177). Tackling the pro-inflammatory state of South Asians could potentially prevent or treat obesity-related diseases (178).

4.2.4. Hormone regulation in South Asians

South Asians exhibit higher leptin levels compared to Europids (179). This may well be due to their increased white adipocyte size. The differences in incretin levels between South Asians and Europids are not well researched; only two studies have investigated GLP-1 levels at fasting and after an OGTT in South Asians compared to Europids. These studies found that South Asians have higher postprandial GLP-1 levels (160, 180). Additionally, the regulation of other hunger and satiety hormones in South Asians, like GIP, ghrelin, and GDF15, remains inconclusive.

4.2.5. Resting Energy Expenditure in South Asians

So far, we have discussed the underlying mechanisms of the increased risk of obesity-related disease leading to an increased energy intake in South Asians. However, South Asians also exhibit lower REE, contributing to a positive energy balance (181, 182). Additionally, exercise-induced EE is also lower in South Asians (183, 184). This lower EE is attributed to a lower fat-free mass in South Asians than in Europids (181). Furthermore, South Asians also have a lower BAT volume than Europids, which may partly underlie their lower REE and adaptive thermogenesis, further contributing to their increased risk of developing obesity and obesity-related diseases (182).

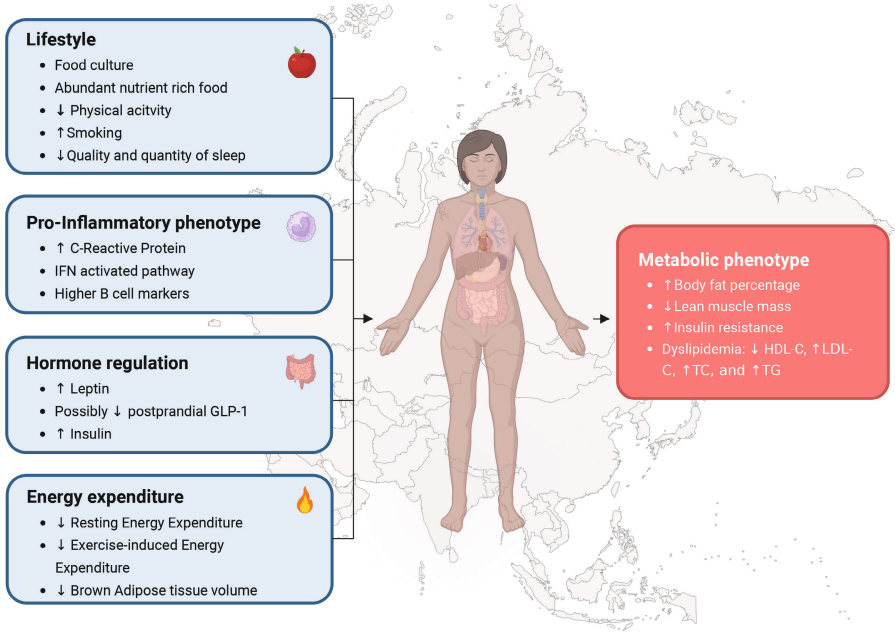

Figure 2. Various factors may contribute to the increased risks of South Asians developing obesity and obesity-related diseases including unhealthy lifestyle, pro-inflammatory phenotype, hormone dysregulation, and low energy expenditure (blue boxes), collectively contributing to an adverse metabolic phenotype (purple box). For more information, see the section 4.2. GLP-1, glucagon-like peptide 1; HDL-C, high-density lipoprotein cholesterol; IFN, interferon; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides.

5. Targets for prevention and treatment of obesity and related diseases

In the preceding sections, we have explored the physiology of and underlying mechanisms contributing to the development and consequences of obesity. This section will discuss possible strategies to counteract obesity and related diseases. Prevention and treatment options fall into two main categories: lifestyle interventions and pharmacological interventions. It is important to note that all individuals living with obesity are advised to adopt a combined lifestyle intervention, especially when additional pharmacological treatments are used (2).

5.1. Nonpharmacological intervention

5.1.1. Combined lifestyle intervention

Combined lifestyle intervention is the cornerstone of the treatment of obesity. Its goal is to help people adopt a healthy lifestyle. Combined lifestyle interventions encompass

advice on diet, exercise, sleep, and cognitive behavioral therapy, with an emphasis on behavioral change (2). People are advised to follow a healthy diet, minimize processed food, and engage in at least 150-200 minutes of exercise per week, including strength training twice a week, while reducing their sedentary lifestyle (2).

For the South Asian population, lifestyle interventions can be more difficult to adopt due to barriers caused by cultural influences (166). In addition, South Asians need to move more to achieve the same results as Europids. A previous study showed that 232 minutes of physical activity for South Asians is equivalent to 150 minutes for Europids in reaching the same cardio-metabolic risk benefits. This was measured using vertical axis accelerations with accelerometers and based on biochemical markers like glycemia variables, lipid measurements, and blood pressure (185). However, culturally tailored dietary and exercise interventions have shown promise in improving glycemic control in South Asians (186).

5.1.2. Cold

Although cold exposure is not currently included in the guidelines as a treatment for obesity, studies have shown that prolonged repetitive cold exposure has beneficial effects on fat mass and metabolic health (187, 188). More specifically, in patients with T2DM, repetitive cold exposure improved insulin sensitivity and even necessitated reducing daily insulin use in some patients after 10 days (187). The improvement of metabolic health by cold exposure may be mediated by increased thermogenesis in BAT and skeletal muscles, the secretion of hormones by BAT (batokines) and skeletal muscle (myokines), as well as decreased inflammation. However, more research and more long-term studies are necessary to confirm this (188). Since South Asians have lower BAT volume and skeletal muscle mass, cold exposure may be a useful therapy for increasing the amount of BAT and increasing skeletal muscle thermogenesis in this population. Although this must be further studied, a previous study showed that cold exposure of healthy South Asians could potentially influence the immune system towards a less pro-inflammatory phenotype by altering the expression of various immune genes (189).

The effects of cold exposure on energy metabolism depend on the time of day. Cold-induced thermogenesis (CIT) has been shown to be higher in the morning than in the evening, at least in males (190). These time-dependent effects of cold exposure in men are possibly due to the rhythmicity in BAT activity during the day (190). In mice, BAT has a higher uptake of TG-derived fatty acids at the onset of the dark period, which is the start of the active period in mice (191). However, the diurnal rhythm of BAT in humans and its secretory function are yet to be elucidated.

5.2. Pharmacotherapy

5.2.1. Pharmacological activation of BAT

Cold exposure can activate BAT but is not suitable or desirable for everyone (192). Therefore, pharmacological activation of BAT is a potentially interesting alternative. In addition, due to the lower BAT volume in South Asians compared to Europids, they may benefit more from pharmacological strategies.

The beta-adrenergic receptor on the cell membrane of brown adipocytes is a potential pharmacological target to activate BAT. ADRB3 is most prominent in the activation of BAT in mice and was assumed to be a prominent receptor for BAT activation in humans as well (193, 194). However, while single administration of the ADRB3 agonist mirabegron to healthy participants resulted in enhanced [^{18}F]DFG uptake by BAT and increased REE, it also resulted in increased heart rate and blood pressure (195), regulated by the ADRB1 and ADRB2 receptors (196, 197), suggesting overflow towards these receptor subtypes. The dose of mirabegron to activate BAT was 200 mg, whereas the advised dose for treating overactive bladder, for which mirabegron is registered, is around 50 mg (198). Thus, a supratherapeutic dose was used to show an increase in BAT activity (199). Therefore, it is possible that the effects of mirabegron on BAT and energy expenditure were also caused by overspill to the ADRB1 and/or ADRB2 receptors rather than directly activating the ADRB3. Indeed, the ADRB2 appeared the dominant beta-adrenergic receptor on human brown adipocytes *in vitro* (200). Whether human BAT can be activated via the ADRB2 *in vivo* remains to be seen.

5.2.2. Metformin

Metformin is the first-line treatment for T2DM; it is also prescribed off-label for obesity due to its modest effects on satiety (2, 201). While the mechanism of metformin's satiety-inducing effect remained unknown for a long time, a recent study revealed that metformin stimulates satiety by increasing the levels of GDF15 (202). Preclinical studies showed that GDF15 induces satiety by binding to the glial cell line-derived neurotrophic factor (GDNF) family receptor alpha-like (GFRAL) located in the area postrema and solitary tract of the hindbrain (109-112, 203, 204).

5.2.3. GLP-1 receptor agonists

A more effective pharmacological treatment for weight loss is incretin-based treatment using GLP-1 receptor agonists (205), mainly by reducing food intake through inducing satiety (206). This is thought to mainly occur via the interaction of GLP-1 receptor agonists with vagal afferent neurons, transmitting a signal to the hindbrain and inducing satiety (207). This is supported by the attenuated anorexic effect of GLP-1 receptor

agonism when the vagal afferents are denervated (208). However, the involvement of other appetite-regulating hormones, including GDF15, in the beneficial effects of GLP-1 receptor agonists on satiety cannot be ruled out. In addition to reducing food intake by inducing satiety, other factors such as delayed gastric emptying, influence on fat distribution, and possible involvement of BAT resulting in enhanced thermogenesis may contribute to GLP-1-induced weight loss (206).

OUTLINE OF THIS THESIS

Obesity is a complex chronic disease with many underlying mechanisms, as described in this **current chapter**. Numerous environmental and physical factors can disrupt energy balance, leading to changes like hormonal imbalances and inflammation. These disruptions ultimately contribute to the development and maintenance of obesity and its related diseases, including T2DM and other cardiometabolic diseases. Unfortunately, some populations, such as South Asians, are more at risk of developing obesity and related disorders compared to Europids. However, the underlying mechanisms are not yet fully elucidated. Novel and sustainable treatment options are necessary to combat the obesity epidemic. Promising approaches include cold exposure or pharmacological activation of BAT, as well as pharmacological options based on the mechanisms of incretin hormones and other satiety hormones.

All in all, in this thesis, we aim to i) unravel additional underlying causes of the disadvantageous metabolic profile of South Asians, and ii) comprehensively understand how different (non-)pharmacological interventions can modulate circulating levels of various hormones and regulate overall energy metabolism in humans with different comorbidities.

To answer the first objective, in **Chapter 2** we first investigated potential differences in circulating levels of inflammation-related proteins in Dutch South Asians compared to Dutch Europids with T2DM. These were measured using a large inflammation panel from Olink proteomics, with findings confirmed via ELISA. Next, in **Chapter 3** we compared circulating incretin hormones and glucagon, between young and lean Dutch South Asians and Dutch Europids before and during a mixed meal tolerance test (MMTT) in relation to glucose and insulin excursions. In **Chapter 4**, in the same cohort of young and lean Dutch South Asians and Dutch Europids, we focused on circulating PYY, ghrelin and leptin before and during the MMTT.

Cold exposure and pharmacological activation of BAT could be potential interventions for obesity. Therefore, for the second objective, in **Chapter 5** we investigated the effect of cold exposure on circulating FGF21 and GDF15 in Europids and examined whether cold-induced changes in FGF21 and GDF15 levels differ between morning and evening in males and females. Furthermore, in **Chapter 6**, we investigated whether pharmacological activation of the ADRB2 receptor using the specific agonist salbutamol increases glucose uptake by BAT of lean Europid males, as assessed by a dynamic [^{18}F] FDG PET/CT scan. We used a cross-over design to compare intravenous salbutamol without and with the oral ADRB1/2 blocker propranolol. Finally, in **Chapter 7**, we

examined whether GDF15 mediates the satiety-inducing effect of the GLP-1 receptor agonist liraglutide in Dutch Europid and Dutch South Asian patients with T2DM.

In the final chapter, **Chapter 8**, we discuss the most important findings of all studies, as well as their implications and future directives.

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