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REVIEW ARTICLE

The roles of personalized nutrition in obesity and diabetes management: a review

Reihaneh Zeinalian[1] · Shonaz Ahmadikhatir[1] · Ensieh Nasli Esfahani[2] · Nazli Namazi[3] · Bagher Larijani[4]

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Abstract

Background & Aims Nutrition is one of main environmental factor affecting obesity and its related complications such as diabetes and dyslipidemia. Due to growing prevalence of obesity across the world, it seems that nutritional advice alone is not able to combat this health problem. The present overview aimed to summarize the roles of personalized nutrition (PN) in obesity and diabetes management.

Methods Scopus, PubMed and Google scholar were searched up to February 2021 to find relevant studies with English language in which the roles of PN in obesity and diabetes management were examined.

Results Recent evidence revealed the importance of gene-environment interactions for management of diabetes mellitus and obesity. Moreover, microbiome research showed that personalized diet based on a combination of clinical and microbial features is likely to improve responses to therapeutic interventions. Epigenetics as well as genetic and environmental factors can also contribute to the treatment. In addition, articles showed significant roles of epigenetics and gut microbiome on providing an individualized diet for obese and diabetic patients.

Conclusion PN compare to conventional diet can better improve metabolic status in obese and diabetic patients. Considering genetic differences and microbiome patterns along with environmental factors and their interactions are recommended for obesity and diabetes management. This approach can increase success in promoting health and preventing complications related to diabetes and obesity.

Keywords Precision Medicine; Nutrition therapy · Gut Microflora · Type 2 diabetes · Obesity

Introduction

Obesity is a global health problem that its prevalence is growing dramatically across the world [1]. The World Health Organization (WHO) estimates that around 700 million adults are obese in the world [2] and a remarkable number is added to the population annually [3]. This can increase the prevalence of metabolic complications such as metabolic syndrome, insulin resistance, hypertension, dyslipidemia and type 2 diabetes (T2DM) [4]. Based on the International Diabetes Federation (IDF) reports, 1 in 11 adults aged 20–79 years (463 million people) suffer from diabetes and 1 in 2 adults with diabetes (232 million people) have remained undiagnosed [5].

To prevent and manage obesity and its related disorders, nutritionists have been using the medical nutrition therapy (MNT) [6] along with other medical interventions. Increasing tendency to take unhealthy diets containing high fat and sugar food, low fruit, vegetables, and whole grain following the industrializations are observed in the recent decades [7]. Such dietary habits play pivotal roles in weight gain and other metabolic disorders. It was expected that nutritional advice to adhere to healthy diet and lifestyle and related interventions can blunt this growth. However, based on this

✉ Nazli Namazi
nazli.namazi@yahoo.com

1 Faculty of Nutrition and Food Sciences, Tabriz University of Medical Sciences, Tabriz, Iran

2 Personalized Medicine Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

3 Diabetes Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

4 Endocrinology and Metabolism Research Center, Endocrinology and Metabolism Clinical Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran

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rising prevalence of obesity, it seems nutritional advices alone cannot be an effective approach. In fact, instead of only a generalized form of nutritional recommendations, a personal form considering genetic, personal differences, environmental conditions and their interactions should be taken into account [8]. Accordingly, personalized nutrition (PN) that considers the interactions between genetics, environmental and personal characteristics such as eating habits, behaviors, physical activity, and microbiota is proposed for obesity and other metabolic disorders.

Although several earlier review articles [9–11] have provided evidence on the roles of PN in obesity and diabetes management, mainly they focus on one aspect of PN (eg. Interactions between genetic or gut microbiota with environmental factors) and they had not been a multi-dimension review. Accordingly, it seems that providing an overview focusing on various aspects of PN can be helpful to shed light on the roles and importance of PN in disease management. Thus, in the present review we aimed to overview the recent and available evidence on the role of PN in obesity and T2DM management.

Method

To collect the relevant articles published in English language, we searched Scopus, PubMed and Google scholar up to February 2021, using the following main keywords and their synonyms: "personalized nutrition", "Gene-nutrient interaction", "nutrigenomic", in combination with "obesity " OR "type 2 diabetes".

Obesity, diabetes and personalized nutrition

Despite the success of health care in the treatment and control of infectious and acute diseases, it seems that health care has not been able to succeed in the management or cure of non-communicable diseases [12]. Non-communicable diseases such as obesity, diabetes, cancer, cardiovascular and pulmonary disease are affected by lifestyle and other environmental factors [13]. For example, in 2015, according to available statistics, 10% of the world's population was obese [14]. Although there is debate about the cause of this condition, it seems that unhealthy nutrition and lack of physical activity and obesogenic environment play an important role in its occurrence [15]. But the environment is not the only cause. According to studies, genotype also plays a role in this situation. In the last several decades, it have been identified more than 50 candidate genes for obesity [16]. Many studies based on nutrigenetics or nutrigenomics are underway to design PN to address the problem of obesity [17, 18]. T2DM is another major health problem that has quadrupled over the past four decades [19], as obesity has increased [20]. T2DM is a multi-genetic disease, but the transcription factor 7-like 2 (TCF7L2) gene is a major candidate for susceptibility to the disease. This gene is responsible for regulating insulin secretion and sensitivity [21]. The nutrigenetics or nutrigenomics studies examine the effect of nutrients on this gene [22, 23]. Due to the complexity of T2DM, this disease is a major challenge to be controlled by the current treatment strategies [24, 25].

PN with various aspects have been assessed in obesity and diabetes management that main views have been provided in the present study. Generally, genetics and gut flora play key roles in suggesting personal nutrition recommendations. Therefore, paying attention to these factors are valuable to achieve success in disease management. The effects of various genes and polymorphisms are observed in the studies on diabetes and obesity and their related metabolic pathways that are mentioned below:

Personalized nutrition and genes

Based on the findings of genome-wide association studies (GWAS), various genes are involved in the pathogenesis of obesity. Some of these genes are as follows: FTO, LEP, NEGR1, FAIM2, THEM18, BDNF1, LEPR, POMC, PCSK1, MC4R, GPR24, NROB2 and ADRB3 [26]. In addition, a number of genes are directly or indirectly involved in the metabolism of carbohydrates and lipids. Some are involved in encoding the proteins of carbohydrates and lipid taste receptors. Based on evidence, several genes are participating in encoding lipid transporters proteins or digestive enzymes in starch and milk. The roles of genes in energy intake or storage, and food reward systems and regulating the mechanisms derived from gut flora have been also revealed [27].

Studies showed that CD36 rs1761667 and TAS1R2 rs35874116 are associated with the consumption of dietary fats and carbohydrates. The link between *FABP2 gene (rs1799883)* and hypertriglyceridemia is indicated and *FTO rs9939609* can increase body fat. High AMY1 copy number protects the body against obesity, while lactase persistence contributes to the body's ability to consume saturated fat in dairy. Furthermore, *CD3MTHFR rs1801133* is associated with hypercysteinemia. Evidence revealed that *DRD2 rs1800497* is likely to interact with the brain–gut microbiota axis, promoting dysbiosis, obesity, and negative emotions [27].

Notably, the strongest gene studied in T2DM is the TCF7L2 gene and TCF7L2 rs790314 C > T polymorphism that associated with the risk of T2DM. Based on data of PREIMED study, the TCF7L2 gene rs790314 TT homozygotes are prone to diabetes, and it seems that the Mediterranean diet can reduce its genetic risks [28].

In summary, after ingestion, complex carbohydrates and lipids in food are broken down by AMY1A oral cavity in

Saliva and Oral lipases, and at this stage, taste perception genes, TAS1R2 for sweets and receptor CD36 for fat, are activated. Brain DRD2, modulated by the neurotransmitter dopamine, is activated to integrate the hedonic nature of eating. Carbohydrate and lipid digestion continue in the stomach and intestines. Milk lactose is hydrolyzed by LCT into glucose and galactose; FABP2 transports long- chain fatty acids to assemble chylomicrons. The bidirectional gut microbiota– brain axis will operate to modulate hunger/ satiety, and emotions related to food reward with gut microbiota components [27]. In addition to the mentioned genes, the FTO / alpha-ketoglutarate-dependent dioxygenase gene is involved in fat storage in adipose tissue, or MTHFR has a nutritional and epigenetic effect on gene expression, or Apo B48 and Apo E are needed to move chylomicrons from the gut to the liver or fat cells by chylomicrons, whereas VLDLs contain ApoB100 and ApoE. HDL-C assembly will require ApoA1 and cholesterol efflux transportation mediated by ABCA1, a key function in macrophages to avoid the formation of foam cells and eventually arteriosclerosis. Thus, hypertriglyceridemia is caused by the interaction of dietary components and various genes that are involved in different stages of food metabolism, and this hypertriglyceridemia is the basis for the development of insulin resistance and T2DM [27].

Genetic and Carbohydrate metabolism

Amylase Alpha 1 Salivary alpha-amylase (EC 3.2.1.1) is a protein secreted in saliva to break down carbohydrates into maltose disaccharides. In humans, the amylase cluster gene is located on 1p21.1 and includes three salivary genes AMY1A, called ID: 275, AMY1B and AMY1C, two pancreatic α- amylase genes (AMY2A and AMY2B), and a related pseudo-gene (AMYP)[29]. Studies have indicated that the average number of copies of the AMY1 gene in populations consuming more starch is higher than those consuming less starch. This may reflect the effect of natural selection [30]. Recent studies suggested a possible association between salivary alpha-amylase content, body mass index (BMI), amylase enzyme activity, and insulin resistance with copy number variation (CNV). Low AMY1 CNVs are also linked with HOMA- IR in asymptomatic Korean men [31]. This may be due to the effect of salivary amylase on post-meal cephalic insulin secretion. This improves glucose tolerance [30]. According to another study, the relationship between low AMY1 and obesity is the fermentation of the microbes of the colon oligosaccharides into short-chain fatty acids, which can affect negatively energy uptake [30]. Meanwhile, two studies conducted in Portuguese and Mexicans showed that high copy number of the AMY1 gene could prevent obesity in children and adolescents [32, 33].

Lactase Intestinal enzyme lactase-polarizing hydrolase (EC 3.2.1.62) breaks down lactose, which is abundant in mammals in the intestines of infants and children. LNP takes place after weaning, a normal physiological phenomenon [34], a downregulation of lactase transcriptional activity and lactase production. But in northern European and Africa, adult LP is recognized as a recent evolutionary trait [35]. This trait has been associated with several allelic polymorphisms at the premotor region of LCT. The most studied SNPs are -13,910 C > T (rs4988235) and—22,018 G > A (rs182549), located in the noncoding region of the neighboring MCM6 gene [27]. However, cow's milk consumption in LNP adults needs further investigation and may be a concern during obesity. In the study conducted in Mexico, it was found that LNP specificity in native Amerindian was higher than that in the genetically admixed subjects with European ancestry. Amerindian Mexicans had higher LP and showed a higher dyslipidemia profile by consuming more milk and saturated fat [36].

Genetic and Lipid Metabolism

Apo-B Apo-B is involved in the catabolism of chylomicrons, very low-density lipoproteins (VLDL-C) and LDL-C and it acts as a ligand for a low-density lipoprotein receptor (LDLR) [37]. The APOB gene (ID: 338) is highly polymorphic and has about 5,000 polymorphic sites. According to the study by Niu et al., the two polymorphisms (rs693 (G > A) and rs17240441 (insertion / deletion)) are associated with triglycerides, total cholesterol and high levels of LDL-C [38].

Apo-E Apo-lipoprotein E (Apo-E) is involved in fat metabolism and can be considered in the development of diabetes. It is mapped at chromosome 19 and is a polymorphic gene, possessing three main alleles (E2, E3, and E4) and six genotypes (E2/2, E2/3, E2/4, E3/3, E3/4, E4/4) [39]. Apo E plays an important role in the development of VLDL-C, intermediate density lipoproteins (IDL), HDL-C and chylomicrons [40]. Apo E also plays a role in regulating plasma and cellular lipid concentrations, acting as a ligand for binding to membrane lipoprotein receptors [41]. In patients with T2DM, high atherogenic levels and insulin resistance are strongly associated with dyslipidemia [40].

Studies have shown that the distribution of APO-E alleles / genotypes in human populations is heterogeneous [42], and this variation in distribution is associated with the differences in the prevalence of dyslipidemia along with other risk factors such as diet and physical activity [43].\

FABP2 FABP2 is a cytosolic protein that is widely expressed in small intestinal epithelial cells and has a high affinity to absorption and intracellular long-chain and unsaturated fatty

acids transport [44]. According to some studies, there are polymorphisms in the FABP2 promoter region that can trigger transcription. These polymorphisms affect body composition, insulin sensitivity, and the risk of T2DM [45, 46]. De Luis et al., found that replacing the Ala54Thr isoform (rs1799883) with the Ala54 in morbid obese patients on FABP2 was more likely to alter insulin resistance, leptin and adiponectin levels [47]. It also appears that in obese individuals with moderate fat diets, the Thr54 allele responds better to weight loss and reduction in BMI, waist circumference, waist to hip ratio, and reactive protein c levels than the Ala54 allele [48]. In contrast, a study conducted in people with T2DM showed that dietary interventions with low glycemic index in both carriers Ala54 and Thr54 decreased the plasma triglycerides and cholesterol. But the response of allele carriers Ala54 was better [49].

ABCA1 ATP-binding cassette subfamily A member1 (ABCA1(is a protein, expressed in hepatocytes and enterocytes and is involved in reverse cholesterol transport, HDL-C biosynthesis and cellular cholesterol homeostasis. The study performed in Mexico demonstrated that type R230C (rs9282541) is involved in changing BMI, the concentration of HDL-C, and obesity-related diseases [50]. However, another research showed that this type is associated with low levels of obesity and T2DM, which may be due to the evolutionary adaptation of the Native American Mexican population [51]. Currently, studies have focused on other types of ABCA1 variants affecting lipid profiles in different populations around the world [52, 53]. One study in Mexico found that R230C carriers underwent dietary intervention on regional foods such as nopal, chia seeds, soy protein and oatmeal, improved body weight, triglyceride levels, adiponectin and glucose tolerance [54]. In addition, R230C carriers on a low-saturated fat, soy protein and fiber diet also had better HDL-c reductions than those with the R230R genotype [55]. Based on these results, it is better to consider the genotype and ethnicity of individuals in designing a diet and achieving better therapeutic results.

Taste Perception Taste receptor genes are responsible for understanding taste and even toxicity of food with sensing bitter taste. They interact with food molecules and are actually responsible for tasting the main components of food. Taste perception is a genetic trait with high variability throughout populations. Genetic variants in taste receptors are known to modulate inter-individual differences in taste perception, which may also affect dietary preferences and chronic disease development [27, 56].

TAS1R2, is a protein, expressed in taste receptor cells and senses natural sugars and non-nutritive sweeteners [57]. In the study conducted on overweight and obese people in Mexico, intake of carbohydrates, fiber, grains and vegetables in whom with Val191Val genotype (rs35874116) was greater than other polymorphism and associated with a higher risk for hypertriglyceridemia (32). According to previous studies, high-carbohydrate diets caused hyper-glycerides, which ultimately lead to obesity and T2DM, by activating de novo lipogenesis, reducing the oxidation of muscle fatty acids, and reducing the secretion of circulating fat [58].

The CD36 protein is another gustatory receptor in taste buds that carries long-chain fatty acids and oxidized lipids [59]. Two SNPs, rs1761667 (G > A) and rs1527479 (T > A) in the CD36 gene, can increase fat consumption by disturbing the taste perception of consumed fats [60]. The TT genotype of CD36 rs1527479 was associated with insulin resistance, higher fasting glucose concentration, and T2DM [61]. Moreover, an association is observed between the A allele of CD36 rs1761667 and higher intake of fat portions and high serum cholesterol [62].

Food Reward

Food reward system is one of the neuro-transformation processes of physiological processes performed by the neurotransmitter called dopamine [63, 64]. This path takes place through binding to the dopamine receptor D2 (DRD2). DRD2 is a G- coupled protein with Ser/ Thr kinase activity codified by the DRD2/ ankyrin repeat domain and content kinase 1 (DRD2/ ANKK1) gene (ID: 1813) [65]. In humans, decreased dopamine and DRD2 activity cause overeating [66]. In the study by Baik et al., the A1 allele of this protein was found to increase L-dopa activity and could modify food reward effects [66] which showed different results in different populations [67]. The synonymous C957T polymorphism (rs6277) located in exon 7 of the DRD2 gene is another genetic polymorphism. Carriers of the cc genotype showed higher reward sensitivity scores as compared with t allele, sucrose and carbohydrates consumption [68].

FTO/ alpha- ketoglutarate Dependent Dioxygenase The gene of Fat Mass and Obesity (FTO) is associated with a genetic factor in obesity [69]. Although many genes are involved in the pathogenesis of obesity, the FTO gene is the best candidate for obesity [70]. Studies showed association of this gene with T2DM [71], but its biological function is still unknown. It appears that the association between FTO rs9939609 / rs8050136 and type 2 diabetes is related to the region [72]. The FTO belongs to superfamily of Fe (II)- and 2-oxoglutarate-dependent dioxygenases. This gene is involved in the de-methylation of nucleic acids [73]. The FTO gene (ID: 79,068) is found in all tissues of the body, but is higher in the hypothalamus, which controls food intake [74]. Evidence revealed that this gene is involved in fat consumption, increasing appetite, reducing satiety, food choice,

eating habits and loss of eating control [27]. The FTO was the first gene to be identified in relation to BMI degree, and this association was found mostly in European, Asian and African populations [75]. Recent studies have shown that Mediterranean diet reduces the risk of obesity in carriers of high-risk FTO alleles [76]. FTO rs9939609 T/A polymorphism is also related to BMI with no link with total energy intake [77].

Personalizing nutrition and microbiome

Neutrigenomics obtains and integrates a person's personalized nutritional omex profile. The individual microbiome is also included in this set and forms the gutoma [78].

Despite the specific and rigid structure of the genome, the microbiome has the property of flexibility, influenced by environmental factors [79]. Diet, as the most important environmental factor, regulates the microbial composition of the intestine and its functional potential. Thus microbiome can be used as a tool to induce microbiome changes for therapeutic purposes [6].

Human microbiota includes 100 trillion microorganisms that share symbiotic properties with the host which even more numerous compared to those contained in the human genome [27, 80]. In gastrointestinal (GI) tract mainly large intestine at least 1014 bacteria have been identified [81]. Variety and abundance of gut flora species depend on many factors such as individual genetics, mode of delivery, demographic characteristics, immune system, gastrointestinal secretions, level of different blood molecules or red blood cell count, consistency stool, medical history, geographical, social, economic and health conditions, smoking, taking antibiotics, and some other medications [82–85].

Studies showed that microbiota can be effective in weight gain and obesity through several interconnected pathways, such as energy harvesting and the production of microbial metabolites [86]. In humans, prolonged weight gain of more than ten years has been associated with low intestinal microbiota diversity, exacerbated by low dietary fiber intake [87]. The intestinal microbiota and brain axis can integrate information from the hypothalamic–pituitary–adrenal system of the hunger satiety circuitry and the dopaminergic reward system with the microbiota in order to obtain energy and seek food from the environment [27]. According to studies, the genetic composition of the host, stress levels, diet composition, negative emotions related to depression and anxiety affect the axis of the brain and intestines [88].

Effects of food on the gut microbiota Diets have been shown to be effective in altering the composition of the microbiome as an environmental factor. Animal-based diets increase the frequency of bile-resistant species, while plant-based diets increase the frequency of plant polysaccharide-fermenting species [79]. Reducing carbohydrates within 24 h can also reduce bacteria that destroy food fibers [89]. In contrast, the study by Deschasaux et al., demonstrated that changes in microbiome composition depend more on the ethnicity and geography of the host rather than diet or indicators of metabolic disorder [90]. In addition, animal studies showed that sugar substitutes may have negative effects on the gut microbiota and disrupt its diversity [91]. Sucralose consumption in mice for 6 month increased bacterial pro-inflammatory genes expression in the gut and disrupted fecal metabolites [92].

Gut microbiota in obesity and diabetes

A metagenomics study showed that gut microbiota in T2DM patients is different from other individuals and the diversity and abundance of butyrate-producing bacteria in these patients is lower [93, 94]. The levels of branched-chain amino acids (BCAAs) can also increase in insulin-resistant individuals. *Prevotellacopri* and *Bacteroidesvulgatus* are two major known species of microbiome that correlates BCAA biosynthesis with insulin resistance. In mice, P.Copri induced insulin resistance, exacerbates glucose intolerance, and increases the BCAA levels in the blood [95]. Therefore, characterization of individual gut microbiota signatures in patients with obesity and T2DM could predict host and microbiota response to dietary interventions [96]. It was shown that postprandial glucose and insulin resistance improved in T2DM patients with a higher Prevotella/ Bacteroides ratio after barley kernel bread diet intervention. This finding suggests that personal approaches are effective in improving metabolism considering the importance of the host microbiota [97].

Epigenetics

Epigenetics are inherited changes in gene function without changes in the DNA sequence. It is a heritable trait. Epigenetics and its association with various diseases is an emerging field of research [98]. Epigenetic mechanisms include DNA methylation, histone modification, and noncoding RNAs that regulate cell differentiation, expression of specific genes, inactivation of the X chromosome, and regulation of genomic stability and structure [98]. In DNA methylation, transcription factor binding is prevented or the binding of methyl-bound proteins is enhanced. In this way, the transcription of many genes is reduced or inhibited [27]. Researchers believe that the high rate of obesity prevalence cannot be explained by genetic factors alone, and the environmental factors are plausible triggers for this phenomenon. It seems that genes are programming to store excess fat or energy [98].

It was found that the variance of DNA methylation in young obese people was more than which in the control group and both differential methylation and variability could predict up to 70% of obesity [99]. In another study, the association was found between increased DNA methylation and increased BMI in adipose tissue [100]. In addition, it was revealed that DNA methylation was also linked with waist circumference [101]. In addition, obesity-related DNA methylation sites also predicted the risk of T2DM [102]. In some studies, increased methylation of T2DM candidate genes such as INS (encoding insulin), GLP1R (encoding the GLP-1 receptor), and PDX1, PPARGC1A (encoding PGC1α) in human pancreatic islets from donors was observed [103, 104]. As a result, the expression of these key genes is reduced and insulin secretion is impaired. High serum glucose and glycated hemoglobin (HbA1c) are also increase the mitigation of these genes [105].

Based on the mentioned studies, the link between genetics and diabetes and obesity has been observed in humans. However, more studies are needed to show whether the identified epigenetic changes are effective in the development of diabetes and disease-related phenotypes or not.

In the new approach to classify humans diseases based on molecular biology, individuals act differently in terms of susceptibility to a particular disease in terms of biology, disease prognosis, or response to treatment [27]. Currently, personal nutrition is still a challenge due to the lack of reproducible results, the high cost of technology and the lack of specialized manpower to understand and interpret data. As mentioned above, several polymorphic genes affect obesity and its related complications, including T2DM. However, the effect of gene polymorphisms depends on the prevalence of the risk allele in different populations. Moreover, dietary patterns of the population is based on personal and cultural (regional/ ethnic) preferences in an area. As a result, a particular diet may not be suitable for all. Due to the fact that personal nutrition tries to adapt nutrition to a specific demographic group to improve therapeutic responses and metabolic effects, some complex algorithms for integrating multidimensional data such as dietary behaviors, anthropometric measurements, intestinal microbiome, blood tests and lifestyles are running. Applying PN as a tool can affect various areas of medical specialty and the design of new strategies will revolutionize the diagnosis, treatment and prevention of various diseases. There are still many challenges that need to be addressed in implementing this approach. Ensuring that the personal diet contains all nutrients a person needs and whether the person can adapt to these interventions in the long term, are issues that need to be addressed and examined more in the future studies. A summary of factors involved in PN in obesity and diabetes management has been shown in Fig. 1.

The present overview has two main limitations that should be addressed. First, as a systematic search was not used for this study, we might miss some relevant studies. Second, quality of the included studies was not examined. However, it examined the roles of PN from various aspects and provide a comprehensive explanation on how PN can be helpful to manage T2DM and obesity. The roles of PN on other non-communicable diseases are suggested to be reviewed in the future study.

Conclusion

The importance of the potential role of personal nutritional interventions from various aspects have been highlighted

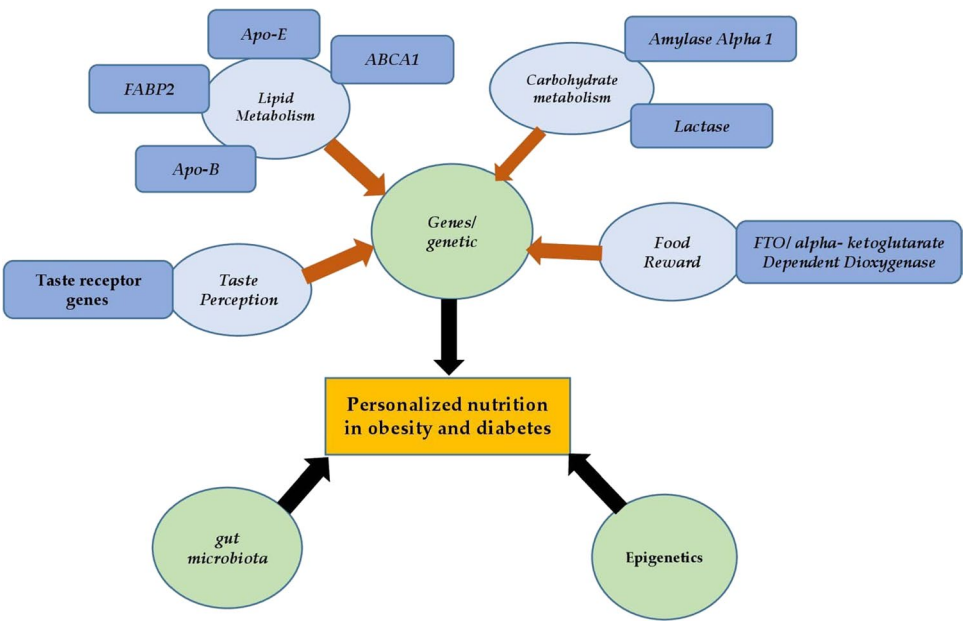

Fig. 1 Major factors related to personalized nutrition in obesity and diabetes

in the present overview. Response to a specific diet varies from person to person. It has been found that this variability depends on a person's genetic background and the composition of the gut microbiome. According to this approach, PN can improve metabolic status and response to diet and/or dietary supplements. Thus, considering genetic differences, microbiota patterns and their interactions with environmental factors are recommended to consider to achieve success in the management of obesity and T2DM. However, PN for disease management is expensive and need specific facilities.

Declarations

Conflict of interest All authors declared no conflict of interest.

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