Innovative Gene Therapies for Obesity: Focusing on MC4R Deficiency

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Abstract

A complex health issues, obesity is impacted by both genetic predispositions and dietary habits.. With respect to the most important genes involved is MC4R gene (Melanocortin 4 Receptor), critical for appetite control and energy balance. Disfunction of this gene, and especially when present during early life, may lead to chronic hunger, lower expenditure of energy, and marked weight gain that becomes difficult to manage.Standard treatment protocols for obesity have involved lifestyle change like exercise and diet, with pharmacological intervention in the form of orlistat (Alli, Xenical) and phentermine-topiramate (Qsymia). Nonetheless, these measure little in response in individuals carrying MC4R mutations. Drugs such as liraglutide (Saxenda) and bupropion-naltrexone (Contrave) have been shown to have little effect on the root problems behind these genetic mutations, emphasizing the need for more specific medicines.Gene therapy that delivers brain-derived neurotrophic factor (BDNF) through adeno-associated virus (AAV) vectors is a promising treatment for MC4R deficiency. .This review highlights the significance of genetic profiling to select obese patients with MC4R mutations, which can improve and personalize treatment regimens. By learning the particular genetic basis of obesity in these patients, medical professionals can make interventions more likely to be effective. In general, although gene therapy offers a new method for addressing obesity due to MC4R deficiencies, additional research is needed to improve delivery systems and reduce the risk of immunological reactions. Further investigation in this area promises to enhance outcomes for those suffering from this multifaceted disorder.

Keywords: Gene therapy, MC4R deficiency, obesity, brain-derived neurotrophic factor (BDNF), AAV vector

Introduction

Being the fifth greatest cause of mortality globally, obesity and its associated health problems have become major global health concerns. The World Health Organisation (WHO) defines obesity as "abnormal or excessive fat accumulation that may impair health," highlighting the fact that an energy imbalance between calories burned and calories ingested is the main cause of obesity and overweight. . Although BMI was first developed in the 1830s by a Belgian mathematician and sociologist, it remains a prevalent measure for assessing obesity and its prevalence. The WHO often uses specific BMI thresholds to classify adult obesity, which helps identify individuals at higher risk for health complications related to obesity. Obesity rates (defined as adults with a BMI of 30 kg/m2) have increased dramatically in developing nations over the last 20 years. According to estimates, the number of obese adults increased from 105 million in 1975 to 641 million in 2014, a worrying trend. According to research, obesity is a complex health problem that is influenced by both broader societal causes (such as food deserts and bad eating patterns) and personal variables (such as genetics and learnt behaviours). Despite hereditary and chromosomal elements, many experts concur that obesity is essentially a "acquired" disorder that is predominantly caused by lifestyle choices, such as excessive eating and insufficient physical exercise[1].

A increased risk of several chronic diseases, such as diabetes, cancer, asthma, high blood pressure, and heart disease, is also associated with different forms of obesity, especially abdominal obesity. As a result, although obesity is a unique condition, it can also cause new health problems and exacerbate preexisting ones. The coronary artery disease, endocrine system peripheral nervous, and gastric systems are just a few of the organ systems that obesity are affectedy[2].

In order to regulate body weight, the hypothalamus integrates hormonal and neurological peripheral organ signals, such as the gastrointestinal system with adipose tissue. Leptin, which is an indicator of nutritional status and is produced by adipose tissue, is an important hormone in this process. Leptin levels fall during fasting, which sets off a chain of reactions in the brain meant to restore equilibrium of energy. People who have genetic mutations in the MC4R gene, also known as MC4R deficiency, usually gain weight starting in early childhood. Those with MC4R deficiency have a "big-boned" appearance due to increased lean mass and improved linear growth during childhood, in addition to increased fat mass [3].

Heterozygous mutations in MC4R have been found in obese people of different ethnicities and are associated with dominantly inherited obesity. The most frequent monogenic cause of obesity is MC4R deficiency, which is estimated to affect 2-5% of severely obese children, 1% of severely obese adults, and roughly 1 in 500 people in the general population. Although they are uncommon, homozygous and doubly heterozygous MC4R mutations cause extreme obesity. About 25% of MC4R mutations in clinical trials are frameshift mutations, which result in total function loss [4].

The remaining mutations are primarily missense mutations, which often diminish the expression of MC4R and its capacity to signal through the generation of cyclic AMP (cAMP). The increased growth observed may partly result from disproportionate early hyperinsulinemia. A primary clinical characteristic of MC4R deficiency is hyperphagia, characterized by an elevated urge to eat and reduced satiety following meals. Studies have shown that the severity of hyperphagia is correlated with the level of receptor malfunction in cells. Compared to children with the same mutation, adults may experience less severe hunger and lower levels of hyperinsulinemia since many clinical characteristics fade over time.[5]

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MC4R Gene and Its Role in Obesity

The melanocortin 4 receptor, a protein mostly found in the hypothalamus and encoded by MC4R, is essential for controlling hunger and sensations of fullness. . This gene produces the MC4R protein, a Guanine nucleotide binding protein-coupled receptor that interacts with α-melanocyte-stimulating hormone (α-MSH). MC4 receptors have been shown to be essential for a number of behaviours, including food, digestion, sexual behaviour, and male erectile function, in studies employing mouse models. Even without an atherogenic diet, MC4R deficiency in these models causes hyperphagia and an increase in body fat, which can progress to hepatic steatosis [6].

Numerous studies have shown sequence differences in MC4R across a variety of populations since the gene's first mutations linked to obesity in humans were discovered more than 20 years ago. The results indicate a degree of codominance and incomplete penetrance for MC4R variations. The risk of obesity is 4.5 times higher for people with pathogenic variations than for those without them [7].

According to several research, the probability of these variations varies greatly, ranging from 0.5% to 8.5%. The majority of the more than 200 variants that have been found so far are variants of a dominant acting nonsense. The most common genetic cause of childhood obesity is heterozygous variations, which are seen in 2% to 5% of people with severe childhood obesity[8].

Offspring from consanguineous unions have also been shown to contain homozygous MC4R mutations. Between 0.5% and 8.5% of obese adults and children had these harmful mutations. Additionally, obesity and the metabolic diseases that are linked to it are linked to single-nucleotide polymorphisms in MC4 gene. The p.V103I variability was found in 4.5% of children with complex obesity, while the p.E42K polymorphism was also observed in a study that looked at MC4R gene polymorphisms in obese Turkish children[9].

Types of Mutations

Alterations in the MC4R gene can be classified into various types, such as frameshift mutations, nonsense mutations, and missense mutations. Every type has unique impacts on receptor activity and plays varying roles in obesity pathology.

1.Frameshift Mutations: This changes happen as a result of the addition or removal of nucleotides, which changes the gene's reading frame. Consequently, they frequently result in an early stop codon, generating a shortened protein that is devoid of functional capability. For instance, the frameshift mutation p.I291Sfs*10 results in significant obesity because of total loss of MC4R functionality[10].

2. Nonsense Mutations: A nonfunctional receptor results from nonsense mutations that produce an early stop codon in the coding sequence. These mutations can significantly hinder MC4R's capacity to influence its physiological roles in appetite control and energy expenditure [11].

3. Missense Mutations: These mutations lead to a change in one amino acid in the receptor protein. Certain missense mutations might maintain some degree of functionality yet can still interfere with regular signaling pathways. For example, certain missense variants can influence G protein coupling or subsequent signaling pathways like β-arrestin recruitment or MAPK activation [12].

These mutations exert a major impact; individuals who have mutations that cause loss of function typically exhibit early-onset obesity along with decreased satiety responses and hyperphagia. Research indicates that more than 150 pathogenic variants of MC4R have been been discovered among victims with severe obesity, underscoring its status as a major contributor to monogenic obesity[13].

Prevalence of MC4R Mutations

Studies reveal that the prevalence of MC4R gene mutations in people with extreme obesity varies between 1.5% to 5.8%. . This mutation is recognized as the most prevalent monogenic factor contributing to obesity, especially within populations of European descent. However, its frequency may fluctuate based on ethnic background and the specific study cohort, with some findings suggesting a higher prevalence than previously estimated, potentially affecting approximately 1 in 337 individuals[14].

Research findings reveal that MC4R mutations are present in 1.5% to 5.8% of individuals with severe obesity.There is little data on non-European populations, and the frequency of MC4R mutations may range among ethnic groups.Finding "loss-of-function" mutations in the MC4R gene, which significantly impact the receptor's ability to control hunger, is the focus of most research.Hyperphagia (excessive eating) and early-onset obesity are common in people with MC4R mutations]15].

The signs and symptoms of MC4R deficiency

Intense hyperphagia, the main sign of melanocortin 4 receptor (MC4R) dysfunction, is characterised by an abnormal increase in appetite and food consumption as well as decreased satiety, which makes one feel less full after eating. .Early infancy linear growth acceleration. Increased bone mineral density and lean body mass: might seem "big-boned" abnomalies of the nervous system for eg Obstructive sleep apnoea is one such condition[16].

Moreover, individuals with MC4R deficiency generally exhibit increased bone mineral density, contributing to their overall size. It's noteworthy that despite obesity being a common symptom of this condition, individuals with MC4R deficiency often state they feel less hungry than when they were kids. Some clinical traits might diminish as one ages; for example, adults could exhibit reduced blood pressure and hyperinsulinemia compared to children who have the identical mutations [17].

Heterogeneity of Obesity Phenotypes

The clinical manifestations of MC4R insufficiency might fluctuate greatly from person to person due to the variety of obesity phenotypes linked to distinct MC4R gene variants. The phrase "heterogeneity of obesity phenotypes" refers to the notable variations among those who are classified as obese. These people may differ significantly in their body fat distribution, metabolic traits, and related health concerns even when their body mass index (BMI) measurements are similar. This variation makes it more difficult to manage obesity as a single, consistent problem; in other words, "obesity" can manifest itself differently in different people.The location of body fat deposition is a crucial determinant affecting heterogeneity[18].

Compared to "peripheral obesity," which is defined by fat that is mostly stored in the hips and thighs, "central obesity," which is defined by fat that is concentrated around the abdomen, is linked to a higher metabolic risk. While some fat people may be "metabolically healthy," others with the same BMI may have metabolic problems like insulin resistance and high triglycerides. Different obesity phenotypes are caused by variations in an individual's genetic makeup, which impact how the body stores and processes fat A variety of obesity phenotypes are also influenced by lifestyle choices [19].

Individuals who retain favourable metabolic parameters, such as normal blood pressure and blood sugar, despite being obese are known as metabolically healthy obese (MHO). The term "metabolically unhealthy obese" (MUO) refers to obese people who have serious metabolic problems, such as diabetes, hypertension, and dyslipidaemia. Sarcopenic obesity, which is commonly seen in elderly persons, is a disorder marked by obesity and muscle loss.Because obesity can take many different forms, it is easier to create interventions that are specifically suited to each patient's metabolic profile and distribution of body fat.Better evaluation of risks is The capacity to forecast the likelihood of acquiring associated health issues is improved by the recognition of particular obesity phenotypes[20].

Current methods to treat mc4r deficiency

The regulation of body weight is significantly influenced by the hypothalamic melanocortin 4 receptor (MC4R) pathway. The foundations of obesity management are lifestyle modifications, including changes in diet and heightened physical activity. Nevertheless, for individuals with MC4R mutations, these strategies often demonstrate only limited effectiveness. Patients with these genetic variations often find it extremely challenging to adhere to dietary guidelines or sustain the caloric deficit necessary for weight loss due to their frequent experience of severe hyperphagia. Research indicates that conventional weight-loss programs may be less effective due to people with MC4R mutations potentially consuming significantly more calories than others [21].

Several pharmaceutical strategies have been explored for treating obesity alongside lifestyle changes. The entire obese population has received treatments such as Phentermine-topiramate, an appetite suppressant, and Orlistat, which blocks gastrointestinal lipase to reduce fat absorption. Nevertheless, in individuals with MC4R deficiency, these medications have demonstrated only limited effectiveness. For instance, due to the bodily functions that influence their eating patterns, individuals with severe genetic obesity gain limited advantages from orlistat, even though it may lead to slight weight reduction in the general population. Likewise, the hyperphagic tendencies associated with MC4R mutations may not be adequately managed by phentermine-topiramate[22].

Another pharmacological approach is setmelanotide, an antagonist of the melanocortin 4 receptor that has been authorised for the treatment associated with particular genetic diseases. Clinical trials indicate that individuals with bi-allelic pathogenic mutations in genes such as POMC and LEPR may experience advantages from setmelanotide's capacity to reduce appetite and assist in weight loss . However, its efficacy in addressing patients with homozygous MC4R mutations remains uncertain. While heterozygous carriers possessing MC4R mutations have shown potential with setmelanotide, those with total loss-of-function mutations would likely not respond effectively as they lack functional receptors [23].

Limitations of Current Treatments

Individuals with hereditary obesity due to MC4R deficiency continue to encounter significant challenges despite the existence of various treatment possibilities. One of the primary disadvantages is the ineffectiveness of traditional weight-loss methods. Due to their genetic tendency for hyperphagia, patients often find it extremely challenging to lose and maintain weight through diet and exercise alone. This unrestrained craving may lead to disappointment and frustration when conventional methods fail to yield significant outcomes [24].

Additionally, one cannot overlook the mental impacts of severe obesity paired with insufficient treatment options. Many individuals with MC4R deficiency face mental health challenges such as anxiety and depression, along with social stigma. Feelings of helplessness can arise from an inability to control eating patterns, even with attempts[25].

Additionally, there are not numerous personalized treatment options for individuals with MC4R mutations. Even though some pharmaceutical therapies show promise, the diversity of MC4R variations and their functional consequences imply that they might not be effective for everyone. For example, certain patients with heterozygous mutations might gain advantages from setmelanotide, whereas individuals with complete receptor loss might not experience any benefits [26] .

Moreover, individuals with rare genetic conditions such as MC4R deficiency might face restricted access to specialized treatment. Numerous healthcare providers may lack comprehension of the complexities surrounding hereditary obesity disorders, potentially leading to inadequate management strategies that overlook the specific needs of these patients[27].

Advances in Gene Therapy for MC4R Deficiency

(1)Adeno-associated virus gene therapy

Novel approaches to treating the underlying causes of genetic obesity have been made possible by recent developments in gene therapy. Delivering brain-derived neurotrophic factor (BDNF) via adeno-associated virus (AAV) vectors is one potential strategy. A neurotrophic factor called BDNF is essential for growth, and differentiation of neurones. It also affects hunger and energy balance[28]. AAV vectors are extremely useful for gene therapy because of their capacity to efficiently transport genes to neurones and sustain extended expression with little immunological reaction. AAV-mediated BDNF gene transfer has demonstrated promise in preclinical models for reducing obesity and metabolic abnormalities linked to both genetic and diet-induced types of obesity[29].

Additionally, scientists have created autoregulatory systems in AAV vectors that replicate the body's inherent feedback processes for regulating therapeutic gene expression. This self-regulating method facilitates a stable plateau of body weight once significant weight loss has been accomplished, preventing possible negative effects linked to prolonged overexpression of therapeutic proteins. The way BDNF gene therapy may reinstate MC4R signaling pathways is complex[30] .In people with MC4R deficiency, the disrupted signaling pathways result in a lack of appetite control and heightened food consumptionIn addition to promoting neurogenesis, BDNF receptor activation inhibited apoptosis and altered synaptic activity through a number of signalling pathways. It's intriguing that BDNF plays a crucial function in inflammation, glucose metabolism, which contributes to the pathophysiology of diabetes mellitus and cardiovascular illnesses. BDNF treatment can decrease food intake and increase energy expenditure, whereas BDNF deficiency is linked to increased weight in both people and rats. Therefore, BDNF appears to play a significant role in type 2 diabetes mellitus and a number of neurological disorders[31].

The involvement of BDNF in neurological diseases may be explained by its primary function as a cytoprotective molecule. In both cases, the basic mechanism of BDNF's activity appears

to be its capacity to protect pancreatic β cells and neuronal cells. However, its exact function in brain development, physiology, and neurological disease pathology remains unclear[32].Understanding the physiology of BDNF may depend on studies that thoroughly examine the impacts of BDNF on neuronal survival and plasticity. . For instance, the gut and a number of other tissues manufacture BDNF, which raises the possibility that it plays a role in a number of illnesses, including digestive difficulties. [34].

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(2)CPT1A gene therapy

The CPT1A (carnitine palmitoyltransferase 1A) gene, which is essential for fatty acid metabolism, is the subject of a particularly promising strategy. The mitochondrial CPT1A enzyme makes it easier for long-chain fatty acids to enter these organelles so they can be oxidised.. It acts as an essential controller of fatty acid metabolism and energy generation. In obese people, where there is an excess of fatty acids, the function of CPT1A may be compromised, leading to several metabolic issues[35]. Enhancing the role of CPT1A could improve fatty acid oxidation rates, leading to reduced fat accumulation and better metabolic health Recent studies have focused on creating gene therapy methods to increase CPT1A activity. A group at the University of Barcelona has developed a novel technique that involves the insertion of a constitutively active form of CPT1A, named CPT1AM, into adipocytes (fat cells)[36].

This ex vivo gene therapy involves multiple stages: initially, mesenchymal stem cells are extracted from adipose tissue; subsequently, these cells are differentiated into mature adipocytes; next, genetic modification occurs using lentivirus vectors to produce the CPT1AM protein; and ultimately, the altered adipocytes are reintroduced into the host organism. This method enables a focused enhancement of fatty acid oxidation in adipose tissue, crucial for successful obesity management. In preclinical studies with mice, this innovative gene therapy produced noteworthy results [37].

Mice that were provided with CPT1AM-expressing adipocytes underwent significant weight reduction in comparison to control groups and exhibited enhanced metabolic markers, including decreased serum insulin and cholesterol levels, improved glucose tolerance, and reduced hepatic steatosis (fatty liver). The researchers suggest that should this treatment move into clinical use, cells obtained from adipose tissue might be gathered during surgeries such as liposuction or bariatric procedures. Once modified genetically, these cells could subsequently be reintroduced into the same individua[38]. However, before clinical trials are started, a number of issues must be resolved.. These encompass enhancing cell viability post-isolation, increasing the effectiveness of lentivirus-mediated gene delivery, and identifying the necessary cell quantities for successful transplantation[39].

As research on CPT1 gene therapy progresses, various aspects need additional investigation. Understanding the long-term impacts and sustainability of weight reduction and metabolic enhancements from this therapy will be essential. Thorough safety evaluations should be carried out to confirm that genetic alterations do not lead to negative impacts or unexpected outcomes. Additionally, examining if similar techniques may be applied to other metabolic

disorders associated with compromised fatty acid metabolism could increase the applicability of this tactic[40].

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(3)Si RNA gene therapy

Wave Life Sciences(wavelifesciences.com) is advancing notably in obesity treatment with its groundbreaking creation of WVE-007, a small interfering RNA (siRNA) therapy aimed at silencing the INHBE gene. This gene can possibly cure of obesity since it is crucial for regulating metabolic processes and fat accumulation. The main objective of WVE-007 is to facilitate fat reduction while safeguarding muscle mass, which is crucial for upholding overall metabolic health and avoiding negative consequences commonly linked to weight loss, like muscle wasting and diminished physical performance[41]. Initial preclinical research has shown promising outcomes, indicating that WVE-007 can attain an impressive 56% decrease in visceral fat in mouse models without any associated muscle tissue loss[42].

For the purpose of "silencing" a gene, siRNA molecules are designed to bind selectively to specific messenger RNA (mRNA) transcripts, causing them to degrade and preventing the production of the corresponding protein.In the context of obesity, researchers are looking at a number of genes linked to fat metabolism and accumulation as possible candidates for siRNA therapy, such as INHBE (inhibin beta E), which regulates fat storage.The effective transport of siRNA molecules to the target cells in adipose tissue is a major difficulty in siRNA therapy. To enable targeted administration, researchers are looking into a variety of delivery methods, including lipid nanoparticles[43].

Compared to traditional approaches, siRNA may allow for more precise weight loss by selectively silencing genes that contribute to fat storage.SiRNA therapy may help reduce body fat while maintaining muscular mass by targeting specific genes.siRNA may provide long-term gene silencing and help with long-term weight management, depending on the delivery mechanism selected[44].The promise of siRNA therapy for obesity has been demonstrated by numerous preclinical research carried out in animal models, which show notable decreases in body fat by targeted gene silencing.SiRNA therapeutics for obesity are being actively developed by companies like Wave Life Sciences, and some of these projects are moving forward into early clinical studies to evaluate their safety and effectiveness in human beings[45].

Preliminary Clinical Research Findings

While much of the current understanding of BDNF gene therapy stems from preclinical studies, preliminary clinical research is beginning to emerge. Initial trials assessing the safety and efficacy of AAV-mediated BDNF delivery are underway, focusing on patients with MC4R mutations and other forms of genetic obesity. Early results indicate promising outcomes regarding weight loss and improved metabolic parametersA recent study, for example, examined the effects of the melanocortin 4 receptor agonist Setmelanotide on patients with genetic obesity disorders associated with MC4R deficiency. Although Setmelanotide primarily targets the melanocortin pathway directly rather than utilizing BDNF signaling, it provides insights into how targeted therapies can yield significant results in this patient population . In

open-label trials involving patients with pro-opiomelanocortin (POMC) or leptin receptor (LEPR) deficiencies, participants experienced substantial weight loss alongside improvements in hunger scores after treatment with Setmelanotide.These findings suggest that similar therapeutic strategies targeting downstream pathways like BDNF may also yield beneficial effects for individuals with MC4R mutations. Ongoing clinical trials will be essential for determining the efficacy of BDNF gene therapy specifically for this population[46].

Wave Life Sciences (wavelifesciences.com) is advancing its innovative approach to obesity treatment through the development of WVE-007, a small interfering RNA (siRNA) therapy targeting the INHBE gene. This experimental treatment seeks to support fat burning while maintaining muscle mass in order to enable long-term weight loss. A single dose of WVE-007 has been shown in preclinical experiments in mice to provide weight reduction equivalent to that of semaglutide, a well-known drug for obesity, and to double the weight loss effect when taken in combination with semaglutide. Target engagement in adults with overweight or obesity will be evaluated for safety, tolerability, pharmacokinetics, and biomarkers in the next Phase 1 clinical trial, which is scheduled to start in Q1 2025. The promising preclinical data suggests that WVE-007 could represent a significant advancement in obesity treatment by potentially allowing for once or twice yearly dosing, thus improving patient compliance and outcomes[47].

Preclinical studies in mice have shown significant weight loss and improved metabolic markers when genetically modified adipocytes expressing an active form of the CPT1A enzyme are implanted, suggesting that CPT1A gene therapy has promising potential to treat obesity by increasing mitochondrial fatty acid oxidation. This suggests that CPT1A gene therapy should be used in conjunction with WVE-007 and Omega fatty acid conversion therapies to provide more targeted and efficient treatment strategies for adult and paediatric populations struggling with obesity and its complications.Gene therapy strategy: In an effort to improve fat burning, researchers are investigating the therapeutic potential of using gene therapy to increase CPT1A expression. Adipocytes that have been genetically altered to express a highly active version of CPT1A have been demonstrated to significantly reduce body weight and enhance metabolic parameters when implanted in mice. This method might provide a fresh way to fight obesity and related metabolic conditions like fatty liver disease and diabetes[48].

Importance of Genetic Profiling

The potential application of genetic discoveries in clinical practice to improve risk assessment and facilitate individualised treatment for obesity is gaining attention. Despite the identification of numerous genetic loci, each mutation has a comparatively minor influence. For example, just 0.34% of the phenotypic diversity in BMI in the overall population can be explained by the polymorphism at the FTO gene that is most significantly associated with obesity. The explained variation increases to 1.45% when all 32 GWAS variants are taken into account, with each extra risk allele causing a 0.17 kg/m2 increase in BMI. The average BMI of people with the fewest risk alleles is 2.73 kg/m² lower than that of people with the greatest risk alleles[49].

With figures for heritability ranging from 40% to 70%, it is clear that genetics play a considerable role in the genetic basis of obesity.Obesity can be classified as monogenic, caused by single-gene mutations, or polygenic, resulting from the combined effect of multiple genes. Genetic profiling helps identify specific variants or mutations that increase obesity risk. The existence of other unknown common and rare genetic variants, their small effects, the dependence on surrogate markers rather than causal variants with greater effects, and the disregard for gene-gene and gene-environment interactions are all reasons for the limited predictive power of genetic variants[50].

Role in Personalized Medicine in obesity management

A novel approach to obesity precision medicine stratifies the disease according to particular biological markers obtained primarily from high-throughput or "omics" assays (such as transcriptomics, microbiomics, genomics, and epigenomics), as well as from additional clinical, physiological, and behavioural traits.The idea of personalised preventive, diagnostic, and therapeutic approaches that take individual variability into account in an effort to enhance illness stratification and optimise treatment efficacy is known as precision medicine. The five objectives of precision medicine are to avoid disease progression, anticipate therapeutic success, predict disease progression, personalise care, and attain appropriate therapy adherence. To accomplish these goals, we must integrate information from 'omics assays with our current knowledge of obesity pathophysiology, taking into account the range of behavioural, psychological, and environmental components that contribute to the development of obesity[51].

Precision medicine and current evidence-based medical practice will be able to connect thanks to this integration.Research based on precision medicine is opening the door to individualised obesity treatment. Improved knowledge of biological variations has made it easier to create therapeutic strategies that may have a bigger effect on the results of treating obesity. Many of these techniques are still in the research stage today, and it is unknown how effective they will be as treatments.More confirmation studies are need to take into account or employ some of these obesity biomarkers as part of predictive models, even if the use of multi-omics evidence has provided a more thorough knowledge of the development of obesity. Optimising treatment outcomes for obesity through the integration of multi-omics data into precision medicine is the ultimate goal[52].

Future Directions

Treatment options necessitate a comprehensive approach, wherein psychological assessments can assist in refining the myriad of available interventions for obesity. It is evident that disadvantaged populations and those facing economic hardships encounter significant barriers to accessing these treatments. Merely emphasizing psychological evaluations will not suffice to address this epidemic without ongoing and substantial collaboration from both government entities and community organizations. Furthermore, it is crucial to prioritize personalized medicine and gene therapies to render obesity treatment accessible and affordable for all individuals, irrespective of their financial circumstances. Consequently, this report underscores

innovative strategies and advocates for the integration of modified successful interventions from the past to tackle this complex disease. We need to make sure this treatment is available to all whether you are rich or poor and also we need to assess the benefits of this treatments from multiple persepectives. Also we need to make the lifestyle changes that are necessary .The current gene therapies are at clinical level ,if successful they provide a viable treatment option for this population[53].

Conclusion

A protein called brain-derived neurotrophic factor (BDNF) controls hunger and energy balance.It is expressed in the gut, brain, and other tissues and is essential for neuronal survival and differentiation. Preclinical research has demonstrated the potential of gene therapy employing adeno-associated virus (AAV) vectors to restore BDNF signalling, leading to weight loss and enhanced metabolic health. BDNF's promise as a treatment target for obesity is further supported by the fact that it increases leptin sensitivity in the hypothalamus. To improve results for people with MC4R-related obesity, more research is necessary to improve these medicines and customise them based on genetic profiles.Precision medicine hasn't been used much for obesity, despite the fact that it may help prevent and treat prevalent multifactorial disorders. The degree of extra weight, the distribution of fat, and its problems are currently used to categorise obesity[54].

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