Clinical Practice GUIDELINE for the Management of Obesity in Adults in Ireland

The Science of Obesity

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KEY MESSAGES

- **The causes of obesity are complex and result from interactions between genetic, biological, behavioural, psychosocial and environmental factors.**
- **Obesity is highly heritable.** Twin studies show a 50%–80% degree of concordance of body mass index (BMI) and regional fat distribution. A Swedish study of identical twins reared apart showed no correlation of BMI with members of their adopted family, but strong correlation with their twin reared in a different family.
- **The neurobiology of appetite, body weight and energy regulation is complex and mediated by a milieu of hormonal signals from the gut, adipose tissue and other organs, and neural signals which influence eating behaviours.** Many of these signalling pathways have been shown to be altered in obesity.
- **Because body weight is homeostatically regulated, when weight loss occurs, physiological adaptations act to drive weight regain.** This includes reduction in energy expenditure, and hormonal changes that increase appetite and reduce satiety.
- **Adipose tissue influences the central regulation of energy homeostasis, and excess adiposity can become dysfunctional, with production of pro-inflammatory cytokines and associated metabolic health complications.**
- **Due to individual differences in body composition, body fat distribution and function, the threshold at which excess adiposity impairs health is highly variable among individuals.**
- **Emerging areas of research in the science of obesity include brown fat, the gut microbiome and immune system dysregulation.**

Introduction

Obesity is a complex chronic disease, characterised by dysfunctional or excess body fat (adiposity), that impairs health. However, due to individual differences in body composition, body fat distribution and function, the threshold to which excess adiposity impairs health is highly variable among adults[1].

Epidemiological and population studies define obesity using the body mass index (BMI, weight in kilograms divided by the height in metres, squared). Obesity is arbitrarily defined as a BMI exceeding 30 kg/m^2. [2] BMI is a fairly reliable anthropometric measurement to stratify obesity-related health risks at the population level. However, weight and BMI should not be the only measures used to assess obesity in individuals. Several factors, such as cardiorespiratory fitness and presence of obesity-related complications substantially modify the risk associated with excess body fat.

Obesity is a chronic disease caused by the complex interplay of genetic, metabolic, behavioural, and environmental factors; the latter are thought to be the proximal cause of the dramatic rise in the prevalence of obesity[3]. The increased availability of processed, affordable and effectively marketed food, abundance of sugar-sweetened beverages, economic growth, behavioural changes and rapid urbanisation in low- and middle-income countries are some of the key drivers that promote overconsumption of food[4]. With respect to energy expenditure, there has been significant changes across all domains of physical activity, domestic, occupational, transport and leisure over the last 50 years[5]. This chapter discusses the cellular and molecular pathogenesis of obesity, to inform a rational approach to management of this complex disease. Ultimately, what these intricate mechanistic insights have shown is that obesity is a complex, highly heritable neurobehavioural disorder, that is strongly influenced by environmental factors[6]. At a specific time within any given population, variations in body mass index within that population are strongly genetically determined. However, changes over time in the population distribution of body mass index have arisen from environmental factors, such as excessive availability of unhealthy food[7].

The neurobiology of appetite control and energy balance dysregulation

In states of energy imbalance, where food intake exceeds energy expenditure, the energy surplus is converted into fat and stored in adipose tissue. Body weight is meticulously regulated for survival in unpredictable periods of feast and famine. For individuals who have a genetic predisposition, even a small surplus of caloric intake (less than 1%) over energy expenditure can accumulate over years to cause weight gain[3].

The brain and obesity

The brain likely plays the most important role in obesity and energy balance. A simple approach to understanding the neurobiology of obesity may be to divide the brain into three main areas that regulate weight: the hypothalamus, the mesolimbic area and the cognitive lobe. Understanding the regulation of each area and the importance of the connections between these areas creates a greater understanding of obesity.

The hypothalamus (homeostatic area)

The hypothalamus, located in the brain, has long been known to play a central role in energy homeostasis by regulating energy intake and expenditure. Recent advances have provided important insights into the complex "central" control of appetite and the neurobehavioral influences on body weight regulation[8-10].

The arcuate nucleus of the hypothalamus, often termed the hunger centre, influences feeding behaviours. There are two sets of neuronal populations that reside in the arcuate nucleus. Neurons co-expressing agouti-related protein (AgRP) and neuropeptide Y (NPY) in the arcuate nucleus, when activated by hormonal and neural signals from the gut, adipose tissue and the peripheral organs, stimulate hunger sensation and trigger food-seeking behaviours[11].

The activity of these neurons is rapidly reduced after feeding. These neurons are primarily involved in "food-seeking" or the homeostatic control of appetite. Their downstream effects are mediated via the melanocortin-4 receptors located in the nearby paraventricular nucleus. The AgRP/NPY neurons project directly to the second set of neurons co-expressing pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), which suppress food intake by firing through the downstream inhibitory Y1 and gamma-aminobutyric acid (GABA) receptors[11]. The homeostatic control of appetite in the arcuate nucleus is influenced by several factors, such as the nutritional status of the organism, nutrient sensing and availability, taste, smell, and food preferences.

The mesolimbic system (hedonic area)

In addition to the homeostatic appetite control centre in the hypothalamus, other neural systems provide the emotional, pleasurable, and rewarding aspects of eating, also known as hedonic eating. Hedonic eating is based on the feelings of reward and pleasure that are associated with anticipating, seeing, smelling or eating food[12]. Through this pathway, food can be craved or enjoyed, even after complete satiation. The signals are transmitted by the dopaminergic, opioid and endocannabinoid pathways via the respective receptors in the downstream targets[13]. Dopamine is released in the brain, signalling a desire to eat, in response to emotional triggers, such as sadness, or environmental triggers, such as the smell or sight of palatable food[14]. Opioid and endocannabinoid signals are released when food is consumed, and are responsible for the feeling of pleasure associated with eating[15]. Some people living with obesity may have a heightened anticipation (wanting) of the pleasure of food driven by a dysregulation of dopamine[16]. Unfortunately, the pleasure of eating the food (liking) is also dysfunctional and is downgraded compared to the anticipation, resulting in a tendency to overeat[17]. This leads to a

vicious cycle and can lead to continuous overeating. Controlling this dysregulation between wanting and liking, with medications, hormonal regulation and cognitive behavioural therapy, is a target for the treatment of obesity.

Other structures in the brain are also important in influencing feeding behaviour and energy intake. The lateral hypothalamus is a brain region that is tied to consummatory behaviours and mediates positive reinforcement[18]. These circuits drive food consumption and hedonic eating. Hedonic eating is also controlled by the corticolimbic system, which consists of cortical areas, basal ganglia, hippocampus and amygdala in the midbrain[10].

The frontal lobe (executive functioning)

The frontal lobe is responsible for executive functioning and overriding primal behaviours driven by the mesolimbic system[19]. Cognitive functioning works best under optimal conditions of rest, adequate oxygenation, decreased stress and can be adversely affected by medications, such as steroids or by the use of alcohol or illicit drugs.

Other areas of executive dysfunction have also been found to be associated with variations in body weight, primarily in decision making, response inhibition and cognitive flexibility[20]. People living with obesity may have disruption of the connection between the frontal lobe and the rest of the brain, which leads to diminished control of eating behaviours[19].

Recent data highlight that the hypothalamic circadian clock network is actively involved in the alignment of fasting and feeding with the sleep-awake cycle through the agouti-related protein (AgRP) neurons by coordinating the leptin response and glucose metabolism with arousal[21]. Cognitive areas in the prefrontal cortex exert executive control on decisions around eating and on food choices.

In summary, the biological control of appetite is extremely complex and involves integration of central neural circuits with endocrine signals from the gut, adipose tissue, and other organs, which ultimately influence homeostatic and hedonic drivers of feeding behaviours, with additional "executive" input from higher brain centres on the decision of when and what to eat. These neural networks have also been shown to be altered in obesity.

Adipose tissue and food intake

Leptin and insulin are the two key hormones that communicate the long-term energy reserve and nutritional status in the body. Leptin is a fat-derived hormone that is secreted by white adipose tissue in proportion to the body's fat mass. Leptin and insulin bind to their respective receptors in the arcuate nucleus to decrease food intake and increase energy expenditure. In states of decreasing body fat stores, circulating leptin levels fall and signal the hypothalamus to inactivate the pro-opiomelancortin (POMC)/CART-expressing neurons to promote feeding, while simultaneously lowering its inhibitory effect on the AgRP/Neuropeptide Y (NPY)-expressing neurons to increase appetite and decrease energy expenditure. As adiposity increases, leptin levels increase in the circulation and exert negative feedback to suppress appetite to prevent further weight gain. While most people with obesity have high leptin levels, it was the discovery of the rare syndrome of leptin deficiency (giving rise to profoundly abnormal eating behaviour and severe obesity) which highlighted for the first time the biological basis for obesity[22].

Gut-derived hormones controlling feeding behaviour

There is significant "crosstalk" between homeostatic and hedonic influences on feeding behaviour, mediated by several complex endocrine and gut-derived factors. For example, leptin, insulin, ghrelin, and glucagon-like peptide-1 (GLP-1) all act on the dopaminergic neurons in the midbrain to modulate food reward and influence hedonic eating[23].

GLP-1 and peptide YY3-36 (PYY), which delay gastric emptying, are potent anorexigenic gut hormones that are secreted by enteroendocrine L-cells in the small bowel in response to food ingestion. They both promote satiation (meal termination) and satiety (fullness) by activating the POMC/PYY neurons, while reducing hunger via the AgRP/NPY neurons[24]. Oxyntomodulin is another peptide secreted concurrently with GLP-1 and PYY which enhances satiety, thus decreasing food consumption[25].

Several other gut hormones are also involved in the control of appetite and energy expenditure. Cholecystokinin (CCK) is secreted in response to fat and protein ingestion and, among other things, slows gastric emptying. CCK also mediates fat and protein satiation as well as glucose-regulatory effects on the hypothalamus, and via the vagal nerve afferent fibres. Pancreatic polypeptide (PP) is secreted by F-cells in the pancreas under vagal control and is released during the postprandial phase to enhance satiety[25]. In contrast, ghrelin is an orexigenic hormone produced in the gastric fundus which increases hunger and stimulates food intake. Ghrelin levels rise in the fasted state and fall rapidly after eating. Sensory information on the volume and composition of the meal is relayed to the nucleus tractus solitarius (NTS) in the brainstem by vagal afferent fibres. The NTS then integrates and transmits nerve signals to the homeostatic control pathways in the hypothalamus, primarily influencing meal termination and satiety[9].

Genetics and obesity

Obesity is highly heritable[26,27]. However, single gene mutations (where there is complete loss of function, such as with leptin gene mutations leading to leptin deficiency) are a relatively rare cause of obesity and tend to be associated with other clinical features, giving rise to specific syndromes[28,29]. Rather, the strong genetic influence on obesity is likely to arise from much smaller variations in function in large numbers of genes, only some of which have been

described to date[30]. The genetic and epigenetic variability within populations influences dietary behaviours and explains why not all people exposed to a "health disrupting environment"[31] will develop obesity[32]. Interestingly, almost all of the common gene variants associated with obesity are expressed in the central nervous system and are mainly involved in the functional and structural aspects of neurotransmission. This is consistent with the mechanistic observations described earlier. Studies with twins have shown a relatively high degree of concordance of body mass and eating behaviours (50%–80%)[33].

Linkage studies in rodents with obesity caused by single-gene mutations and candidate-gene-based approaches in humans with severe obesity have identified a number of mutations in genes involved in appetite control[34]. Loss of function mutations in leptin, leptin receptor, POMC and melanocortin receptor-4 are examples where individuals display intense hyperphagic and food-seeking behaviours arising from mutations in single genes. Correction of these rare defects, such as treatment of leptin-deficient patients with recombinant leptin, can result in significant weight loss and improvements in metabolic health[22]. Eleven monogenic forms of obesity have been discovered. They are rare, and the most common cause, heterozygous mutation in MC4R, accounts for about 2%–5% of severe obesity in the pediatric population[27]. Syndromic forms of obesity are also uncommon; they include Prader-Willi, Bardet-Biedl and Cohen syndromes[35].

Adipose tissue and excess adiposity

Adipose tissue has traditionally been viewed as a passive energy repository of stored fat in the form of triglycerides, which can be released during periods of energy demand, such as starvation or exercise. Adipose tissue is a dynamic organ that can respond to alterations in energy stores through adipocyte hypertrophy and hyperplasia (see Figure 1)[36]. In adults, subcutaneous fat accounts for about 85% of total body fat, and intra-abdominal or visceral fat accounts for the remainder. Adipose tissue expansion is accomplished via adipocyte hypertrophy, where cell size can increase up to seven-fold.

A second process, adipocyte hyperplasia, relies on adipogenesis, which involves recruitment, proliferation and differentiation of preadipocytes to acquire the phenotype of mature adipocytes. Regulation of adipogenesis is meticulously controlled by a process called transcription. The key players in this process are CCAAT (cytosine-cytosine-adenosine-adenosine-thymidine) enhancer-binding proteins and peroxisome proliferator-activated receptor gamma (PPARγ)[37]. These transcription factors are subject to modulation by circulating hormones and nutrients, and they largely determine body fat distribution. Visceral fat is different to subcutaneous adipose tissue as it has lower insulin sensitivity, increased lipolytic activity, lower angiogenic potential, increased expression of pro-inflammatory adipokines and decreased production of "good" hormones and cytokines.

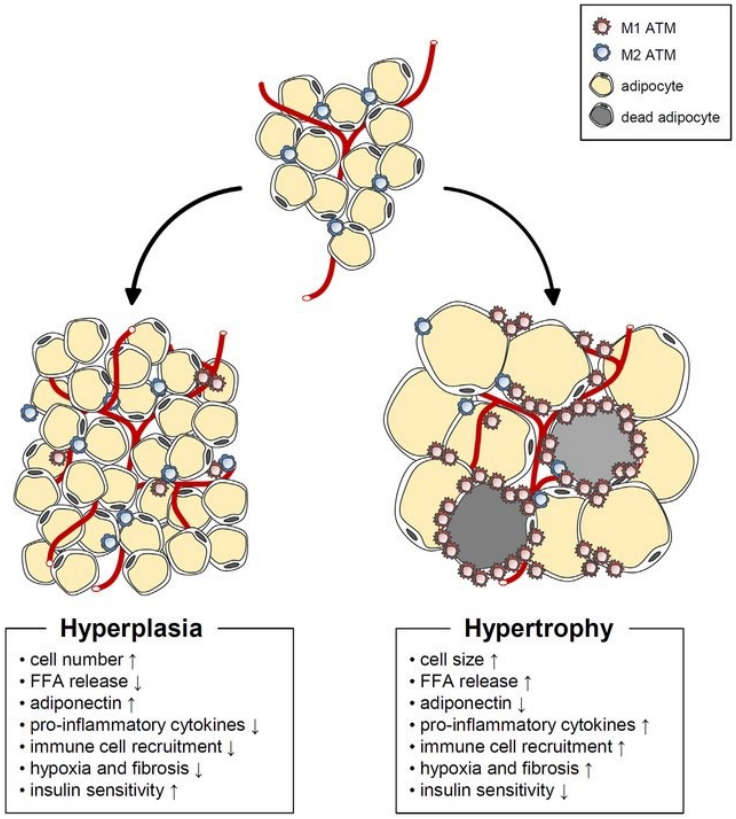

Figure 1: **Characteristics of hypertrophic and hyperplasic adipocytes reproduced from Choe *et al.*** (2016)[38]
(M1 ATM: M1 Adipose Tissue Macrophage, M2 ATM: M2 Adipose Tissue Macrophage, FFA: Free Fatty Acids)

Adipose-tissue-derived hormones and cytokines

Among the adipose-tissue-derived proteins, leptin and adiponectin have been extensively studied and provide new insights into adipose tissue biology and regulation. Leptin is secreted by adipocytes, and its plasma levels increase with weight gain and decrease with weight loss, in keeping with its key role as a signal of adipose tissue stores. Leptin binds to specific receptors, which belong to the interleukin-6 receptor family of class I cytokine receptors. It exerts an inhibitory effect on food intake and appetite. Its effect is not limited to appetite regulation and energy homeostasis; it also exerts a wide range of metabolic influences in the body, such as suppressing insulin secretion from the pancreas and modulating insulin resistance[39].

Adiponectin is a hormone abundantly produced by adipocytes. It also exerts wide-ranging physiological effects on energy homeostasis, vascular function, systemic inflammation, and cell growth. One of its most relevant and important functions is to increase insulin sensitivity. Adiponectin levels are inversely correlated with insulin insensitivity. Circulating adiponectin levels are lower in people with polycystic ovarian syndrome, impaired glucose tolerance or type 2 diabetes mellitus (T2DM). Decreased adiponectin levels predict incident T2DM in otherwise healthy people[40].

Adipose tissue dysfunction

Adipose tissue dysfunction may develop under conditions of continuous positive energy balance in people with an impaired expandability of subcutaneous adipose tissue. The inability to store excess calories in healthy subcutaneous fat depots can lead to increased visceral fat accretion and ectopic fat deposition in the liver, muscle, and epicardium of the heart. Adipose tissue expansion often leads to dysfunctional changes, which are characterised by inflammation, inappropriate extracellular matrix remodelling and insufficient angiogenic potential. Cellular hypoxia is thought to be the driver for adipose tissue dysfunction[41]. A consequence of dysfunctional adipose tissue, especially in the visceral depots, is augmented production of fat-derived pro-inflammatory cytokines. These include tumour necrosis factor-α, interleukins, C-reactive protein, and monocyte chemotactic protein-1. They can accelerate the progression to adipose tissue fibrosis, accelerated angiogenesis, apoptosis, and autophagy by promoting the migration of immune cells into adipose tissue. Importantly, dysfunctional adipose tissue can lead to the development and progression of a myriad of adiposity-related complications (even in the absence of an excessive volume of fat tissue, such as with lipodystrophy), such as T2DM, hypertension, dyslipidemia, non-alcoholic fatty liver disease, cardiometabolic risks and atherosclerotic cardiovascular disease (CVD)[42].

Emerging areas

Brown and beige fat

Emerging data indicate that, in addition to white adipose tissue, brown adipose tissue, which is involved in whole-body energy homeostasis through non-shivering thermogenesis, also exists in small quantities in adult mammals and humans. Beige adipocytes, which are inducible forms of thermogenic adipocytes, have also been reported in white adipose tissue. Recruitment of beige adipocytes, or "beiging" of white fat, can be induced by chronic exposure to cold temperatures and, to some extent, exercise[43]. Uncoupling protein 1, which is exclusively expressed in brown and beige adipocytes and known for its capacity to elevate thermogenesis, has also been shown recently to regulate liver immune cell infiltration, and to antagonise liver inflammation and systemic glucose intolerance[44]. Further elucidation of the potential roles of brown/beige fat in the regulation of whole-body energy metabolism and glucose/lipid homeostasis may open new avenues for obesity management in the future.

Gut microbiome and obesity

The gut microbiota is the collection of all the micro-organisms in the gastrointestinal tract[45]. Recent data suggest that gut microbiota may influence weight gain, CVD, and insulin resistance through different pathways, including energy harvesting from bacterial fermentation, short-chain fatty acid signalling and bile acid metabolism[46,47]. Recent Irish research in this area has shown that in older adults, groups of microbes are significantly correlated with metabolic health markers[48]. Also, in mice fed a high fat diet microbiome transfer of short-chain fatty acid-producing microbiota was associated with greater body weight gain, hepatic lipid accumulation, adipocyte hypertrophy and hyperinsulinemia[49].

Most of the research in gut microbiota has been conducted in animal studies. These studies have determined that certain microbiota profiles are associated with energy retention, and others with energy expenditure[50]. Observational human studies have indicated that the primary bacteria associated with body weight homeostasis are the Firmicutes, associated with higher weight, and the Bacteroidetes, that are more often present in lean individuals[51]. Understanding the environments that would favour greater levels of Firmicutes compared to Bacteroidetes may lead to greater understanding of the evolution of obesity, and possible treatments. While preliminary findings suggest that altering the microbiome may have favourable health and metabolic effects in humans[52], adequate evidence for the use of this approach in clinical practice is lacking, with intervention studies not showing the benefits that were anticipated from observational studies. Surgery and medications may have an impact on the gut microbiome, explaining some of the reasons for outcomes seen with these interventions[53-55]. This field is developing and may result in new interventions specifically targeted towards gut microbiota, but as yet there are limited practical applications.

Obesity and the immune system

Obesity is associated with a low-grade systemic inflammatory process which stems from alterations in the circulating and adipose tissue resident immune system. Adipose tissue is now known to be rich in populations of innate and adaptive immune cells. Research

is gradually identifying the important cell types and the alterations that are involved in driving the complications of obesity, such as insulin resistance. These include macrophages, T cells, B cells, natural killer (NK) cells, mucosal associated invariant T (MAIT) cells and their contribution to the production of soluble factors, such as interleukin (IL)-1β, IL-6, IL-8, IL-10, IL-17, transforming growth factor-β, tumour necrosis factor (TNF)-α and monocyte chemotactic protein. Several of these factors are now known to disrupt homeostatic processes, such as insulin signalling.

Arguably the macrophage is the predominant immune cell subset in obesity-related inflammation, where there is an accumulation of the pro-inflammatory M1 adipose tissue macrophage (ATM) in adipose tissue, paired with a repolarisation/loss of the anti-inflammatory M2 macrophage population[56-58]. Activation of the M1 ATM in obesity contributes to the release of cytokines, such as TNF-α and IL-1β, which disrupt insulin-signalling pathways, leading to systemic insulin resistance[59,60]. An intervention in a cohort of Irish adults with obesity and T2DM showed that GLP-1 analogue therapy impacted macrophage polarisation in vitro reducing the production of IL-1β[61].

Another area of ongoing research in Ireland is the study of the effect of dietary fatty acids on metabolic inflammation in obesity. Saturated fatty acids are potent pro-inflammatory fatty acids that promote insulin resistance and are associated with hypertrophic adipose morphology, while monounsaturated fatty acids are associated with a hyperplastic adipose morphology coincident with improved insulin sensitivity[62].

The frequency of CD8+ T cells are also increased in the adipose tissue of mice and humans with obesity[63-65], where they produce pro-inflammatory mediators including interferon (IFN)-γ, IL-6 and TNF-α[63,66,67]. Recent Irish research has shown that CD8+ T cell infiltration is suppressed in obesity, and while higher BMI negatively correlates with CD8+ T cell infiltration in human endometrial cancer, the suppressive effects on CD8+ T cell anti-tumour immunity, can partially be reversed by weight loss and/or immunotherapy[68].

NK cells (a subset of innate lymphocytes) play an important role in early host protection against viruses and cancerous cells[69,70], and also shape subsequent immune responses through their rapid production of cytokines (IFN-γ, TNF-α, IL-6 and granulocyte macrophage colony-stimulating factor). Data from Irish research details alteration of NK cells in people living with obesity[71], including reduced NK cell frequencies and defective NK cell cytotoxic capabilities[72-78] due to defective cellular metabolism[75]. NK cells isolated from people living with obesity have dysregulated metabolism and failure to engage glycolytic metabolism due to increased uptake of free fatty acids. Murine models of malignancy show diminished anti-tumour immunity with free fatty acid treated NK cells, highlighting a direct link between obesity-induced NK cell defects and cancer.

Invariant natural killer T (iNKT) cells (a rare population of innate cells T cells)[79,80] are potent producers of cytokines, such as IL-2, IL-4 and IFN-γ[81,82]. They are resident in adipose tissue but depleted in obesity[83-86]. Unlike their circulating counterparts, adipose tissue iNKT cells readily produce IL-10[87]. It is thought that the loss of IL-10 and IL-4 with iNKT cell depletion in obesity, results in an increase in M1 ATM frequency and insulin resistance in murine models of diet-induced obesity[84,85]. Upon adoptive transfer of iNKT cells into deficient mice, this increase in M1 ATM is rapidly reversed and improvements in body weight, glycaemia and adipocyte size are observed[84,86]. Irish research reported that iNKT cells in adipose tissue are a unique regulatory population, lacking the PLZF transcription factor found in iNKT cells from other sites. PLZF negative iNKT cells were shown to maintain and control T-reg function in adipose tissue via their production of IL-2[88]. Frequencies of circulating iNKT cells are also reduced in adults with obesity[84,89]. Interestingly, circulating iNKT cell frequencies recover after Roux en Y gastric bypass surgery and GLP-1 therapy even though the mean BMI of the patient cohort remained > 30 kg/m^2, suggesting that metabolic health, as opposed to body weight, may impact iNKT cell frequency[84,90].

MAIT cells (a population of innate T cells) are also dysregulated in obesity, with a significant increase in the level of IL-17 producing MAIT cells found in both circulation and adipose tissue particularly in populations with obesity and T2DM[89,91].

Adiposity-related medical complications

Adipose tissue dysfunction and excessive adiposity predispose the development of many medical complications. The most common metabolic complication is insulin resistance and, in susceptible individuals, T2DM. The predominant theory between the link of obesity and cardiometabolic risk considers that obesity induces an insulin-resistant state through two primary mechanisms: a defective insulin signal, and chronic tissue inflammation and increased adipose tissue macrophages[92]. Adipose tissue is a source of increased levels of circulating free fatty acids due to increased lipolysis. In the liver, increased free fatty acid flux results in increased glucose production, triglyceride synthesis and secretion of very low-density lipoprotein. Other lipid abnormalities include reductions in high-density lipoprotein and increased levels of "small dense" atherogenic low-density lipoprotein particles. High levels of circulating free fatty acids are also taken up by muscle and the pancreas, leading to "ectopic fat" and altered insulin signalling in these tissues. Triglyceride accumulation impairs pancreatic insulin secretion, muscle, and liver insulin signalling, ultimately causing insulin resistance in these organs. Visceral fat accumulation has a more detrimental effect on adipose inflammatory processes than subcutaneous fat[93,94]. Adiposity is also linked to increased risk for many forms of cancer, through the release of hormonal growth factors and inflammatory adipokines[95].

Benefits of weight loss

Obesity management, as well as cardiorespiratory fitness, are critically important in improving the overall cardiovascular health of people who have overweight and obesity. Indeed, obesity management benefits most patients with obesity, independent

of the amount of weight loss. Patients with a weight loss of 5%–10% of their initial weight will experience a reduction in CVD risk factors, improvement in lipid profiles, reductions in blood glucose and glycosylated haemoglobin and a decreased risk for developing T2DM and other obesity- related complications[96].

The benefits of weight loss are worth emphasising with respect to the prevention and management of T2DM. In the landmark National Institutes of Health-sponsored multi-centre Diabetes Prevention Program, 3,234 participants living with overweight and obesity who also had impaired glucose tolerance and were sedentary, were randomised to usual treatment (control) or to an intensive behavioural intervention. The aim was to achieve and maintain a reduction of 7% of their initial body weight through a -500 kilocalorie/day deficit hypocaloric diet and 150 minutes or more per week of moderate-intensity physical activity. A third group received metformin, 850 mg twice daily. After a 2.8-year follow-up, the behavioural lifestyle intervention group lost 5.6 kg (6%) whereas the metformin group lost 2.1 kg (2.2%) and the control group lost 0.1 kg. Compared with the control group, the incidence of diabetes was reduced by 58% with behavioural intervention and by 31% with metformin[97]. The benefits of modest weight loss from the 2.8-years of intensive behavioural intervention persisted in the 10-year Diabetes Prevention Program Observation Study. The researchers concluded that each kilogram (1.1%) of body weight loss through intensive behavioural support was associated with a 16% relative risk reduction in the development of T2DM in individuals with impaired glucose tolerance and delayed the onset of disease[98]. The Da Qing Diabetes Prevention study examined a lifestyle intervention in individuals with impaired glucose tolerance and found delayed onset of T2DM, a reduced incidence of cardiovascular events, cardiovascular and all-cause mortality, and increased life expectancy, with a modest 1.2 +/- 3.3 kg/m^2 BMI point change across the 30-year follow-up period[99]. Metformin treatment was half as effective as intensive behavioural intervention and weight loss. A meta-analysis was undertaken of 17 randomised clinical trials on the effectiveness of behavioural intervention to prevent or delay diabetes. In over 8,000 trial participants with impaired glucose tolerance, the pooled hazard ratio was 0.51 for behavioural intervention against standard counselling; this corresponded to numbers needed to treat for benefit of 6.4[100].

Rational approach to obesity management

Behavioural interventions aimed at treating obesity and improving health through medical nutrition therapy and physical activity are one of the pillars of the therapeutic approach for most people with obesity. Medical nutrition therapy consists of reduced-energy intake along with dietary patterns that have been shown to be effective in obesity management and for improving CVD risk factors.

The energy expenditure system is a complex physiological system and its influence on body weight regulation varies depending on an individual's phenotype[101,102]. Routine physical activity has a beneficial and regulatory effect on this system[102]. The disease of obesity has progressive and detrimental effect on physical function, musculoskeletal health, exercise capacity, pain, and mobility. This erosion of physical capacity negatively affects participation in all domains of physical activity[8]. For those who manage to maintain physical activity levels that approach international guidelines, there appears to be an ameliorative effect on the decline in physical function, musculoskeletal health and pain[103]. There are also positive influences on wider health outcomes, including psychological, cardiometabolic, some cancers and overall mortality risk[104-107].

Behavioural changes are an important component for integrating eating and activity patterns over the long term, but which dietary, physical activity, medical, surgical, pharmacological or psychological approaches are indicated will depend on the specific needs of the affected individual. They may include self-monitoring or recording a food and activity diary, wearable technologies such as step counters and smart watches, peer support or individual or group counselling. Short-term behavioural changes lead to average weight loss of 3%–5%, which is often difficult to sustain. Weight regain is common, because our bodies are designed to resist weight loss. Reduction in energy expenditure and adaptive hormonal responses after weight loss may favour weight regain. A systematic review found that the mean rate of resting energy expenditure decreased by approximately 15 kcal/kg of weight lost, as observed in 2997 individuals. This decrease may be associated with body weight regain[108]. Moreover, after long-term diet-induced weight loss, levels of circulating hormones, such as leptin, insulin, GLP-1, CCK, PYY and ghrelin do not revert to levels recorded before weight loss and instead act to encourage weight regain[109]. The anorexigenic hormones (leptin, insulin, GLP-1) are reduced, whereas levels of the orexigenic hormone ghrelin are increased. Regular physical activity has been shown to be an integral component of long-term sustained weight loss[110,111].

When behavioural interventions are not sufficient to meet obesity-management health goals, psychological therapy, pharmacological therapy, and bariatric surgery are treatment options that can facilitate and maintain the necessary weight loss and help prevent weight regain. Obesity pharmacotherapy, when used as adjunctive therapy to medical nutrition therapy and physical activity, can produce an additional average weight loss of 5%–25%, depending on the drugs and the dosing. Bariatric surgery has rapidly emerged as a viable, realistic, and successful long-term treatment option for many patients living with severe and complicated obesity[112].

Conclusion

Obesity is a complex chronic disease, characterised by dysfunctional or excess body fat (adiposity) that impairs health. The causes of obesity are complex and result from interactions among genetic, biological, behavioural, psychosocial, and environmental factors. Healthcare systems should focus on health impairment rather than having a narrow focus on weight loss. A better understanding of the cellular and molecular pathways leading to the genesis of excess adiposity that impairs health will guide the practitioner to develop a rational approach to management of this complex disease.

The Science of Obesity chapter is adapted from the Canadian Adult Obesity Clinical Practice Guidelines (the "Guidelines"), which Obesity Canada owns and from whom we have a license. ASOI adapted the Guidelines having regard for any relevant context affecting the Island of Ireland using the ADAPTE Tool.

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References

1. Bluher M. Adipose tissue dysfunction contributes to obesity related metabolic diseases. Best Pract Res Clin Endocrinol Metab 2013; 27(2): 163-77.
2. World Health Organisation. Obesity: preventing and managing the global epidemic. Report of a WHO consultation. Geneva, 2000.
3. Hill JO. Understanding and addressing the epidemic of obesity: an energy balance perspective. Endocr Rev 2006; 27(7): 750-61.
4. Swinburn BA, Sacks G, Hall KD, et al. The global obesity pandemic: shaped by global drivers and local environments. Lancet 2011; 378(9793): 804-14.
5. Church TS, Thomas DM, Tudor-Locke C, et al. Trends over 5 decades in U.S. occupation-related physical activity and their associations with obesity. PLoS One 2011; 6(5): e19657.
6. O'Rahilly S, Farooqi IS. Human obesity: a heritable neurobehavioral disorder that is highly sensitive to environmental conditions. Diabetes 2008; 57(11): 2905-10.
7. Rogers NT, Power C, Pinto Pereira SM. Birthweight, lifetime obesity and physical functioning in mid-adulthood: a nationwide birth cohort study. International Journal of Epidemiology 2019; 49(2): 657-65.
8. Andermann ML, Lowell BB. Toward a Wiring Diagram Understanding of Appetite Control. Neuron 2017; 95(4): 757-78.
9. Berthoud HR, Munzberg H, Morrison CD. Blaming the Brain for Obesity: Integration of Hedonic and Homeostatic Mechanisms. Gastroenterology 2017; 152(7): 1728-38.
10. Sternson SM, Eiselt AK. Three Pillars for the Neural Control of Appetite. Annu Rev Physiol 2017; 79: 401-23.
11. Dhillo WS, Small CJ, Stanley SA, et al. Hypothalamic interactions between neuropeptide Y, agouti-related protein, cocaine- and amphetamine-regulated transcript and alpha-melanocyte-stimulating hormone in vitro in male rats. J Neuroendocrinol 2002; 14(9): 725-30.
12. Papies E, Stroebe W, Aarts H. Pleasure in the mind: Restrained eating and spontaneous hedonic thoughts about food. Journal of Experimental Social Psychology 2007; 43(5): 810-7.
13. Barbano MF, Cador M. Opioids for hedonic experience and dopamine to get ready for it. Psychopharmacology (Berl) 2007; 191(3): 497-506.
14. Meye FJ, Adan RA. Feelings about food: the ventral tegmental area in food reward and emotional eating. Trends Pharmacol Sci 2014; 35(1): 31-40.
15. Gosnell BA, Levine AS. Reward systems and food intake: role of opioids. Int J Obes (Lond) 2009; 33 Suppl 2: S54-8.
16. Bello NT, Hajnal A. Dopamine and binge eating behaviors. Pharmacol Biochem Behav 2010; 97(1): 25-33.
17. Volkow ND, Wang GJ, Baler RD. Reward, dopamine and the control of food intake: implications for obesity. Trends Cogn Sci 2011; 15(1): 37-46.
18. Hurley SW, Johnson AK. The role of the lateral hypothalamus and orexin in ingestive behavior: a model for the translation of past experience and sensed deficits into motivated behaviors. Front Syst Neurosci 2014; 8: 216.
19. Cserjesi R, Luminet O, Poncelet AS, Lenard L. Altered executive function in obesity. Exploration of the role of affective states on cognitive abilities. Appetite 2009; 52(2): 535-9.
20. Fagundo AB, de la Torre R, Jimenez-Murcia S, et al. Executive functions profile in extreme eating/weight conditions: from anorexia nervosa to obesity. PLoS One 2012; 7(8): e43382.
21. Cedernaes J, Huang W, Ramsey KM, et al. Transcriptional Basis for Rhythmic Control of Hunger and Metabolism within the AgRP Neuron. Cell Metab 2019; 29(5): 1078-91 e5.
22. Farooqi IS, Matarese G, Lord GM, et al. Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. J Clin Invest 2002; 110(8): 1093-103.
23. Mebel DM, Wong JC, Dong YJ, Borgland SL. Insulin in the ventral tegmental area reduces hedonic feeding and suppresses dopamine concentration via increased reuptake. Eur J Neurosci 2012; 36(3): 2336-46.
24. Secher A, Jelsing J, Baquero AF, et al. The arcuate nucleus mediates GLP-1 receptor agonist liraglutide-dependent weight loss. J Clin Invest 2014; 124(10): 4473-88.
25. Bliss ES, Whiteside E. The Gut-Brain Axis, the Human Gut Microbiota and Their Integration in the Development of Obesity. Front Physiol 2018; 9: 900.
26. Wallis N, Raffan E. The Genetic Basis of Obesity and Related Metabolic Diseases in Humans and Companion Animals. Genes 2020; 11(11): 1378.
27. van der Klaauw AA, Farooqi IS. The hunger genes: pathways to obesity. Cell 2015; 161(1): 119-32.
28. Huvenne H, Dubern B, Clément K, Poitou C. Rare Genetic Forms of Obesity: Clinical Approach and Current Treatments in 2016. Obes Facts 2016; 9(3): 158-73.
29. Farooqi IS, O'Rahilly S. Monogenic obesity in humans. Annu Rev Med 2005; 56: 443-58.
30. Rohde K, Keller M, la Cour Poulsen L, Blüher M, Kovacs P, Böttcher Y. Genetics and epigenetics in obesity. Metabolism 2019; 92: 37-50.
31. Kirk SF, A. Alberga, S. Russell Mayhew. Are we over weight yet? New guidelines aim to reduce obesity stigma in health care. 2020. https://theconversation.com/are-we-over-weight-yet-new-guidelines-aim-to-reduce-obesity-stigma-in-health-care-130060 01/06/2022).
32. Fall T, Mendelson M, Speliotes EK. Recent Advances in Human Genetics and Epigenetics of Adiposity: Pathway to Precision Medicine? Gastroenterology 2017; 152(7): 1695-706.
33. Thornton LM, Mazzeo SE, Bulik CM. The heritability of eating disorders: methods and current findings. Curr Top Behav Neurosci 2010; 6: 141-56.
34. Thaker VV. Genetic and Epigenetic Causes of Obesity. Adolesc Med State Art Rev 2017; 28(2): 379-405.

35. Karam JG. Secondary causes of obesity. Clin Pract 2007; 4(5): 641.

36. Clarys JP, Martin AD, Marfell-Jones MJ, Janssens V, Caboor D, Drinkwater DT. Human body composition: A review of adult dissection data. Am J Hum Biol 1999; 11(2): 167-74.

37. Ma X, Lee P, Chisholm DJ, James DE. Control of adipocyte differentiation in different fat depots; implications for pathophysiology or therapy. Front Endocrinol (Lausanne) 2015; 6: 1.

38. Choe SS, Huh JY, Hwang IJ, Kim JI, Kim JB. Adipose Tissue Remodeling: Its Role in Energy Metabolism and Metabolic Disorders. Front Endocrinol (Lausanne) 2016; 7: 30.

39. Seufert J. Leptin effects on pancreatic β-cell gene expression and function. Diabetes 2004; 53: S152-S8.

40. Fasshauer M, Bluher M. Adipokines in health and disease. Trends Pharmacol Sci 2015; 36(7): 461-70.

41. Crewe C, An YA, Scherer PE. The ominous triad of adipose tissue dysfunction: inflammation, fibrosis, and impaired angiogenesis. J Clin Invest 2017; 127(1): 74-82.

42. Guh DP, Zhang W, Bansback N, Amarsi Z, Birmingham CL, Anis AH. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health 2009; 9: 88.

43. Ikeda K, Maretich P, Kajimura S. The Common and Distinct Features of Brown and Beige Adipocytes. Trends Endocrinol Metab 2018; 29(3): 191-200.

44. Mills EL, Harmon C, Jedrychowski MP, et al. UCP1 governs liver extracellular succinate and inflammatory pathogenesis. Nat Metab 2021; 3(5): 604-17.

45. Cresci GA, Bawden E. Gut Microbiome: What We Do and Don't Know. Nutr Clin Pract 2015; 30(6): 734-46.

46. Bouter KE, van Raalte DH, Groen AK, Nieuwdorp M. Role of the Gut Microbiome in the Pathogenesis of Obesity and Obesity-Related Metabolic Dysfunction. Gastroenterology 2017; 152(7): 1671-8.

47. Murphy K, O'Donovan AN, Caplice NM, Ross RP, Stanton C. Exploring the Gut Microbiota and Cardiovascular Disease. Metabolites 2021; 11(8).

48. Zhong X, Harrington JM, Millar SR, Perry IJ, O'Toole PW, Phillips CM. Gut Microbiota Associations with Metabolic Health and Obesity Status in Older Adults. Nutrients 2020; 12(8).

49. Ralston JC, Mitchelson KAJ, Lynch GM, et al. Microbiome Transfer Partly Overrides Lack of IL-1RI Signaling to Alter Hepatic but not Adipose Tissue Phenotype and Lipid Handling following a High-Fat Diet Challenge. Mol Nutr Food Res 2021; 65(1): e2000202.

50. Backhed F, Ding H, Wang T, et al. The gut microbiota as an environmental factor that regulates fat storage. Proc Natl Acad Sci U S A 2004; 101(44): 15718-23.

51. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. Nature 2006; 444(7122): 1027-31.

52. Zhang Z, Mocanu V, Cai C, et al. Impact of Fecal Microbiota Transplantation on Obesity and Metabolic Syndrome-A Systematic Review. Nutrients 2019; 11(10).

53. Guo Y, Huang ZP, Liu CQ, Qi L, Sheng Y, Zou DJ. Modulation of the gut microbiome: a systematic review of the effect of bariatric surgery. Eur J Endocrinol 2018; 178(1): 43-56.

54. Angelakis E, Armougom F, Million M, Raoult D. The relationship between gut microbiota and weight gain in humans. Future Microbiol 2012; 7(1): 91-109.

55. Al-Assal K, Martinez AC, Torrinhas RS, Cardinelli C, Waitzberg D. Gut microbiota and obesity. Clinical Nutrition Experimental 2018; 20: 60-4.

56. Lumeng CN, Bodzin JL, Saltiel AR. Obesity induces a phenotypic switch in adipose tissue macrophage polarization. J Clin Invest 2007; 117(1): 175-84.

57. Fujisaka S, Usui I, Bukhari A, et al. Regulatory mechanisms for adipose tissue M1 and M2 macrophages in diet-induced obese mice. Diabetes 2009; 58(11): 2574-82.

58. Shaul ME, Bennett G, Strissel KJ, Greenberg AS, Obin MS. Dynamic, M2-like remodeling phenotypes of CD11c+ adipose tissue macrophages during high-fat diet--induced obesity in mice. Diabetes 2010; 59(5): 1171-81.

59. Olefsky JM, Glass CK. Macrophages, inflammation, and insulin resistance. Annu Rev Physiol 2010; 72: 219-46.

60. Jager J, Grémeaux T, Cormont M, Le Marchand-Brustel Y, Tanti JF. Interleukin-1beta-induced insulin resistance in adipocytes through down-regulation of insulin receptor substrate-1 expression. Endocrinology 2007; 148(1): 241-51.

61. Hogan AE, Gaoatswe G, Lynch L, et al. Glucagon-like peptide 1 analogue therapy directly modulates innate immune-mediated inflammation in individuals with type 2 diabetes mellitus. Diabetologia 2014; 57(4): 781-4.

62. Roche HM. Dietary modulation of energy homoeostasis and metabolic-inflammation. Proc Nutr Soc 2019; 78(3): 313-8.

63. Rocha VZ, Folco EJ, Sukhova G, et al. Interferon-gamma, a Th1 cytokine, regulates fat inflammation: a role for adaptive immunity in obesity. Circ Res 2008; 103(5): 467-76.

64. Rausch ME, Weisberg S, Vardhana P, Tortoriello DV. Obesity in C57BL/6J mice is characterized by adipose tissue hypoxia and cytotoxic T-cell infiltration. Int J Obes (Lond) 2008; 32(3): 451-63.

65. McLaughlin T, Liu LF, Lamendola C, et al. T-cell profile in adipose tissue is associated with insulin resistance and systemic inflammation in humans. Arterioscler Thromb Vasc Biol 2014; 34(12): 2637-43.

66. Nishimura S, Manabe I, Takaki S, et al. Adipose Natural Regulatory B Cells Negatively Control Adipose Tissue Inflammation. Cell Metab 2013; 18(5): 759-66.

67. Yang H, Youm YH, Vandanmagsar B, et al. Obesity increases the production of proinflammatory mediators from adipose tissue T cells and compromises TCR repertoire diversity: implications for systemic inflammation and insulin resistance. J Immunol 2010; 185(3): 1836-45.

68. Dyck L, Prendeville H, Raverdeau M, et al. Correction: Suppressive effects of the obese tumor microenvironment on CD8 T cell infiltration and effector function. J Exp Med 2022; 219(3).

69. Cerwenka A, Lanier LL. Natural killer cells, viruses and cancer. Nat Rev Immunol 2001; 1(1): 41-9.

70. Morvan MG, Lanier LL. NK cells and cancer: you can teach innate cells new tricks. Nat Rev Cancer 2016; 16(1): 7-19.

71. Lynch LA, O'Connell JM, Kwasnik AK, Cawood TJ, O'Farrelly C, O'Shea DB. Are natural killer cells protecting the metabolically healthy obese patient? Obesity (Silver Spring) 2009; 17(3): 601-5.

72. O'Shea D, Cawood TJ, O'Farrelly C, Lynch L. Natural killer cells in obesity: impaired function and increased susceptibility to the effects of cigarette smoke. PLoS One 2010; 5(1): e8660.

73. Theurich S, Tsaousidou E, Hanssen R, et al. IL-6/Stat3-Dependent Induction of a Distinct, Obesity-Associated NK Cell Subpopulation Deteriorates Energy and Glucose Homeostasis. Cell Metab 2017; 26(1): 171-84.e6.

74. Tobin LM, Mavinkurve M, Carolan E, et al. NK cells in childhood obesity are activated, metabolically stressed, and functionally deficient. JCI Insight 2017; 2(24).

75. Michelet X, Dyck L, Hogan A, et al. Metabolic reprogramming of natural killer cells in obesity limits antitumor responses. Nat Immunol 2018; 19(12): 1330-40.

76. Perdu S, Castellana B, Kim Y, Chan K, DeLuca L, Beristain AG. Maternal obesity drives functional alterations in uterine NK cells. JCI Insight 2016; 1(11): e85560.

77. Bähr I, Goritz V, Doberstein H, et al. Diet-Induced Obesity Is Associated with an Impaired NK Cell Function and an Increased Colon Cancer Incidence. J Nutr Metab 2017; 2017: 4297025.

78. Viel S, Besson L, Charrier E, et al. Alteration of Natural Killer cell phenotype and function in obese individuals. Clin Immunol 2017; 177: 12-7.

79. Porcelli S, Yockey CE, Brenner MB, Balk SP. Analysis of T cell antigen receptor (TCR) expression by human peripheral blood CD4-8- alpha/beta T cells demonstrates preferential use of several V beta genes and an invariant TCR alpha chain. J Exp Med 1993; 178(1): 1-16.

80. Lantz O, Bendelac A. An invariant T cell receptor alpha chain is used by a unique subset of major histocompatibility complex class I-specific CD4+ and CD4-8- T cells in mice and humans. J Exp Med 1994; 180(3): 1097-106.

81. Exley M, Garcia J, Balk SP, Porcelli S. Requirements for CD1d recognition by human invariant Valpha24+ CD4-CD8- T cells. J Exp Med 1997; 186(1): 109-20.

82. Matsuda JL, Mallevaey T, Scott-Browne J, Gapin L. CD1d-restricted iNKT cells, the 'Swiss-Army knife' of the immune system. Curr Opin Immunol 2008; 20(3): 358-68.

83. Lynch L, O'Shea D, Winter DC, Geoghegan J, Doherty DG, O'Farrelly C. Invariant NKT cells and CD1d(+) cells amass in human omentum and are depleted in patients with cancer and obesity. Eur J Immunol 2009; 39(7): 1893-901.

84. Lynch L, Nowak M, Varghese B, et al. Adipose tissue invariant NKT cells protect against diet-induced obesity and metabolic disorder through regulatory cytokine production. Immunity 2012; 37(3): 574-87.

85. Schipper HS, Rakhshandehroo M, van de Graaf SF, et al. Natural killer T cells in adipose tissue prevent insulin resistance. J Clin Invest 2012; 122(9): 3343-54.

86. Ji Y, Sun S, Xu A, et al. Activation of natural killer T cells promotes M2 Macrophage polarization in adipose tissue and improves systemic glucose tolerance via interleukin-4 (IL-4)/STAT6 protein signaling axis in obesity. J Biol Chem 2012; 287(17): 13561-71.

87. Sag D, Krause P, Hedrick CC, Kronenberg M, Wingender G. IL-10-producing NKT10 cells are a distinct regulatory invariant NKT cell subset. J Clin Invest 2014; 124(9): 3725-40.

88. Lynch L, Michelet X, Zhang S, et al. Regulatory iNKT cells lack expression of the transcription factor PLZF and control the homeostasis of T(reg) cells and macrophages in adipose tissue. Nat Immunol 2015; 16(1): 85-95.

89. Carolan E, Tobin LM, Mangan BA, et al. Altered distribution and increased IL-17 production by mucosal-associated invariant T cells in adult and childhood obesity. J Immunol 2015; 194(12): 5775-80.

90. Hogan AE, Tobin AM, Ahern T, et al. Glucagon-like peptide-1 (GLP-1) and the regulation of human invariant natural killer T cells: lessons from obesity, diabetes and psoriasis. Diabetologia 2011; 54(11): 2745-54.

91. Magalhaes I, Pingris K, Poitou C, et al. Mucosal-associated invariant T cell alterations in obese and type 2 diabetic patients. J Clin Invest 2015; 125(4): 1752-62.

92. Longo M, Zatterale F, Naderi J, et al. Adipose Tissue Dysfunction as Determinant of Obesity-Associated Metabolic Complications. Int J Mol Sci 2019; 20(9).

93. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: the linking mechanism and the complications. Arch Med Sci 2017; 13(4): 851-63.

94. Chen L, Chen R, Wang H, Liang F. Mechanisms Linking Inflammation to Insulin Resistance. Int J Endocrinol 2015; 2015: 508409.

95. Zhang Z, Scherer PE. Adipose tissue: The dysfunctional adipocyte - a cancer cell's best friend. Nat Rev Endocrinol 2018; 14(3): 132-4.

96. Ryan DH, Yockey SR. Weight Loss and Improvement in Comorbidity: Differences at 5%, 10%, 15%, and Over. Curr Obes Rep 2017; 6(2): 187-94.

97. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346(6): 393-403.

98. Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. Lancet 2009; 374(9702): 1677-86.

99. Gong Q, Zhang P, Wang J, et al. Morbidity and mortality after lifestyle intervention for people with impaired glucose tolerance: 30-year results of the Da Qing Diabetes Prevention Outcome Study. Lancet Diabetes Endocrinol 2019; 7(6): 452-61.

100. Gillies CL, Abrams KR, Lambert PC, et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ 2007; 334(7588): 299.

101. King NA, Hopkins M, Caudwell P, Stubbs RJ, Blundell JE. Beneficial effects of exercise: shifting the focus from body weight to other markers of health. Br J Sports Med 2009; 43(12): 924-7.

102. Careau V, Halsey LG, Pontzer H, et al. Energy compensation and adiposity in humans. Current Biology 2021; 31(20): 4659-66.e2.

103. Dong HJ, Dragioti E, Rivano Fischer M, Gerdle B. Lose Pain, Lose Weight, and Lose Both: A Cohort Study of Patients with Chronic Pain and Obesity Using a National Quality Registry. J Pain Res 2021; 14: 1863-73.

104. Riebe D, Blissmer BJ, Greaney ML, Garber CE, Lees FD, Clark PG. The relationship between obesity, physical activity, and physical function in older adults. J Aging Health 2009; 21(8): 1159-78.

105. Lang IA, Llewellyn DJ, Alexander K, Melzer D. Obesity, physical function, and mortality in older adults. J Am Geriatr Soc 2008; 56(8): 1474-8.

106. Dowd JB, Zajacova A. Long-term obesity and physical functioning in older Americans. International Journal of Obesity 2015; 39(3): 502-7.

107. Rhynehart A, Dunlevy C, Hayes K, O'Connell J, O'Shea D, O'Malley E. The Association of Physical Function Measures With Frailty, Falls History, and Metabolic Syndrome in a Population With Complex Obesity. Frontiers in Rehabilitation Sciences 2021; 2.

108. Schwartz A, Doucet E. Relative changes in resting energy expenditure during weight loss: a systematic review. Obes Rev 2009; 11(7): 531-47.

109. Steinert RE, Feinle-Bisset C, Asarian L, Horowitz M, Beglinger C, Geary N. Ghrelin, CCK, GLP-1, and PYY(3-36): Secretory Controls and Physiological Roles in Eating and Glycemia in Health, Obesity, and After RYGB. Physiol Rev 2017; 97(1): 411-63.

110. Goldberg JH, King AC. Physical activity and weight management across the lifespan. Annu Rev Public Health 2007; 28: 145-70.

111. Turk MW, Yang K, Hravnak M, Sereika SM, Ewing LJ, Burke LE. Randomized clinical trials of weight loss maintenance: a review. J Cardiovasc Nurs 2009; 24(1): 58-80.

112. Cardoso L, Rodrigues D, Gomes L, Carrilho F. Short- and long-term mortality after bariatric surgery: A systematic review and meta-analysis. Diabetes Obes Metab 2017; 19(9): 1223-32.