Acta Scientific NUTRITIONAL HEALTH (ISSN:2582-1423)

Volume 7 Issue 3 March 2023

Mini Review

Obesity and Mutations in Mc4r and Mc3r

Mercedes Dejuán Bitriá*

Department of Nutrition Health, Spain

***Corresponding Author:** Mercedes Dejuán Bitriá, Department of Nutrition Health, Spain.

DOI: 10.31080/ASNH.2023.07.1213

Received: January 25, 2023

Published: February 26, 2023

Abstract

Obesity is a multisystemic disease of great importance in global public health as it is one of the major risk factors for comorbidities such as type 2 diabetes mellitus, cardiovascular disease or cancer. Several studies looking for the aetiology of this disease relate several external and internal factors to the development of the disease. Genetics has been shown to be an individual-specific factor with a broad effect on the development of obesity.

There is a rs17782313 polymorphism in homozygous MC4R that has shown increased hyperphagia and hyperinsulinemia, leading to early obesity. In turn, the heterozygous mutation shows milder forms of obesity with increased weight gain in response to large amounts of fat in the diet, thus inferring a dose-gene effect [1]. Another polymorphism with a similar condition but still under investigation is the MC3R receptor mutation.

The various alternatives to solve this disease allude to weight loss through a combination of physical exercise and the search for early satiety. It is clear that the treatment of these patients must be both individual and comprehensive to address all the predisposing and developmental factors of the disease [2]. For this reason, the aim of the study is deepening in this little-known disease and name some of the dietary interventions used to handle the effects of the mutation.

Keywords: Obesity; Overweight; Polymorphism; MC3R; MC4R

Abbreviations

MC4R: Melanocortin 4 Receptor; MC3R: Melanocortin 3 Receptor

Introduction

Obesity

The World Health Organisation (WHO) defines overweight and obesity as an excessive accumulation of fat that poses a health risk [3]. This store of fat will serve as a natural energy reserve, but too much fat can be dangerous. The prevalence of this disease is increasing in recent decades in both undeveloped and developed countries.

It is a multifactorial disease in which the aetiology is the result of a combination of environmental and genetic factors and their interactions. There are both modifiable and non-modifiable environmental factors. Among the modifiable ones, we could highlight diet, physical activity, unhealthy ifestyle habits such as smoking or the usage of alcohohl and sleep patterns [3]. Within the diet, there are different diets with greater or lesser benefits in relation to the prevention or induction of obesity. The Mediterranean diet, for example, is high in complex carbohydrates and fibre, uses monounsaturated fatty acids (oleic) as the exclusive fat for cooking and seasoning and contains adequate protein intake with a low proportion of red meat. It has been shown to reduce obesity and thus cardiovascular risk. Therefore, a higher intake of certain food groups over others can lead to imbalances that increase the likelihood of obesity.

Obesity can also lead to psychological disorders such as depression, anxiety and an increased tendency to suicide. The most

prominent reason for this is the discrimination that exists in society at large leading to less education, decreased employment and social isolation [3].

To determine whether a person is overweight and obese, epidemiologists use the Body Mass Index (BMI). This method is recommended for its high reproducibility and ease of use as it only requires the height and weight of each individual. However, it is not fully representative as it does not indicate the amount of fat mass, lean mass and body water. In athletes with a lot of muscle mass or in the elderly it would not be a good indicator of obesity. Other techniques to measure obesity are ultrasound, neutron activation, computed tomography, double photon absorptiometry (DEXA), magnetic resonance imaging (MRI), dilutional techniques, anthropometric measurements and imaging techniques such as densitometry [3].

The main classification of obesity is made depending on the location of the excess fat. Android or central obesity will be that where the greatest amount of fat is found in the trunk or abdominal area. It has been linked to a higher risk of cardiovascular and metabolic diseases. On the other hand, we would have gynoid obesity, where the fat mass is in the hips, thighs and lower trunk. This type of obesity presents fewer risks. Gynoid obesity is more common in women [3].

Etiology

Obesity may be due to an imbalance between food intake and daily energy expenditure. This energy expenditure is due to physical activity, basal metabolism and that resulting from thermogenesis of food. Basal metabolism consumes energy to perform functions such as maintaining basal temperature, contracting muscles or other metabolic processes.

However, the regulation of energy balance is a dynamic process in which certain components try to compensate for the alteration of others. There is a potential biological and behavioural adaptation to restore the body's energy homeostasis. Thus, anything that affects this imbalance in homeostasis will increase the risk of obesity. Examples could be failures in the regulation of lipid stores, imbalances in the distribution of nutrients in the tissues or lack of control of intake [3]. There are several factors that will influence this disease. These are examined under their respective sections.

Lifestyle, demographic and environmental factors

Other findings show how socio-cultural, nutrigenetic, demographic and other omic science factors, such as microbiota, increase the incidence of obesity [3].

Most of the studies carried out in the adult population in Spain, it can be observed that there is a greater probability of this disease in men and its incidence increases with age. At the age of 60, it is estimated that it can reach its maximum weight [3].

There is, in turn, an inverse relationship between obesity and the level of education received. At younger ages, such as childhood or adolescence, it also depends on the education of the caregiver in charge of the individual's diet.

The lack of physical exercise due to both technical and mechanical advances and the general pursuit of comfort has increased the prevalence of obesity. This is because physical activity will lower blood pressure, increase the production of high density lipoproteins (HDL), modulate blood glucose, increase the ability of muscles to utilise oxygen properly by increasing their work capacity, reduce stress, improve the effectiveness of the immune system, activate and regulate metabolism and maintain the body's energy balance by reducing the amount of fat accumulated in adipose tissue [3].

Another important factor is the quality of sleep. Changes in the circadian system through sleep disruption can increase the degree of obesity. This is due to a direct effect on proteins involved in circadian physiology and rhythm. These are BMAL1 (Brain and muscle ARNT-like protein-1), CLOCK (Circadian Locomotor Output Cycles Kaput) and PER2 (Period Circadian Protein-2). Stress, in turn, will produce an alteration in hormonal, behavioural and cognitive mechanisms that will increase body fat and weight [3].

Genetic factors

Common genetic obesity groups together all those cases where there is a multifactorial problem resulting from an imbalance between the intake and use of energy ingested [4]. There are more than 600 genes, chromosomal regions and markers linked to obesity in humans and more and more interactions are being discovered [3].

Mendelian or monogenic obesity is when the obesity phenotype is derived from mutagenic changes in a gene, such as that reported for the leptin gene and its receptor or mutation in the melanocortin receptor (de Jesús Peralta Romero 578-587). It affects 5% of the population [3]. There are two forms of this type of obesity: syndromic or X-linked and non-syndromic. Most of these variations are shown by the manifestation of an extreme phenotype and early onset of obesity. On the other hand, obesity caused by many genes would be called polygenic. The presence of many disease-inducing genes together with other risk factors can increase susceptibility by producing variations in the phenotype. This type of obesity is due to the fact that genes involved in the regulation of appetite, the distribution of nutrients in the tissues and the regulation of lipid reserves are affected. The 8 most known monogenic mutations are currently the leptin gene (LEP), leptin receptor (LEPR), carboxypeptidase E, prohormone convertase 1 (PCSK1), propiomelanocortin (POMC), melanocortin receptors 3 and 4 (MC4R), brain-derived neutrotrophic factor (BDNF), neurotrophic tyrosine tyrosine kinase receptor type 2 (NTRK2) and single-minded homolog 1 (SIM1) [3].

On the other hand, there are syndromic disorders in which most are caused by chromosomal abnormalities, both autosomal and X-linked. Almost all of them are associated with mental retardation as well. Examples include Prader-Willi syndrome, pessudohypoparathyroid syndrome type 138 and Bardet-Biedl syndrome [4].

For the identification of genetic structures related to obesity, modern molecular biology techniques are used in conjunction with statistical analysis. The GWA (Genome Wide Association) is a methodology that identifies the association of human diseases with specific regions of chromosomes, called loci, representing specific gene clusters. It is based on the premise that the gene explanation of the variance of a trait can be broken down into three components that can be analysed. These are: additive effects between genes, gene dominance and gene-gene interaction or epistasis. In turn, an assessment of the contribution of environmental effects and the addition of chance effects will be necessary. There are two general approaches to GWA, genomic ligand analysis and genomic association analysis [4]. In ligand analysis, genetic variants related to a phenotype or trait will be sought on the basis of a genome-wide study of individuals who are related by family. The aim is to identify loci that are related to certain traits or phenotypes throughout the generations in families. On the other hand, in the genomic analysis of association, the use of all known variants in human genes of polymorphisms called single nucleotide polymorphisms or SNPs is proposed. In this way, the association of polymorphisms with an obesity-related trait that needs to be independently replicated in other populations can be assessed [4].

Inflammatory profile

In obesity and type 2 diabetes mellitus, we have pro-inflammatory and anti-inflammatory cytokines. Interleukin-6 (IL-6) is a pro-inflammatory cytokine that will be synthesised in up to 40% of adipose tissue. Elevated levels of IL-6 are associated with reduced insulin secretion and increased risk of developing type 2 diabetes. This is because it will increase insulin resistance indirectly, through its effect on the hypothalamic-pituitary-adrenal axis, causing hypercortisolemia [4].

We would also highlight tumour necrosis factor-alpha (TNF-α). This cytokine will be present in the acute phase of inflammation and will contribute to insulin resistance by inhibiting the activity of the insulin-1 receptor substrate by inactivation through activation of threonines and serines and phosphorylation of tyrosine residues [4].

On the other hand, there are anti-inflammatory cytokines such as adiponectin. This has the function of enhancing insulin sensitivity. In this case, sensitivity to the gene will be decreased in subjects with obesity. Proliferation activating factor (PPAR-γ) will be closely related to adiponectin, as it will induce its synthesis and secretion, unlike TNF-α, which inhibits it [4].

A BMI modulating locus was found to be the gene coding for melanocortin receptor 4 (MC4R), identified in autumn 2007 from a combined GWA study involving 16876 European individuals, followed by genotyping of a further 75000 individuals, including extremely obese cases and controls. SNPs at this intergenic locus associated with obesity were subsequently shown to modulate the phenotype related to appetite regulation in both adults and children [4].

Other factors influencing obesity.

Other influencing factors are for example calcium intake. A high dietary calcium intake is inversely related to BMI and also reduces insulin resistance.

On the other hand, smoking has been shown to increase the prevalence of obesity by increasing the accumulation of body fat. Nicotine intake causes an immediate stimulus that releases epinephrine from the adrenal cortex which will stimulate the central nervous system and certain endocrine glands. This will release more glucose and promote weight gain. The binding of nicotine to certain receptors will produce a structural change and open channels allowing the flow of nuerotransmitters and ions. The release of serotonin, dopamine and γ-aminobutyric acid (GABA) is induced [3].

Certain drugs such as hormones (contraceptives), corticosteroids, antiepileptic drugs (valproate), antiglycaemic drugs and psychoactive drugs (antidepressants and antipsychotics) increase an individual's weight, although it will always depend on the type and dose of the drug [3].

Cushing's syndrome is caused by an increase in plasma cortisol, which increases adiposity. Endocrine diseases such as hypothyroidism can also contribute to overweight [3].

Regulation of body energy balance

To regulate homeostasis between intake and satiety, the hypothalamus and other brain areas produce input and output of humoral signals that circulate at concentrations proportional to body fat content. Hormonal signals will come from the small intestine, pancreas, liver, adipose tissue and brainstem. The central nervous system will influence energy balance so that behaviour (intake and physical activity) will depend on it, the autonomic nervous system will regulate energy expenditure and will have some effect on the neuroendocrine system in the secretion of hormones such as cortisol, growth hormone, thyroid, insulin and sex steroids [5].

There are several signals related to the neuroendocrine system that can be of central (central nervous system) or peripheral (or-

gans and tissues) origin. These signals can be divided into the anabolic (orexigenic) system and the catabolic or anorexigenic system [5].

The anabolic system will be responsible for stimulating intake while the catabolic system will stimulate the mechanisms of increased energy expenditure and decreased intake. Both are integrated in the hypothalamus and their action is complemented by other centres in the brain. In the arcuate nucleus of the hypothalamus we will have hormones with a high affinity for the MC3R and MC4R receptors (POC/CART) that will stimulate the reduction of food intake and the reduction of body weight. Another type of population with orexigenic action will release agouti-related peptide (NPY/AgRP) and neuropeptide Y that antagonise the action of melanocortin (especially MC4R) with orexigenic action. These two systems will be affected by external hormones and other peripheral factors interacting with other brain centres such as the dorsal vagal complex or the corticolimbic system through environmental, hedonic and homeostatic influences [5]. The vagus nerve will have a special role in the transmission of afferent and efferent neural signals between the nucleus of the dorsal vagal complex and the gastrointestinal system. Examples of peripheral anorexigenic regulatory hormones are leptin, insulin, glucose, peptide YY, fatty acids, glucagon-like peptide-1 or adiponectin. Those of central origin would be peptides derived from proopiomelanocortin, oxytocin, histamine, serotonin and corticotropin-releasing hormone, among others. On the other hand, hormones of central orexigenic origin would be agouti-related peptides, ghrelin, orexin, melanin-concentrating hormone and opioids as examples. At the peripheral level we would have ghrelin and INSL 5 [5].

More specifically, we could focus on the melanocortin system. This system is composed of proopiomelanocortin (POMC) and POMC-derived peptides that act as ligands for the melanocortin receptors: α-, ß- and γ-MSH (α-, ß- and γ-melanocyte-stimulating hormones), as well as adrenocorticotropic hormone (ACTH). It also consists of a family of five melanocortin receptors (MC1R-MC5R) [6]. Finally, peptides that antagonise the effect of POMC-derived ligands: AGRP (agouti-related protein) and ASIP (agouti signalling protein). Melanocortin receptors are attached to G-proteins and are expressed in regions of the central nervous system which are related to appetite control [6].

MC3R AND MC4R

There are a large number of genes associated with obesity and the number is increasing as new technologies are being developed to identify them. Several variants associated with obesity are being studied, such as changes in food consumption, lipid and glucose metabolism, changes in sleep patterns, variants associated with taste perception and the tendency to increase the consumption of certain foods [7].

More specifically, we can focus on the MC4R (Melanocortin 4 Receptor) gene. The MC4R gene is located at position 21.32 of the long arm on chromosome 18 and is one exon with a length of 1.9 kb. This gene is expressed in adipose tissue, muscle and regions of the brain, more specifically in the nucleus of the hypothalamus and is a G protein-coupled receptor. It is here that it will perform the function of controlling energy balance and food intake [8]. The melanocortin system consists of proopiomelanocortin (POMC) and POMC-derived peptides that act as ligands for the melanocortin receptors: α-, ß- and γ-MSH (α-, ß- and γ-melanocyte-stimulating hormones), as well as adrenocorticotropic hormone (ACTH). It also consists of a family of five melanocortin receptors (MC1R-MC5R). Peptides that antagonise the effect of POMC-derived ligands are themselves part of the melanocortin system. These are: AGRP (agouti-related protein) and ASIP (agouti signalling protein) [9].It was in 1997 that a disruption of this gene was first linked to hyperphagia, hyperinsulinemia and obesity in mice [10].

Most MC4R mutations are heterozygous and inherited in a dominant manner, although cases of homozygosity or compound heterozygosity with an autosomal recessive pattern have been described [11]. The polymorphisms observed so far are: rs17782313, rs571312, rs12970134, rs2331841, rs6567160, rs8089364, rs7227255 and rs2229616, all affecting the subject's BMI [4].

Variants in the MC4R gene, which codes for the melanocortin receptor, have been linked to obesity in humans, increased cardiovascular risk, increased type 2 diabetes mellitus and insulin resistance. This is all due to the C allele of the MC4R receptor rs17782313 which will affect food intake. Individuals with the CC genotype are more susceptible to diabetes because of the insulin resistance mentioned above. Diet, in turn, will be one of the most inflammation-related factors affecting the systemic inflammation produced by obesity [12].

Melanocortin receptor 3 (MC3R) is also a G protein-coupled receptor for adrenocorticotropic and melanocyte-stimulating hormone. It has a chromosomal location 20q13.2. There are also data regarding MC3R in relation to the development of obesity. Heterozygous mutations have been found in a small number of the population, sometimes even leading to loss of receptor function. Two polymorphic variants (T6L and V81I) have also been described [13]. This is associated with an increase in weight and adipose tissue percentage as well as an increase in plasma insulin and leptin levels. These effects have been observed in subjects with the presence of both variants in homozygosis. In the double mutant there would be a partial reduction in receptor activity. These mutations are still under study because they have not been shown with the same evidence as mutations in the MC4R gene to be a monogenic cause of obesity [13].

Prevalence

Transmission is autosomal dominant with incomplete penetrance and lack of a characteristic phenotype. The severity of the phenotype is variable (severe to moderate obesity), depending on the role of the environment and other potentially modulating genetic factors [1].

SNPs are the most prevalent genetic cause of obesity. Some 12 SNPs in the MC4R gene have been described that are directly associated with increased body mass index and obesity. Among these polymorphisms, rs17782313 is one of the most studied. It has the C and T alleles, where C would be the risk allele with a prevalence of 24% in the population, and T would be the ancestral allele. This polymorphism has been associated with higher body index, waist circumference, type 2 diabetes mellitus, insulin resistance and lipid intake. The C allele would also lead to uncontrolled food intake [8].

The penetrance of MC4R mutations varies in different ethnic groups. Given the large number of possible influences on body weight, it is not surprising that genetic and environmental modulators may have greater effects in some genealogies. This could explain the differences in clinical severity observed in different populations [1].

Discussion

Melanocortins are hormones produced in the hypothalamus that have the function of regulating appetite. It has been shown that there is some relationship between melanocortin stimulation and decreased food intake and total body weight. Similarly, it could be seen how various mutations and defects in the melanocortin receptor (MC4R) could lead to weight gain [2].

In the leptin-melanocortin system, axons from AGRP/NPY and POMC/CART neurons project to other hypothalamic regions important in the regulation of intake such as the lateral hypothalamic area, the paraventricular nucleus, the ventromedial nucleus and the dorsomedial nucleus, which express MC4R. MC4R expression has also been described in the nucleus of the solitary tract, where it would act, induced by factors generated in the gut, on satiety. In addition, it has been reported that serotonin, a neurotransmitter related to the suppression of ingestion, may also modulate the release of MC4R agonists and antagonists. Recently, it has been proposed that synthetic MC4R antagonists could block the satiety effect induced by the neurotransmitter nesfatin [9].

Binding of melanocortin ligands to MC4R leads to inhibition of intake by mechanisms that appear to involve the brain-derived neurotrophic factor BDNF. This neurotrophin promotes neuronal proliferation, regeneration, plasticity and connectivity during maturational development [9].

What normally happens is that activation of MC4R and MC3R after ligand binding stimulates G-proteins. This leads to a subsequent increase in cAMP levels. However, the effect of this increase will depend on the type of mutation. Various defects in the intracellular transport of the mutated receptor have been shown to be due to the intracytoplasmic retention that occurs in most mutations of these receptors. This would explain the insufficient response to agonists. Similarly, the constitutive function of the MC4R receptor will not require the presence of the ligand in a basal activity. Thus, it would be the r-agouti protein (AgRP) that would function as an inverse agonist. Without the ligand, the MC4R receptor would exert an inhibitory effect on food intake. It is also known that mutations in MC4R can increase the risk of obesity through a haploinsufficiency mechanism by affecting the functions of homodimerisation and heterodimerisation in G-protein synthesis [7].

The polymorphisms in rs17782313 and rs571312 are the most common and have been shown to be associated with obesity in adults, adolescents and children. It has not yet been possible to demonstrate the exact mechanism that causes this, but it has been shown that changes in intake occur, such as an increase in the amount of food eaten and hyperphagia of high-fat foods. MC4R rs17782313 has not been linked to changes in micro- or macronutrient intake in general. However, the rs17782313 C homozygosis has been linked to increased pleasure in eating sweets. The way in which the presence of this genetic risk in the receptor affects changes in intake and body mass index (BMI) occurs through two main pathways: overeating and increased depression [2].

The MC4R receptor is involved in serotonin and dopamine cycling, linking the latter to mood regulation. Signalling of this receptor triggers the response to stress-induced adaptations in the nucleus accumbens, where dopamine plays an important role in the reward system. The relationship with dopamine induces the reward system and, in addition, this neurotransmitter has been linked to overeating. Administration of agouti-related protein, an inverse agonist of melanocortin, activates dopaminergic neurons causing increased turnover in the prefrontal cortex and thus reduces sucrose seeking behaviour [2].

As it is also related to the serotonin cycle regulating intake and mood, the possibility of treatments with MC4R agonists such as BIM-22493 and BIM-22511 or serotonin agonists for this type of obesity and intake disruptions is being investigated [2].

It is the C allele of rs17782313 that affects the emotional side of eating and food cravings. It is associated with increased enjoyment of fast food and sweets [2]. Binge eating disorder is also more prevalent in people with this polymorphism. Mutations in this receptor lead to hyperphagia and changes in intake. The reward system and the MC4R receptor may play a role in this disorder [8].

High levels of inflammatory index in diets have been associated with lower HDL levels and increased triglyceride levels. By affecting the lipid profile, the risk of cardiovascular disease is also affected. The CC genotype has higher cholesterol values compared to other genotypes [12].

Thus, a polymorphism in the melanocortin receptor is the most common genetic cause of obesity. Cycling of melanocortins affects both metabolic and behavioural responses related to intake. Regulation of mRNA for MC4R together with IL-6 in the hypothalamus would regulate lipid intake and fat accumulation in white adipose tissue [12].

In patients with the polymorphism, they have been shown to have increased postprandial ghrelin levels, while postprandial IL6 levels decreased [8].

In obesity, cytokines increase generating chronic inflammation. TNF-Alpha does not vary between genotypes, but IL6 is affected [8].

The hormones leptin and ghrelin produce regulatory effects on the expression of inflammatory cytokines, with leptin playing a pro-inflammatory role and ghrelin an anti-inflammatory role by reducing the expression of TNF alpha and IL6. Some authors say that ghrelin is involved in the transcription of pro-inflammatory cytokines where it would inhibit the formation of TNFalpha and IL6 through the growth hormone cycle [8]. This would indirectly inhibit ghrelin and increase insulin levels.

The mutation in this gene has also been linked to a reduction in the expression of pro-opiomelanocortins (POMC), which is associated with morbid obesity as the sensation of satiety is changed [8].

It has also been shown that hyperinsulinaemia and increased linear growth can occur in early childhood. This acceleration in linear growth is not due to dysfunction of the growth hormone axis, but a consequence of hyperinsulinaemia.

MC4R deficiency is not associated with altered thyroid axis or impaired reproductive function [1].

A link could be established between this polymorphism and increased intake of saturated fats and a reduction in fibre. A relationship has also been found with higher intakes of sodium, potassium and magnesium and lower intakes of vitamins A, D, E, B6, B9 and B5, calcium, iodine, copper, iron, magnesium and zinc. However, it cannot be deduced with complete reliability that this is directly related to the polymorphism. Studying these parameters is more complicated as there are no standardised methods and there are many factors that affect the bioavailability of these parameters [8].

Diagnosis

It is of great importance to clinically detect the rare forms of genetic obesity that exist as this allows progress in the knowledge of the disease and also because they require management by a specialised and multidisciplinary team [1].

Most cases of MC4R deficiency detected to date have been identified by genetic screening of large cohorts of obese patients; however, the diagnosis can be intuited by the clinical features of the disease and confirmed by the detection of a mutation in MC4R [7].

As with other forms of obesity, the prognosis depends on the complications present; obese patients are at increased risk of cardiovascular disease, cancer and type 2 diabetes [7].

The severity of obesity decreases with age and the degree of hyperphagia in these patients will depend on the level of receptor dysfunction, which is generally less than in leptin-deficient patients [1].

Treatment

There is currently no treatment for these abnormalities. However, studies show that recovery of cell surface expression of MC4R mutants may have some therapeutic benefit as obesity-causing MC4R mutations induce intracellular retention of receptors through a cellular quality control system [6].

A recovery of expression on the cell surface of MC4R mutants has been shown to have therapeutic benefit, as most obesity-causing MC4R mutations lead to intracellular retention of receptors by the cellular quality control system. Thus, chaperones would have an important pharmacological role in the treatment of patients with MC4R mutations.

Similarly, there are new drugs still in development with pharmaceutical effect that could help to reduce the effect of the mutation. These could be those with peripheral action aimed at reducing nutrient absorption, such as lipase inhibitors or inhibitors of the intestinal microsomal triglyceride transport protein. We would also have those that generate anorexigenic stimuli and inhibition of orexigenic stimuli such as intestinal and pancreatic peptide analogues associated with satiety and ghrelin antagonists. Those that increase energy expenditure at the peripheral level such as beta-adrenergic receptor number 3 agonists, TGR5 agonists or situin 1 (SIRT1) agonists. There are also certain drugs with central action on appetite and energy expenditure such as combinations of psychotropic drugs or ciliary neurotrophic factor [13].

In the leptin-melanocortin system, human recombinant leptin therapy is only applied to patients with genetic leptin deficiency.

This is in addition to the administration of amylin analogues (pancreatic peptide with satiating effect) and is associated with greater influence on body weight loss in multifactorial obesity. Ciliary neurotrophic factor (CTNF) can also be administered to these patients as a weight- and intake-reducing agent. This could be applicable to treatment to increase satiety in patients with a mutation in the MC4R receptor gene [9].

Modified MC4R agonists have also been studied for their acute effects and their effects after chronic administration. Elements with a high similarity and affinity to the MC4R receptor have been developed and were also found to cross the blood-brain barrier. MTII (melatonan II) and the urea-based piperazine produce some weight reduction. However, they have been found to reduce erectile function and develop taste aversion as well as increase blood pressure. It has been noted that due to the low bioavailability of MC4R agonists, oral administration, which is most common in chronic diseases, cannot be performed [14]. Ro-3225 is an MC4R analogue that is very similar and is not seen to have as many adverse effects compared to MTII. It has even been shown to reduce the need for intake over a 4-hour period. ACTH and certain derivatives reduce intake for two hours after fasting, but it does not seem to reduce food intake after a meal period. This is why science continues to investigate these analogues and further treatment targets are being sought in order to reduce this disease [14].

Thus, the overall goal of obesity treatment is to achieve and maintain a healthy weight. This improves overall health and reduces the risk of developing obesity-related complications. You may need to work with a team of health professionals, including a dietitian, behavioural counsellor or obesity specialist, to help you understand and make changes to your eating and activity habits. Individuals will not consume food just because they feel hungry, but also because of the palatability of the food. This influences food choices. Foods with a higher fat content have been found to increase palatability and will therefore form part of the majority of these individuals' food choices. These types of food have less satiating effects both during and after the meal. However, foods high in fibre or high in protein do seem to have a more satiating effect [8] A diet with foods that make individuals feel satiated will result in less food consumption and therefore less energy density at each meal. Protein amino acids have been found to be crucial in determining satiety. An elevation of serum amino acids reduces the sensation of hunger and the amount of food ingested in humans. In order of increased satiety, macronutrients are ranked highest in protein, followed by carbohydrates and finally lipids. The gastrointestinal response to protein reaches the brain via an indirect neural pathway through the vagus nerve, and through a direct humoral pathway [8]. The presence of amino acids in the gastrointestinal tract will result in the release of the hormone CCK (cholecystokinin). This hormone will be released before the meal is finished and thus contributes to both satiety and satiation. Anorexigenic substances are also released by the presence of amino acids such as GLP-1 (glucagon-like peptide type 1) and PYY (peptide YY). However, hormonal factors have also been shown to contribute to macronutrients providing more or less satiety. The hormone ghrelin will stimulate appetite and is in high concentrations before meals and is reduced in quantity after ingestion and thus the sensation of hunger is also reduced. This drop in ghrelin levels has been found to be higher when the intake has been rich in carbohydrates [8]. There is also a relationship between the administration of micronutrients and changes in satiety. Calcium supplementation in obese people with calcium deficiency is associated with an increase in the anorexigenic hormone PYY. Several studies show how the administration of multivitamins in women with OBESITY produces changes in appetite. This is explained by the production of peptides and neurotransmitters that control intake. In this way, maintaining a homeostasis between the individual's requirements and their micronutrient intake leads to better satiety management. There are also certain ingredients that will have an effect on the body's homeostasis of intake such as soluble fibre, especially glucomannan. This is due to its ability to bind water and thus promote satiety [8]. Coffee will have an effect on reducing energy intake when given before breakfast as a decaffeinated coffee drink. Capsaicin has also been shown to reduce hunger sensation after a meal and thus reduce food intake. This compound is found in foods such as hot peppers, ginger, cumin or curry. This is because it has some effect on the sympathetic nervous system. The combined administration of capsaicin and green tea will have an effect on reducing hunger and increasing the feeling of satiety. In addition to these non-nutrient compounds, there is the important role of the microbiota. An intake of high-fat foods leads to changes in the composition of the microbiota that favour the onset of obesity. Certain prebiotics will increase the amount of Bifidobacteria and lead to reductions in intake in individuals. These prebiotics are obtained from fermentable fibre such as fructo-oligosaccharides which, after fermenting in the colon, reduce energy intake and thus reduce epididymal fat. They also exert anorexigenic effects by activating peptides such as PYY and GLP-1. Foods high in fermentable fibre such as whole grains, eaten in the morning or midday, will have a satiating effect for the rest of the day [8].

As a general rule, treatment would consist of increasing aerobic exercise to at least 30 minutes per day in combination with the anaerobic exercise necessary to maintain muscle mass. A calorie restricted diet with an increase in fruit, vegetables and complex carbohydrates (whole grains and pulses) is the most effective method of weight loss. This would translate into recommending a Mediterranean diet. However, it should be noted that satiety in these people has been impaired and techniques to increase satiety should be considered. Eating protein and fibre, especially soluble fibre, at each meal would increase the feeling of satiety, without forgetting water intake. Milk, eggs, poultry and mussels, among others, would be high in protein and low in fat, which is what we are looking for in this case to induce satiety and maintain weight.

It has been recognised that exercise has an effect on appetite control as it will modulate body composition and increase sensitivity to certain hormones. There will also be changes in gastrointestinal peptides responsible for satiety signalling. The effect of each type of exercise, its intensity and duration, varies from person to person. An increase in fat mass will increase energy demand thus increasing basal hunger. Less muscle mass leads to more satiety inhibition as well as reduced increases in insulin sensitivity and leptin. Exercise will generally increase muscle mass and reduce fat mass. A person with a mutation in MC4R could be asked for further genetic studies to look at certain mutations that may exist and would indicate whether there is more or less capacity for weight loss and benefit from physical exercise and what type would work best for them [15]. Mutations in the HIF1A gene with a Rs11549465 polymorphism will indicate what type of exercise will benefit the subject the most, as will the Rs 11549467 polymorphism. If the ADRB3 gene has arginine, it has been shown that there is greater resistance to weight loss through physical activity and the Glu2 allele of the ADRB2 gene is also associated with less benefit from physical activity.

Conclusion

Obesity is a universal epidemic that people from all walks of life are trying to prevent. Severe early-onset obesity generally frames a multifactorial obesity resulting from the interaction between genetic predisposition and environmental factors. Monogenic mutations in the MC4R receptor are the most common genetic cause [1]. The presence of the C allele is an important risk factor for the development of this disease especially when combined with other risk factors such as nicotine and postmenopausal status [16].

Although polymorphism in the receptor may increase the risk of this disease, but the expression of the phenotype is in turn determined by environmental factors such as the quality and quantity of diet and physical exercise.

Weight loss interventions based on lifestyle modification in the obese may be useful for patients with MC4R mutations even though they will have some difficulty maintaining their weight [9]. In the future, the development of MC4R agonists could become the first example of a personalised treatment for obesity, thus reducing bariatric surgery in young individuals [9]. Another point to note is that the aim is to increase the feeling of satiety in these patients, as this is the first aspect to be affected. Both direct and indirect effects of nutrients should be investigated with both short and long term effects to ensure adherence to diets with varying standards of macro- and micronutrients. It is clear that the factor that will most affect satiety will be the distribution of macronutrients with protein being the most satiating. Greater satiety will lead to better energy intake and a reduction in body weight [15].

Early diagnosis is important because specific and multidisciplinary management is needed. Although molecular confirmation is not yet available in our country, if there is suspicion, reference centres should be consulted to advance the diagnosis [1].

Bibliography

1. Ulloa María Eugenia., *et al*. "Obesidad monogénica". *Medicinal Infant* (2017): 294-302.

2. Yilmaz Zeynep., *et al*. "Association between MC4R rs17782313 polymorphism and overeating behaviors". *International Journal of Obesity* 39.1 (2015): 114-120.

3. Barragán Arnal Rocío. "Estudio de los factores del estilo de vida, genéticos y epigenéticos, que influyen en la obesidad y enfermedades relacionadas en población mediterránea". Tesis. (2017).

4. de Jesús Peralta-Romero., *et al*. "Genética de la obesidad infantil". *Revista Médica Del Instituto Mexicano Del Seguro Social* 52.1 (2014): S78-S87.

5. de Eguilaz., *et al*. "Influencia multisensorial sobre la conducta alimentaria: ingesta hedónica". *Endocrinología, Diabetes y Nutrición* 65.2 (2018): 114-125.

6. González Jiménez., *et al*. "Obesidad monogénica humana: papel del sistema leptina-melanocortina en la regulación de la ingesta de alimentos y el peso corporal en humanos". *Anales del sistema sanitario de Navarra* Gobierno de Navarra. Departamento de Salud 35.2 (2012).

7. Rachmi Cut Novianti., *et al*. "Stunting, underweight and overweight in children aged 2.0-4.9 years in Indonesia: prevalence trends and associated risk factors". *PloS one* 11.5 (2016): e0154756.

8. Magno., *et al*. "Association of the MC4R rs17782313 polymorphism with plasma ghrelin, leptin, IL6 and TNFα concentrations, food intake and eating behaviors in morbidly obese women". *Eating and Weight Disorders-Studies on Anorexia, Bulimia and Obesity* 26.4 (2021): 1079-1087.

9. Santos José Luis. "Sistema leptina-melanocortinas en la regulación de la ingesta y el peso corporal". *Revista Médica De Chile* 137.9 (2009): 1225-1234.

10. Quesada Fabiana Vilma., *et al*. "Polimorfismos genéticos implicados en la predisposición a obesidad infantil". (2013).

11. Tremblay Angelo and France Bellisle. "Nutrients, satiety, and control of energy intake". *Applied Physiology, Nutrition, and Metabolism* 40.10 (2015): 971-979.

12. Yarizadeh Habib., *et al*. "The interaction between the dietary inflammatory index and MC4R gene variants on cardiovascular risk factors". *Clinical Nutrition* 40.2 (2021): 488-495.

13. Martos-Moreno Gabriel Á., *et al*. "Aspectos genéticos de la obesidad". *Revista Española Endocrinología Pediátrica* 8.1 (2017): 21-32.

14. Fani Lana., *et al*. "The melanocortin-4 receptor as target for obesity treatment: a systematic review of emerging pharmacological therapeutic options". *International Journal of Obesity* 38.2 (2014): 163-169.

15. Blundell JE., *et al*. "Appetite control and energy balance: impact of exercise". *Obesity Reviews* 16 (2015): 67-76.

16. Brodowski Jacek., *et al*. "Searching for the relationship between the parameters of metabolic syndrome and the rs17782313 (T> C) polymorphism of the MC4R gene in postmenopausal women". *Clinical Interventions in Aging* 12 (2017): 549.