Exploring obesity through diet-gene interactions

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Abstract:

The increasing prevalence of obesity is becoming a global health concern due to its association with chronic diseases including type 2 diabetes, non-alcoholic fatty liver disease, and cardiovascular diseases. Obesity occurs when energy intake outweighs energy expenditure, leading to a conventional intervention strategy being "eat less and move more." However, this strategy does not consider the influence of genetic factors and their interactions with environmental factors (diets and physical activity), making obesity prevention and management inefficient. To better understand obesity, research in nutrigenetics and nutrigenomics seek to explore the influence of genetic variations on dietary responses, and how dietary components alter gene expression in obese individuals. Current evidence suggests that variations in genes involved in lipid regulation, carbohydrate metabolism, and energy homeostasis are strongly associated with the risk of obesity and its related metabolic syndromes. In addition, diet-gene interactions influence intervention effectiveness for obesity management. By examining obesity-related metabolic pathways, we can reveal the functional basis of diet-gene interactions in relation to obesity risk. Although limitations exist within the current literature, emerging evidence indicates that obesity risk and intervention can be affected by diet-gene interactions, and continued research is needed for further exploration.

Obesity is a trending global health concern that affects over 35% of the world population, and 60% of adults in Canada [1, 2]. Obesity is more than just excessive fat in our body; it is a medical condition that contributes to the development of chronic diseases including type 2 diabetes, non-alcoholic fatty liver disease (NAFLD), cardiovascular diseases, and some cancers [3]. Most pressingly, emerging evidence revealed that obese individuals faced increased risk of intensive care admission for SARS-CoV-2 infection (commonly known as COVID-19) [4, 5], implicating obesity as a potential risk factor in COVID-19 severity that requires increased clinical attention. The cause of obesity has been well-recognized as a long-term unbalanced energy status in our body, which means higher energy intake coupled with lower energy expenditure for an extended period of time [6]. The old adage "you are what you eat" highlights the role that one's diet plays in preventing disease and improving overall health. Therefore, conventional population-based intervention strategies used to combat obesity often include reduction and modification of food/energy intake (e.g. caloric restriction, low-fat/low-sugar diet, etc.) [7]. However, the number of obese individuals around the world per year continues to increase, especially amongst children and young adults [1], indicating the lack of effective interventions for the prevention and management of obesity. With increasing awareness of individual differences, we now realize this conventional "one size fits all" strategy to weight reduction does not always work [8, 9]. The reason behind an unbalanced energy status is more complicated than "eating too much and moving too little." Past studies have recognized that people respond differently to certain foods [10], thus researchers are now attempting to tailor dietary components to a person's genetic profile for a better understanding of individual differences in obesity, promising a personalized intervention strategy for obesity management [11].

The ongoing research exploring the interactions between genome and diet are termed nutrigenetics and nutrigenomics. Nutrigenetics aims to identify and characterize gene variants associated with differential responses to diets, whereas nutrigenomics aims to determine the influence of dietary ingredients on changes to gene expression and cellular response in biological systems [11, 12]. Evidence from current studies suggest that interactions between one's genetic make-up and environmental factors (diets and physical activity) play more important roles than environmental factors alone [11, 13, 14]. The most well-studied example showing the significance of the diet-gene interaction is caffeine consumption. Nutrigenetics studies revealed that the individual differences in response to caffeine consumption are caused by genetic variations in the *CYP1A2* gene. This gene encodes the enzyme CYP1A2 which metabolizes over 95% of caffeine in our

https://doi.org/10.29173/hsi297
Received 2 February 2020
Accepted 5 May 2020

body [15]. Variations in the *CYP1A2* gene can alter CYP1A2 enzyme activity, leading to a "faster" or "slower" metabolism of caffeine amongst individuals [15]. Recently, more studies have applied the same research strategy from studying caffeine-gene interactions to explore diet-gene interactions in obesity and its associated chronic diseases [14]. With an increased appreciation for precision medicine (personalizing drugs and therapies to a patient's genetic profile) in recent years [16], and the emerging link between diet-gene interactions and obesity, current research now seeks to answer the following questions: why are some individuals more susceptible to obesity-related risk factors, while others are not? Why do individuals respond differently to the same dietary intervention? And how big of a role do diet-gene interactions play in obesity and its associated diseases? Various scientific approaches have been applied to this field including clinical research, molecular biology, genetics, and bioinformatics, to help obtain a comprehensive understanding of both nutrigenetics and nutrigenomics perspectives[14, 17].

A nutrigenetic persepctive: how genetic variations affect dietary responses involved in obesity

Genetic variation is the difference in DNA sequences between individuals within a population [18]. Major advances in genome sequencing techniques and the formation of large global collaborative networks (e.g. Genome-Wide Association study and the International HapMap Project) have led to the comprehensive knowledge of genetic variations in the human genome [18, 19]. Interestingly, genetic variation between individuals are minimal. Despite the fact that 99% of our genetic makeup is identical, the remaining 1% of genetic variation leads to large variability in health outcomes [20]. Common forms of genetic variation include single nucleotide polymorphisms (SNPs: substitution mutation in a single nucleotide) and copy number variations (CNVs: change in gene copy-number) [18]. In recent studies, several SNPs have been found to be corelated with obesity risk or its associated metabolic syndromes through interactions with dietary intake [21-24]. For example, a three-year study of 479 men and women in Finland revealed that a SNP in the fat mass and obesity associated (*FTO*) gene is associated with higher body mass index (BMI) in individuals consuming a high fat diet [21]. Likewise, another study found that SNPs in the *FTO* gene are associated with an increased risk of obesity amongst Asian-Indian individuals with high-carbohydrate diets [22]. Moreover, when consuming a Western diet high in refined grain products, sweets, and processed meats, individuals with certain genetic variations in *APOC3, APOC1* (encoding lipid-binding proteins for lipid transportation), and *MC4R* (encoding a key regulator for energy homeostasis) showed a higher risk of developing obesity-related metabolic syndromes [23, 24]. In addition to SNPs, studies on CVNs also found a significant association between low copy numbers of the salivary amylase gene (*AMY1*) and increased BMI and obesity, indicating a genetic link between carbohydrate metabolism and obesity risk [25].

SNP-diet interactions have also been investigated in differential responses to dietary interventions. An early study conducted in 1990 set a milestone in the field. 12 pairs of sedentary monozygotic (identical) male twins between the ages of 19 and 27 were overfed by 1,000 kcal/day for 6 days a week for a total of 84 days during a 100-day period. At the end of the study, researchers found that overall weight gain was three times more similar amongst twin pairs than between non-twins [26]. This indicates a critical role for genetic factors in dietary intervention. Recent studies found that several SNP-diet interactions were also associated with different responses in weight loss, insulin resistance, and serum lipid levels. Notably, high protein diet interventions induced greater weight loss in individuals with SNPs in *FTO*, and less weight loss in women with SNPs in *MTNR1B*, which encodes a receptor for melatonin [27, 28]. These nutrigenetics studies provide evidence that genetic variation is associated with obesity risk and dietary intervention, suggesting that individual genetic differences interact with dietary factors and can result in different responses to obesity management.

A nutrigenomic perspective: how diets/ nutrients change gene expressions involved in obesity

In contrast to nutrigenetics studies, nutrigenomics studies provide evidence that diet and/or nutrients have direct impact on gene expression and metabolic pathways involved in obesity and its related metabolic syndromes, leading to differences in health risk [29-33]. For example, diets high in fat and sugar increase the expression of *LEP, SREBF1*, and *PLIN* (genes encoding regulators for lipid synthesis and uptake), resulting in an increased risk of obesity [29]. High saturated fatty acids have also been shown to induce obesity and inflammation through increased expression of proinflammatory cytokines such as *TNF* and *IL6* [30]. Diets deficient in choline and folate have also been associated with increased risk of non-alcoholic fatty liver disease (NAFLD) through the dysregulation of genes involved in lipid metabolism, such as *APOE, FOXA1,* and *PPARGA* [31, 32]. On the contrary, studies have also suggested that some dietary components have beneficial effects on obesity management through the regulation of gene expression. For example, diets high in polyunsaturated fatty acid (PUFA) modulate the expression of genes involved in energy balance, such as *POMC* and *GALP*, and lead to obesity prevention [33]. Moreover, apple polyphenols were found to reduce the risk of obesity by modulating the expression of lipid metabolic genes: decreasing the expression of *LEP, SREBP1* and *PLIN*, and increasing the expression of *PPARGC1A* and *AQP7* [29]. Results from nutrigenomics studies indicate that different dietary components can differentially affect obesity management through modulating the expression of genes involved in obesity-related metabolic pathways, providing insights into the functional basis and causal relationships involved in diet-gene interactions in obesity.

Limitations and future directions

Despite emerging evidence in recent years that suggest diet-gene interactions have significant impact on obesity and its related metabolic diseases, gaps and limitations in the knowledge still exist. Given that approximately 700 SNPs have been found to be directly or indirectly associated with obesity [34], and that the field of nutrigenetics is relatively new, there is little replicated evidence to show the relationship between obesity-related genetic variations and diet [35, 36]. The only exception is the *FTO* gene [36]. Since the first genetic variation associated with obesity risk was found in *FTO* in 2007 [37, 38], a wide range of replicated studies have emerged [35, 36]. However, controversial results exist among them. Some studies found a strong association between *FTO*-diet interactions and obesity risk [21, 22, 27], whereas some found no significant associations [39, 40]. The opposing conclusions may be explained by differences in study settings and sample populations. Some studies [39, 40] were cross-sectional and had long-term lifestyle exposures, whereas other studies [21, 22, 27] were prospective with a relatively short intervention time. Additionally, different populations with varying samples sizes were used in different studies, which may cause bias and influence whether interaction effects could be readily detected [36]. Therefore, more studies with refined standardization are needed to verify and extend the current evidence. While nutrigenetics studies provide association-based evidence between diet-gene interactions and obesity risk, further exploration into the functional basis of diet-gene interactions and causal relationships is needed because association-based evidence alone is not sufficient to support a clinical decision [41]. Ultimately, more nutrigenomics research on mechanisms of actions is needed to support the evidence coming from nutrigenetic studies.

In addition to the limitations of current nutrigenetics/nutrigenomics studies, limited evidence has also been found regarding psychological issues raised by genotype-based intervention strategies. The success of personalized dietary intervention largely depends on whether individuals consider genetic testing results as a destined fate or a motivation for lifestyle changes [42]. One study showed that individuals who received genetic testing results were more likely to respond to dietary recommendations than those without genetic testing [43], whereas another study found no changes in lifestyle behaviors following a genetic test result [44]. These contradictory conclusions highlight the need for greater investigation into psychological aspects that shape the acceptance of, and adherence to, genetic-based intervention strategies for obesity management.

In conclusion, emerging evidence from current studies indicate that the diet-gene interaction plays a role in obesity risk and dietary intervention outcomes. The old adage "you are what you eat" is still a golden rule when it comes to health improvement and disease prevention, especially obesity management. However, with increasing awareness of individual differences and a rapid expansion of nutrigenetics and nutrigenomics research [8, 9, 11], the health determinant focus is shifting from "you are what you *eat*" to "you are what *you* eat." Despite the existence of inconsistent conclusions and the need for greater mechanistic studies to support current evidence, the rationale behind exploring obesity through diet-gene interactions remains strong and continues to motivate research in this field [11, 36, 41].

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