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Precision Medicine and Obesity

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Introduction

In the last decades, the prevalence of obesity has increased globally, reaching epidemic proportions[1]. Its worldwide prevalence has almost tripled between 1980 and 2016[2]. In the United States, in 2013–2014, the prevalence of obesity among Americans was 39%[1,3]. Obesity has been attributed to about $480 billion in increased medical spending[4].

The etiology, clinical presentation, and complications of obesity differ significantly from patient to patient, making it difficult to prevent and treat this disease. Within the current health care system, the treatment of obesity follows an algorithm that starts with lifestyle modification and later progresses to the use of pharmacologic agents, endoscopic devices and/or bariatric surgery based on the patient's response. Lifestyle modification is not always successful, and even when combined with behavioral therapy and pharmacologic agents, weight loss outcomes are not only modest but also vary among patients.

The rising prevalence of obesity and the lack of established and validated treatment options warrant the exploration of alternative therapeutic strategies that can complement current paradigms. Preferably, novel strategies would be personalized to the individual for enhanced effectiveness and tolerability in the form of precision medicine. Although there are many ongoing initiatives with this goal, much needs to be resolved before precision obesity medicine becomes common practice.

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1. What is precision medicine?

Precision medicine is constructed on the premise that most current therapeutic and prevention approaches for a certain disease are based on the average patient and do not take into consideration interpersonal variability. This approach can be successful for some people but not for others. Contrary to this one-size-fits-all tactic, precision medicine takes into consideration individual variability in genetics, metabolites, intestinal microbiome, and environmental factors that can affect all these, with the objective of predicting which disease treatment and/or prevention strategy will work better in which group of people[5].

The human genome sequencing and subsequent development of population genetics are the foundation of precision medicine. These tools have been used to help identify hundreds of gene variants associated with obesity and its related traits through genome-wide association studies (GWAS). The recent advances in high-resolution characterization of a variety of biological variants such as transcripts, proteins, metabolites, microbiota, epigenetic markers, among others, has expanded our capability to understand the conduits that link a person's biological idiosyncrasies to disease susceptibility.

Although precision medicine could potentially improve the prevention and treatment of common multifactorial diseases, its application for obesity has been limited to date. Currently, obesity is classified based on the degree of excess weight, fat distribution, and its complications. Approaches centered on data mining of high-resolution biotechnologies have the potential to identify subgroups without bias in order to generate new pathophysiologic hypotheses. Identifying specific subgroups may lead to gene-oriented treatments, more novel therapeutic strategies, and drug discovery and development.

2. Current Obesity Classifications

Traditionally, obesity classification is based on body mass index (BMI). Although all individuals with obesity have excess body fat, there are important heterogenic differences among this population. Anthropometric classification of obesity therefore, has limitations when it comes to guiding clinical decisions in patients. Research over the past decades has provided new knowledge that has led to identifying different subtypes among patients with obesity. These classifications have provided important information on underlying pathophysiologic mechanism driving obesity and its complications, and have helped pave the way towards precision obesity medicine.

- BMI: Obesity has been traditionally diagnosed by calculating the BMI (ratio of body weight in Kg and height squared in m^2). BMI allows classification of individuals by grade, from overweight to morbid obesity (Table 1)[6]. BMI correlates well with percentage of body fat, with the exception of people who have increased lean weight (e.g. body builders). However, because of obesity's remarkable heterogeneity, this index does not always discriminate the risk of metabolic abnormalities and complications that are frequently associated with obesity. For instance, although obese patients are as a group at a higher risk of comorbidities compared to normal-weight individuals, some obese patients may show no metabolic complications (i.e. the metabolically healthy obese)[7].

- Distribution of fat/Body shape: Various studies have shown that the common complications of obesity, such as cardiovascular disease, metabolic syndrome, dyslipidemia and type 2 diabetes mellitus, are more closely associated to the body fat distribution than to the absolute fat percentage. Central obesity, characterized by proportionally greater amount of fat in the trunk compared with the hips and lower extremities, has been associated with increased risk for the aforementioned obesity complications. On the other hand, lower-body adiposity is less associated with those complications [8,9]. This classification has led to some understanding of obesity pathophysiology, but its use in precision medicine has been limited to date.
- The Edmonton Obesity Staging system: This five-stage system classifies obesity considering physical, metabolic, and psychological parameters with the goal to determine the optimal treatment (Table 2)[10]. It was developed to assist in identifying and prioritizing individuals who would benefit the most from resource-intensive and aggressive management, allowing a more individualized approach. This system has been suggested to be a better mortality predictor compared to BMI [11].
- Genetics: Obesity can be classified into polygenic or monogenic disorders. The majority of obesity cases are multifactorial or polygenic, i.e. attributed to the interaction between multiple loci. Research has shown that there are many genetic factors that play a permissive role and when interacting with environmental factors result in obesity[12]. On the contrary, monogenic disorders are the result of a single mutated gene and account for the minority of cases of obesity (less than 1%). Clinically, monogenic disorders can be associated or not with a syndrome. In non-syndromic monogenic obesity, there are well characterized genes that play a role in energy homeostasis regulation by the leptin-melanocortin pathway[13]. In syndromic monogenic disorders, obesity presents in association other features such as dysmorphic features, cognitive delay and other abnormalities[14]. Understanding the genetics of a disease can potentially lead to developing genetics-based treatments, particularly for monogenic disorders.

3. Overview of Major Obesity Precision Medicine Initiatives

Through complex mechanisms, genetic and environmental factors impact the two processes that are key drivers of obesity: caloric intake and physical activity levels. Although genetic studies have helped untangle this complex landscape, genetic polymorphisms alone do not explain the obesity epidemic. Nowadays, high-resolution biotechnologies have helped characterize other biological variants such as transcripts, proteins, metabolites, microbiota, and epigenetic markers among others, that could potentially provide a detailed fingerprint of a person’s phenotype and how they might respond to different anti-obesity treatments. This knowledge can substantially improve the prediction, prevention and treatment of obesity. Here we summarize how these biological variants may be targeted to individualize obesity treatment.

Genetics

The heritability of BMI is between 40 and 70%[15,16]. GWAS for adiposity traits (waist-to-hip ratio, BMI, visceral adiposity, and total body fat among others) have so far identified >300 single nucleotide polymorphisms (SNPs). Table 3 lists the better characterized SNPs and their associated phenotype. Individually, these SNPs have a modest effect on the risk of obesity and simulation studies have shown that currently known SNPs do not account for more than 20% of variance in BMI[17,18]. The discovery of SNPs may potentially lead to the development of new preventative and therapeutic options to treat obesity. However, such developments will take time because they require a deep understanding of how a SNP influences the expression of target genes, and how these affect phenotype. At the moment, this information is largely unavailable for most SNPs.

The potential of genetics-directed therapy can be exemplified with monogenic obesity disorders such as in the case of leptin and proopiomelanocortin (POMC) deficiency. Recombinant leptin and Setmelanotide (a melanocortin-4 receptor agonist, receptor through which POMC signals) used respectively in patients with leptin and POMC deficiency have resulted in significant weight loss[19,20]. Interestingly, both treatments have been used in common obesity with variable results, suggesting that some SNPs may have common mechanistic gene of action[20,21]. If these SNPs are identified, we could potentially recognize a subset of patients with common obesity that may benefit from these treatments.

Gene by environment interactions

Studies have suggested that when individuals have a genetic predisposition to obesity, they are more prone to gain weight when they are exposed to hostile environments. Because SNPs have modest effect size on obesity traits, researchers have aggregated several risk-increasing SNP variants into genetic risk scores. Genetic risk scores have a superior power compared to individual SNPs to detect the interaction between genes and environment[22]. Data suggest that the following factors amplify the association of genetic risk scores with BMI: low socio-economic status, chronic psychosocial stress, decreased sleep duration, gender, increased consumption of sugar-containing beverages, increased fried food intake, decreased physical activity[12].

The clinical application of this knowledge is still limited. Data from gene by environment interaction studies have provided ground to commercially available GWAS-based genetic profiling. GWAS-based genetic profiling is now easily accessible for individuals to learn their risk of obesity or difficulties with weight loss. Although this has potential for precision-medicine, data suggest that genetic risk-based knowledge does not change behavior[23]. Specifically, for obesity, although genetic risk based counseling increased the participant's motivation to make lifestyle changes, this did not translate necessarily in weight loss[24].

Epigenetics

The rapid emergence of obesity epidemic is not fully explained by genetics, which could not have changed dramatically over such short period of time. Unlike genetics, many key environmental factors have changed over this timeframe, most notably diet and physical

activity. Environmental factors interact with our genes through epigenetic modifications of the genome that can alter gene activity[25]. Epigenetic changes are dynamic and removing the inducing factor(s) can often reverse these changes.

There are many studies providing evidence for a strong correlation between epigenetic modifications with obesity traits. For instance, researchers have analyzed methylation patterns of genes that may participate in obesity pathophysiology such as eating behavior, glucose metabolism, lipid metabolism, adipogenesis, circadian rhythm, and inflammation, among others. Data show that methylation of these genes correlate with obesity, obesity traits and its complications[26]. Emphasizing the importance of epigenetic modifications in obesity, interventional studies have demonstrated that physical activity and bariatric surgery alter epigenetic modification patterns that are sometimes tissue-specific and may consequentially result in beneficial metabolic changes [27,28].

There are currently relatively inexpensive microarrays permitting high-throughput epigenetic changes profiling. Although these changes may be highly relevant in the pathophysiology of obesity, their net effect in human populations has yet to be quantified. This information taken together suggests that epigenetic markers by themselves may not be enough to come up with precision obesity therapies. However, the effect size of the correlation with obesity traits could potentially be informative as a prognostic and diagnostic tool. Table 3 lists the better characterized epigenetic modifications and their associated phenotype.

Metabolomics

Metabolites are elemental units of cellular function. Disruption in their regulation results in changes that can have clinical ramifications. Consequently, the metabolome contains information that can provide insights into the mechanisms of a specific disease. Metabolomics is a tool aimed at detecting and measuring changes in metabolite profiles in response to physiological or pathological conditions. Researchers have identified profound disruption of the metabolome in obesity as well as metabolic signatures of this condition that are strongly correlated with BMI, other obesity traits and metabolic co-morbidities[29]. Table 3 lists the better characterized metabolic pathways disruptions and their associated phenotype. Within obese patients, studies in this field have been able to identify different metabolomic patterns between healthy obese individuals and obese individuals with metabolic complications such as cardiovascular disease, dyslipidemia, metabolic syndrome and diabetes. Furthermore, studies show that in healthy obese and even healthy lean individuals, an abnormal metabolome is associated with increased cardiovascular events compared to controls matched for BMI and with opposite metabolomes[30].

In this era of precision medicine, researchers have investigated the potential of weight loss interventions based on metabolome signatures. Published data suggest that weight loss variation among individuals following a low calorie diet can be predicted by their baseline metabolic profile[31,32]. Although this field is actively evolving, metabolomics can identify clinically meaningful heterogeneity in obesity that could potentially lead to the identification of a metabolic fingerprint that cannot only help phenotype a patient but can also help select certain patients for certain specific therapies.

Microbiome

Gut microbiome genes have unique functions that complement the genetic catalog of humans[33]. Growing evidence reveals that the gut microbiome is sensitive to dietary, environmental and host factors. These factors can alter microbiome very precisely, resulting in metabolic changes that can consequently cause a disease. Despite the mounting evidence establishing a robust association between alterations of the gut microbiome and obesity, the exact underlying mechanisms have yet to be characterized.

In animal studies, the gut microbiome was observed to regulate the host's ability to harvest energy from food[34]. Further work has provided direct evidence of a transmissible obesity microbiota[35] where opportunistic pathogens could participate in the development of obesity by altering host gene expression and by inducing insulin resistance mediated by metabolic endotoxemia[36] or by altering the brain-gut-axis[37]. On the contrary, certain bacteria clusters have been associated with reduced risk of cardio-metabolic disease by having genomes with higher capability for methane production and mucin degradation, for instance[38].

Most human data come from studies that have compared the gut microbiome of exceedingly different populations: individuals from westernized and industrialized countries versus individuals from hunter-gatherer societies. The main difference is in the diversity of the gut microbiome, with the former having decreased diversity compared to the latter[39,40]. Weight loss intervention clinical studies have shown shifts in the gut microbiome that have been implicated in the resulting reduction in weight as well as improved metabolic function[41,42]. Specific microbiome changes associated with obesity or the risk of developing obesity include higher *Bifidobacterial* and lower *Staphilococcus aureus* concentrations, and an increased in the ratio of *Fermicutes:Bacteroidetes*, with the latter increasing abundantly with weight loss[43,44].

Microbiome manipulation could lead to prevent and/or treat obesity. Approaches could potentially include designer probiotics and fecal matter transplant. Currently, there is little information available on the efficacy and safety of probiotic formulations[45]. In terms of fecal matter transplant, few human studies have shown that this treatment is efficacious for metabolic disorders, results have been variable and therefore utility is limited[46]. Currently, any potential ability to foster the growth of 'healthy' bacteria through diet changes could be highly valuable in optimizing the use of nutrition to combat disease. Achieving this intermediate objective could provide a practical alternative, while serving as a stepping stone as we continue to investigate the physiologic (or pathophysiologic) roles of singular microbes.

Pharmacogenomics

Pharmacogenomics studies how genetics affect an individual's response to particular pharmaceutical compounds. This field integrates pharmacology and genomics to develop effective, safe medications and dosages that are tailored to variations in an individual's genes. Pharmacogenomics could play an important role in obesity management. First of all, there are a number of medications that results in weight gain as an adverse effect [47], and researchers have demonstrated the impact of genetic variants and the risk of metabolic

adverse events associated with weight gain-promoting medications [48–52]. Second of all, the effect of anti-obesity medications on weight loss is highly variable among patients[53] and studies have shown that gene variants may partially explain the variability in response to treatment. For instance, genetic variants in the insulin receptor gene and the GLP-1 receptor gene have been associated with differential weight loss in those treated with topiramate and liraglutide, respectively [54,55]. No genetic variants associated with differential weight loss have been identified for the other currently FDA-approved anti-obesity medications.

Personalized pharmacotherapy for obesity has been slowly adopted by clinical practice; however, emerging evidence has shown its substantial potential. Incorporating genetic variants that may affect the susceptibility of an individual to drug-induced gain weight and/or the susceptibility for anti-obesity drug weight loss into obesity medicine can be useful in drug selection and/or dose optimization, positively affecting the efficacy and safety of pharmacologic agents for a determined individual.

Nutrigenetics and Nutrigenomics

Diet is an important environmental factor that interacts with genes. Furthermore, nutrients do not affect individuals in the same way. With the information currently available, there has been a growing necessity to improve personalized nutrition to treat obesity and its associated medical conditions taking into consideration the interaction between diet and the genome. From this interest, the fields of nutrigenetics and nutrigenomics have evolved. Nutrigenetics is the science of the effect of genetic variation on dietary response. On the other hand, nutrigenomics is defined as the role of nutrients and bioactive food components in gene expression[56]. Exploitation of this information is essential to understanding how nutrient-gene interactions are affected by the genotype, with the ultimate goal of developing targeted and clinically useful dietary and lifestyle recommendations for optimal health and disease prevention. Table 3 lists the better characterized SNPs-diet interactions and their putative disease risk.

Studies have demonstrated the importance of these fields in individualizing obesity patient's care. For instance, researchers have developed personalized weight reduction programs based on calorie-controlled diets using gene variants that are involved in metabolism. In one study, participants receiving dietary advice to optimize nutrient intake tailored to their genotype lost more weight during the weight loss period, and also had better weight loss retention over time[57]. Although these results are promising, larger studies have failed to demonstrate the interaction between genetic variants, dietary recommendations and weight loss[58].

Clinical quantitative traits

Improving phenotyping in large numbers of patients with obesity is crucial to elucidating the factors that account for variability in response to the different treatments for obesity. In this respect, researchers have identified the following quantitative traits in food intake regulation that may be specifically targeted by current available therapies: satiety and satiation, gastric motility, behavioral influences, and gastric sensorimotor factors [59]. In a proof of concept clinical trial, these quantitative traits predicted response to anti-obesity

pharmacotherapy[60–62]. These data suggest that phenotypic subgroups identified based on pathophysiological mechanisms offers the opportunity to select patients for anti-obesity drugs based on the mechanisms of action of the medication. This approach could potentially enhance drug efficacy.

4. Challenges

Precision medicine implementation in clinical practice poses various challenges. First, precision medicine practice contrasts with the practice of evidence-based medicine that has modeled the one-size-fits-all approach. This traditional approach has provided inadequate solutions for outliers that can potentially be better served by precision medicine. Responsible data sharing will permit bridging of both approaches.

Second, health practitioners may be skeptical about ordering specialized testing that may allow a better characterization of a condition. Furthermore, in health professions' curricula, topics on this individualized approach are scarce. The achievability of the obesity precision medicine will depend on the cooperation of all actors involved.

Third, although there exists a vast amount of information that will help pave the way to obesity precision medicine, there is a knowledge gap between the association of biological markers and obesity, and the mechanisms behind these associations. This gap needs to be filled in order to be able to develop specific interventions that will facilitate individualized medicine for obesity.

Fourth and last, precision medicine research depends deeply on large and interconnected cohorts and biobanks. These data are highly sensitive and could be broadly disseminated to address research questions that cannot yet be conceived. Emphasis should be placed on protecting privacy, while facilitating the responsible and safe storage, transmission, and use of data.

Summary and conclusions

Current obesity therapies are still based on the assumption that one-treatment-fits-all. This treatment strategy varies in its effectiveness from individual to individual and suggests that specific patient characteristics dictate risk factors susceptibility and treatment response. Precision medicine has offered a new ground that theoretically provides the basis that will allow individualized treatments based on data obtained from bio samples, digital images, wearable devices and conventional data from medical records.

Although there have been major advances in this field, much needs to be resolved before precision obesity medicine becomes a prevailing practice. Current available information gathered from genetic, epigenetic, metabolic, pharmacologic, microbiologic and clinical studies has revealed that there are numerous intermediary processes that contribute to obesity. These intermediary processes have provided an outline to understand, although only partially, the pathophysiologic mechanisms behind the heterogeneity of obesity and its clinical consequences. Some of these processes have or are currently being targeted to individualize obesity therapy with some success.

Although the evolving arena of precision medicine grants new opportunities for fighting obesity, it also presents with new challenges related to integration of data, health literacy and data privacy. As we continue to gather information, new disease classifications, which can be coupled with more effective, cheaper and with fewer side effects, will be defined.

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Key Points

1. Obesity has reached epidemic proportions. Weight loss outcomes with current available therapeutic options are not only modest but also very variable among patients. Precision medicine is an emerging arena that offers new opportunities to dealing with this condition.
2. High-resolution biotechnologies have provided evidence that there are numerous intermediary processes that contribute to obesity.
3. These processes have led to partially understand some of the pathophysiologic processes involved in obesity and its clinical consequences and have been targeted to individualize obesity therapy with some success.
4. As we continue to gather information, it is anticipated that we will be able to substantially improve the prediction, prevention, and treatment of obesity.

Synopsis

The highly variable response to obesity therapies justifies the search for treatment strategies that are best suited to individual patients to enhance their effectiveness and tolerability via precision medicine. Precision Medicine development in recent years has been driven by the emergence of powerful methods to characterize patients (‘omic’ assays). Current available information has revealed that there are numerous intermediary processes that contribute to obesity and have provided a framework for partially comprehending the mechanisms behind the heterogeneity of obesity and its clinical consequences. Some of these processes have or are currently being targeted to individualize obesity therapy with some success.

Table 1.

Body Mass Index (BMI) Classification

Weight status	BMI (kg/m^2)
Underweight	<18.5
Normal range	18.5–24.9
Overweight	25.0–29.9
Obesity class I	30.0–34.9
Obesity class II	35.0–39.9
Obesity class III	⩾40

Table 2.

The Edmonton Obesity Staging System

Stage	Description	Management
0	No apparent obesity-related risk factors, no physical symptoms, no psychopathology, no functional limitations and/or impairment of well being	Identification of factors contributing to increased body weight. Counseling to prevent further weight gain through lifestyle measures including healthy eating and increased physical activity.
1	Presence of obesity-related subclinical risk factors (e.g., borderline hypertension, impaired fasting glucose, elevated liver enzymes, etc.), mild physical symptoms (e.g., dyspnea on moderate exertion, occasional aches and pains, fatigue, etc.), mild psychopathology, mild functional limitations and/or mild impairment of well being	Investigation for other (non-weight related) contributors to risk factors. More intense lifestyle interventions, including diet and exercise to prevent further weight gain. Monitoring of risk factors and health status.
2	Presence of established obesity-related chronic disease, moderate limitations in activities of daily living and/or well being	Initiation of obesity treatments including considerations of all behavioral, pharmacological and surgical treatment options. Close monitoring and management of comorbidities as indicated.
3	Established end-organ damage such as myocardial infarction, heart failure, diabetic complications, incapacitating osteoarthritis, significant psychopathology, significant functional limitations and/or impairment of well being	More intensive obesity treatment including consideration of all behavioral, pharmacological and surgical treatment options. Aggressive management of comorbidities as indicated.
4	Severe (potentially end-stage) disabilities from obesity-related chronic diseases, severe disabling psychopathology, severe functional limitations and/or severe impairment of well being	Aggressive obesity management as deemed feasible. Palliative measures including pain management, occupational therapy and psychosocial support.

From Sharma AM, Kushner RF. A proposed clinical staging system for obesity. *International Journal of Obesity.* 2009;33(3):289–295.

Table 3.

Common SNPs, Epigenetically Modified Genes, SNPs-diet Interactions and Metabolic Pathways Associated with Obesity and Obesity Traits.

SNPs [12]	
Gene	**Phenotype**
FTO	BMI, waist circumference, fat percentage, extreme obesity
MC4R	BMI, waist circumference, extreme obesity
MC3R, SLC6A14	Obesity
BDNF, TMEM18	BMI, extreme obesity
POMC, NEGR1, PCSK1, GNPDA2, MAP2K5, SEC16B	BMI
Epigenetically modified genes [26]	
Gene	**Phenotype**
POMC, NPY, SLC6A4, MCHR1	Overall obesity
FTO, LPL, IRS 1, TMEM18	Fat distribution
PPARG	Percentage body fat
LEP	Overall obesity, fat distribution, BMI

SNPs-diet interactions [63]		
Gene	**Diet Interaction**	**Putative disease risk**
FTO	High Fat and High carbohydrate	Obesity
LCT	Dairy products	
PPARG, G1PR	High fat	
TXN	Low vitamin E	Abdominal obesity
MC4R	Western dietary pattern and high saturated fatty acids	Metabolic syndrome
APOB	High fat	
TCF7L2	High saturated fatty acids	
APOC3, APOA1	Western dietary pattern	

Deregulated metabolic signatures [64]	
Metabolic pathway	**Phenotype**
Branched-chain amino-acid metabolism	Obesity and insulin resistance
Androgen synthesis	Childhood obesity

Data from Refs [12, 26, 63, 64]