Review of studies on the fat mass and obesity-associated (FTO) gene interactions with environmental factors affecting on obesity and its impact on lifestyle interventions

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Review Article

Abstract

BACKGROUND: The prevalence of obesity is influenced by environmental and genetic factors. Recently, it has been reported that an interaction between genotype and environmental factors can affect each other's effects on the phenotype. The purpose of this study is to evaluate the recent studies on the fat mass and obesity-associated (FTO) gene interactions with environmental factors affecting on obesity and the impact of these interactions on the success level of the lifestyle intervention.

METHODS: All articles published in English from June 1990 to June 2015 were studied.

RESULTS: In most studies, the role of the FTO risk alleles for obesity is significantly intensified through reduced physical activity and high calorie diet. Furthermore, the results of studies about the effect of FTO on the success level of lifestyle interventions have been contradictory. Some studies show that FTO genotype influences on the success of lifestyle interventions, while other studies did not report it.

CONCLUSION: The results of these studies generally indicate that the effect of the FTO gene on obesity may be influenced by environmental factors and lifestyle. In the other hand, the FTO genotype can affect the success of lifestyle interventions in the prevention and treatment of obesity. Future studies are crucial to elucidate relationships between FTO gene and lifestyle.

Keywords: Fat Mass and Obesity-Associated Gene, Life Style, Obesity

Date of submission: 24 Dec 2015, ***Date of acceptance:*** 15 Aug 2016

Introduction

Overweight and obesity are defined as abnormal and excessive fat accumulation that may impair health.[1] Obesity has a huge negative impact on socioeconomic indicators of health. From health point of view, obesity underlies a large number of diseases, including coronary heart disease, Type 2 diabetes, cancer, hypertension, dyslipidemia, and stroke.[2] From the economic dimension, obesity has a direct negative consequences (costs associated with prevention, diagnosis, and treatment of obesity) and indirect consequences (costs associated with diseases and death caused by obesity).[3-5]

Obesity statistics are worriedly increasing in the worldwide. More than one-third of the adult population (34.9%) and 16.9% of 2-19 years Americans are obese.[6] Obese adolescents (12 to 19) were reached from 5% to 21% from 1980 to 2012.[7] The prevalence of obesity in Iranian men and women has been reported 27.3% and 13.7%, respectively.[8]

The role of various factors in the formation and progression of obesity has been proven. Genetics, behavioral and environmental factors are the most important factors that have been associated with obesity.[9] Most studies reported that unhealthy lifestyle including low physical activity and poor nutrition are the main cause of occurring obesity,[10-13] and therefore, strategies to combat obesity are to change lifestyle.[14-23]

On the other hand, it is seen in various studies of that people who do not have a healthy lifestyle

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are unaffected with obesity or even with lifestyle changes; the success rate in reducing obesity is not always satisfactory.[24] Here, the role of genetics in obesity is highlighted. Therefore, lack of a suitable conclusion of lifestyle interventions to reduce the prevalence of obesity in the desired level and also the results of recent studies in the field of nutritional genomics create uncertainties in the context of importance of lifestyle in occurring obesity and/or decrease in the imagined role of the lifestyle in obesity.

After many different studies on the interactions between genomics and diet and its relationship with hyperlipidemia and hypertension,[25-29] recent studies in the field of nutritional genomics have demonstrated that genetic background plays an important role not only in the chance of occurring obesity but also in people's responsiveness to the lifestyle intervention.[30-38] Several genes have been studied in relation to obesity, which one of the most important genes is fat mass and obesity-associated protein (FTO). FTO gene expression is associated with regulation of food intake and energy balance.[39] Furthermore, Single nucleotide polymorphisms (SNPs) in the FTO gene that almost 45% of them are in white,[40] causes to increase in food intake and the desire for high-calorie foods and then increase the risk of obesity (1.67 times more than others).[41] Although the mechanism of this effect is not still understood well, it has also been found that the link of FTO gene with obesity is related to age and most influence of these genes can be seen in the 7-20 years.[42] Furthermore, recent studies have been shown that the success of lifestyle interventions (such as changes in physical activity and intake of micronutrients) may be affected by obesity-related genes.[43-47] The results of various studies in this field have been inconsistent[48,49] that may be due to lack of considering to various aspects of this relationship. Hence, this study aimed to assess the FTO gene interactions with environmental factors affecting on obesity and its impact on lifestyle interventions using the lessons learned in previous studies and by taking into account the various aspects of the relationship.

Considering that so far (according to researchers' information) a study has not been carried out on a comprehensive review of interactions of FTO gene with environmental factors and the impact of FTO genotype on obesity successful interventions in obesity context, so the aim of this study was to review the studies on this field.

Materials and Methods

PubMed and ScienceDirect databases were used for gathering articles published in related fields. Appropriate keywords including FTO, lifestyle intervention, diet, physical activity, and obesity (alone and together) were used to collect the papers. All articles published in English from June 1990 to June 2015 were studied. Of the 277 articles, 162 articles were excluded because of failing to address the role of the FTO gene in obesity, and 90 articles for lack of sufficient information on the impact of the interaction of genes with the environment on the consequences of obesity and 25 articles were included. Of these studies, 14 studies were on the relationship between the FTO gene and obesity, 7 studies were about the interaction of the FTO gene with lifestyle factors and 4 were related to the FTO genotype influence on the success of prevention and treatment interventions of obesity.

Results

FTO gene and obesity: For the first time, FTO gene was identified in animal models as an effective gene on programmed cell death. Mice with mutations in this gene have joined fingers (fused toes), and they have larger thymus than other mice.[49-52]

FTO gene encodes a dependent oxygenase related to 2-exoglotarate that has a role in DNA demethylation.[53] This gene is located on chromosome 16 of region 12.2. Duplication of this gene region causes mental retardation, obesity, and other disorders.[54] FTO gene is expressed in all tissues of the body although its highest expression is in the brain and hypothalamus.[55]

The relationship of FTO with obesity in childhood and adolescence is confirmed through SNPs. The most important SNPs include: rs7202116, rs9930506, rs1421085, rs3751812, rs9939609, and rs17817449. There is no agreement on the mechanisms of FTO impact on obesity yet. Studies have shown that variations in the FTO play a key role in the regulation of food intake and energy expenditure. People with alleles A and AA than the carriers TT allele in rs9939609 polymorphism had 1231 kilojoules higher calorie intake.[56] In other studies, it was observed a positive relationship between the FTO gene mRNA levels in subcutaneous fat tissue with body mass index (BMI).[30,57-59] Furthermore, those who carry allele associated with obesity in FTO had lower fat cell lipolysis, indicating a possible role of FTO in fat metabolism in the body.[60] In another study that the

FTO gene expression was suppressed in mice, decrease in ratio of white adipose tissue (WAT) to brown adipose tissue (BAT) was reported. This finding means that the FTO deficiency may be involved in the conversion of WAT to BAT. In these mice, energy intake and energy consumption also increased significantly.[61]

Interactions of environmental factors and FTO genotype: Six of seven studies about the interaction of the FTO gene with lifestyle factors (i.e. diet and physical activity) reported that improvements of these factors might reduce the effects of FTO polymorphisms on body weight and body composition; while one study showed that these factors do not have a role in the interaction between FTO gene and obesity. The summary of these studies is presented in table 1.

FTO genotype influences on the success of lifestyle interventions on obesity: Three of four studies on the influence of FTO genotype on the success of lifestyle interventions did not find a significantly association between FTO gene polymorphisms with success rate of the interventions, while one study showed that dietary intervention is most useful in subjects with FTO risk allele. The summary of these studies is presented in table 2.

Discussion

Based on this review of studies focusing on the interactions between FTO genotype with lifestyle and obesity, there is some evidence that suggest FTO polymorphisms interact with the effects of environmental factors. Also, the success of lifestyle interventions to reduce obesity might be influenced by FTO genotype.

Andreasen et al.[45] were evaluated the effect of rs9939609 polymorphism in the FTO on obesity and diabetes at different levels of physical activity in 3856 patients with diabetes and 4861 healthy subjects. Information on physical activity and data related to genotype were collected by questionnaire and TaqMan allelic discrimination, respectively. The minor allele of rs9939609 (allele A) was associated with occurring diabetes and obesity. However, when the results were adjusted for BMI, no association was observed between this allele and diabetes. Furthermore, there was a correlation between genotype rs9939609 and physical activity. Sedentary subjects who were carriers of the A allele, compared with patients with homozygous T allele had higher BMI at a rate of 1.95 kg/m^2. These results suggest that low physical activity would accelerate the effect of rs9939609 in FTO on accumulation of fat in the body.

Rampersaud et al.[62] studied a possible link between increased physical activity and reduce the harmful effects of gene polymorphisms in the FTO. 704 adults were selected from the Heredity and Phenotype Intervention Heart Study. Information was collected on the physical activity of the study subjects and was evaluated the 92 SNP using whole blood samples and the method of Gene Chip Human Mapping and Genotyping Analysis Software (GTYPE) GTYPE (Affymetrix company). The study results showed that 27 SNP in the FTO gene were associated with BMI ($P = 0.040$ to < 0.001) and rs1861868 and rs147719 polymorphisms in those had low activities physical are associated with higher BMI after adjustments for age, gender. This relationship was not seen in people whose physical activity rated above average. The results demonstrated that physical activity can adjust the effect of the FTO gene on obesity.

Scott et al.[63] were examined FTO genotype effects as well as its interaction with physical activity and energy intake. 1980 children 1-5 years old and 949 adolescents 11-18 years old were selected from GENESIS study and evaluated for the phenotypes associated with obesity and existence of rs17817449 polymorphism in the FTO gene using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method. Adolescents were classified into two categories (active and inactive) based on self-report of physical activity. In adolescents, FTO genotype was associated with weight ($P = 0.001$) and BMI ($P = 0.007$). Furthermore, there was a significant correlation between physical activity interaction and SNP with BMI among men ($P = 0.016$). The amount of BMI in inactive boy adolescents who had the GG genotype was 3 kg/m^2 higher than carriers of T allele ($P = 0.008$). Totally, the results of this study showed that physical activity can improve the FTO genotype effects.[63]

Hubacek et al.[64] investigated the mediating role of diet and physical activity in influence of their FTO gene variation. Existing diversity (G > T in rs17817449 polymorphism in the first intron) in 6024 adults 45-69 years old were evaluated. The subjects were selected from among the participants in the health, alcohol and psychosocial factors. In Eastern Europe project, their DNA was extracted from blood samples through the salting out method and existence of SNP was evaluated using PCR-RFLP method.

Table 1. The review of the fat mass and obesity-associated (FTO) gene interactions with lifestyle factors and its impact on obesity

Writer	The aim of study	The subjects of study	Methodology	The main findings	The related diversity in FTO gene	Environmental factors
Andreasen et al.[45]	The effect of rs9939609 in the FTO gene on obesity and at different levels of physical activity	3856 patients with diabetes and 4861 healthy people	Physical activity by questionnaire and genotype by using Taqman allelic discrimination	Low physical activity accelerates the rs9939609 effect on the accumulation of fat in the body	rs9939609	Physical activity
Rampersaud et al.[62]	Possible association between increased physical activity and reduce the harmful effects of FTO gene polymorphisms	704 adults	Affymetrix Gene Chip Human Mapping 500 K array set and software GTYPE	Physical activity can adjust the FTO gene effects on obesity.	rs1861868 and rs147719	Physical activity
Scott et al.[63]	FTO genotype effects as well as its interaction with physical activity and energy intake	1980 children 1-5 years and 949 adolescents 11-18	PCR-RFLP and self-report of physical activity	Physical activity can adjust the FTO genotype effect	rs17817449	Physical activity
Hubacek et al.[64]	Checking the intermediary role of dietary intake and physical activity on the effects of the FTO gene polymorphism	6024 adults 45-69 years old	PCR-RFLP, food frequency questionnaire and physical activity questionnaire	Physical activity and diet have no meditation role in effects of FTO polymorphism on obesity but may play such a role in change of the BMR.	rs17817449	Physical activity and food intake
Ahmad et al.[65]	Checking the effect of diet modification and physical activity on the effects of FTO gene polymorphism	21675 healthy white women	Illumina's infinium HD bead chips	Lifestyle factors adjust the influence of FTO genotype on obesity, but will not be able to remove the full effects.	rs8050136	Diet and physical activity
Kilpelainen et al.[66]	Is physical activity able to mitigate the impact of FTO on the risk of obesity or not	218, 166 adults and 19,268 children	Meta-analysis	The effect of FTO risk alleles can be adjusted by 27% through physical activity	rs9939609	Physical activity
Ruiz et al.[67]	Does physical activity moderate FTO polymorphism effect on the amount of body fat or not	752 healthy adolescents	Illumina and accelerometer	Adolescents who have a good level of physical activity may overcome the adverse effects of rs9939609 polymorphism	rs9939609	Physical activity

PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism; FTO: Fat mass and obesity-associated; BMR: Basal metabolic rate; HD: High-density

Table 2. A review of studies on the effect of the fat mass and obesity-associated (FTO) genotype on the success of lifestyle interventions on obesity

Writer	The purpose of the study	Subjects	Duration of intervention	Main findings	The variation in the FTO gene	Environmental intervention
Haupt et al.[68]	The relationship between the FTO genotype with fat distribution and body weight changes in a lifestyle intervention	In 1466 the Germans	9 months	Despite the effect on body weight and fat distribution, rs8050136polymorphism had no effect on the success of lifestyle interventions	rs8050136	1. Diet with the aim of losing weight, reducing fat intake and increasing fiber intake 2. Physical activity 3. Nutritional Counseling
Lappalainen et al.[69]	Effects of long-term intervention on weight change considering rs9939609 polymorphism in the FTO gene and its effect on body weight and BMI	522 individuals 40-65 years with a BMI above 25	4 years	rs9939609 Polymorphism in the FTO gene had no effect on the success of lifestyle interventions to reduce obesity	rs9939609	Diet and physical activity
Razquin et al.[70]	The effect of the polymorphism rs9939609 (T/A) in the FTO gene on weight loss after a Mediterranean diet in people at risk for cardiovascular disease	776 individuals 65-80 years old	3 years	Appling dietary intervention is most useful in people with FTO risk allele	rs9939609	Mediterranean diet
Dlouha et al.[71]	The effect of rs17818902 polymorphism in the FTO gene on obesity lifestyle intervention	107 female adults with overweight	10 weeks	Change in BMI and other anthropometric parameters have no correlation with FTO gene variant	rs17818902	Reducing calories and increasing physical activity

FTO: Fat mass and obesity-associated; BMI: Body mass index

Diet was defined by a 140 items food frequency questionnaire and intake of total calories, fat, protein, carbohydrates, and alcohol were achieved using McCance and Widdowson's food composition. Basal metabolic rate (BMR) was estimated through Schofield formula. FTO variation was significantly correlated with BMI (BMI in carriers of genes GG, GT, and TT were 28.7, 28.2 and 27.8 and BMR were 1603, 1588 and 1576 kcal/day, respectively). However, there was no significant correlation between this SNP with energy intake, physical activity and energy intake of each macronutrient. Adjusting results with regard to physical activity and diet did not reduce the effect of FTO polymorphism. In general, the results of this study showed that physical activity and diet have no mediating role in the effects of FTO polymorphism on obesity, but change in the BMR may play such a role to some extent.

Ahmad et al.[65] investigated the effect of diet and physical activity effects on the link of FTO with obesity. Polymorphism rs8050136 in the FTO was assessed using the Illumina's Infinium high-density (HD) Bead Chips method. Physical activity, caloric intake and the anthropometric data were also collected through self-report and related questionnaire from 21,675 healthy white women participated in the study of Women's Genome Health Study. The results showed that the risk allele A in women who are inactive and receive a higher energy resulted in greater effect on people's BMI [odds ratio 13.9, 95% confidence interval (CI): 73.1-27.1 per-allele risk]. Totally, the results of this study showed that lifestyle factors adjust influence the genetic risk factors for obesity in the FTO gene although it is not able to completely eliminate its effects.

Kilpelainen et al.[66] designed a meta-analysis by 45 studies on adults (n = 218,166) and 9 studies on children (n = 19,268) to survey whether physical activity could moderate the effect of FTO on the risk of obesity or not. All studies included information related to the varieties of rs9939609 in FTO. In all studies, the study subjects were divided into two categories: active and inactive. Overall, 25% of adults and 13% of children were classified as inactive. The results showed that in adults, rs9939609 minor allele increases the risk of obesity by as much as 1.23 times [95% confidence interval (CI): 1.26-1.20], whereas physical activity neutralizes this effect. Such an effect was not seen in children and adolescents. At last, the results suggest that FTO risk alleles associated with risk of obesity can be adjusted by 27% by physical activity.

Ruiz et al.[67] examined whether physical activity moderates FTO polymorphism effect on the amount of body fat. 752 healthy adolescents participated in this cross-sectional study. FTO genotype was determined on polymorphism of rs9939609 by the method of illumina. Physical activities were measured using accelerometers. People carry accelerometer at all wake times except water activities for 7 days. Those who had used accelerometer less than 3 days were excluded. Weight, height, waist and subcutaneous fat (in triceps and subscapular) were evaluated, and BMI and percentage of body fat were calculated. The results showed that there was a significant relationship among the A allele of FTO polymorphism with BMI (0.42 per risk allele) and percentage of body fat (1.03% per allele risk) and waist (0.85 per risk allele). Moreover, a significant association was found between physical activity and body fat estimates (P = 0.020, 0.060 and 0.100, for BMI, body fat percentage and waist, respectively). The effect of rs9939609 polymorphism in FTO on the parameters of obesity in adolescents who had higher physical activity (that is 60 minutes a day, moderate to vigorous physical activity) was much lower than others (0.17 vs. 0.65 for BMI, 0.40% vs. 1.70% for body fat percentage and 0.60 vs. 1.15 cm for waist per allele risk). At last, the results of this study showed that teens who have an appropriate level of physical activity may overcome on the adverse effects of rs9939609 FTO polymorphism on occurring obesity. Table 1 shows summary of findings of the studies on the interactions between FTO gene and lifestyle factors.

Haupt et al.[68] investigated the relationship between the FTO gene with fat distribution, insulin resistance, and body weight changes after a lifestyle intervention. In this study, 1466 German people at risk for Type 2 diabetes were evaluated for the presence of polymorphism rs8050136 in intron 1 of FTO gene. The oral glucose tolerance test was taken. Also, to evaluate body fat mass, magnetic resonance imaging was performed in 298 people of them. The prepared kit for the isolation of DNA from blood samples was used for evaluating the subjects' genotype. By using Taqman analysis, people were analyzed for the presence of polymorphisms. Also, 208 of the subjects participated in the lifestyle intervention program and were re-evaluated after 9 months follow-up. A cross-sectional analysis was reported that related polymorphism is associated with the increased BMI, body fat and lean body mass (P < 0.001). After the

lifestyle intervention, this polymorphism was not associated with intervention effects on body weight and lifestyle. So despite effect on body weight and fat distribution, this polymorphism has no impact on the success of lifestyle interventions.

Lappalainen et al.[69] surveyed the effect of long-term intervention of changing weight on the effects of rs9939609 polymorphism in the FTO gene on body weight and BMI as part of the Finnish Diabetes Prevention Study. 522 individuals 40 to 65 years with a BMI over 25 and defect in glucose tolerance participated in the study and were divided into intervention and control groups. The rs9939609 genotype was determined in 502 patients. At the beginning of study, BMI of individuals that had allele A was significantly higher than others (P = 0.006). After adjustment for gender, this relationship was observed only in women. After 4 years, individuals with the allele A had the highest BMI among the study subjects. The amount of weight loss in the intervention group was more than the control group, but the studied allele had no impact on the effectiveness of the intervention. As a whole, the results of this study showed that polymorphisms rs9939609 in the FTO gene had no effect on the success of lifestyle interventions to reduce obesity.

Razquin et al.[70] evaluated the effect of polymorphism rs9939609 (T/A) in the FTO gene on the effect of Mediterranean diet in weight loss in people who are at the risk of cardiovascular disease. 776 subjects 65 to 80 years old participated in the study. They were divided into three groups: two intervention groups who received Mediterranean diet and the control group that was recommended to consume low-fat diet. Dietary intake was assessed by semi-quantitative food frequency questionnaire at baseline and after 2 years of intervention. Individuals' Genotype was determined by reverse transcription-PCR and after that Taqman allelic differentiation. The results showed that people with homozygous alleles A had the highest BMI among whole participants. After 3 years of intervention, they showed the lowest weight gain regardless of diet intervention (P = 0.022). In addition, the corresponding result in people carrying allele A was significant in the group receiving Mediterranean diet, but this relationship was not seen in the control group (P = 0.018). In general, the relationship between the polymorphism rs9939609 in the FTO gene and body weight were confirmed and more importantly it was showed that at the beginning of the study the A allele was associated with patients' higher weight, after 3 years intervention, the lowest weight gain was accounted. Therefore, in this study applying a dietary intervention was most useful in patients with FTO risk allele.

Dlouha et al.[71] investigate the role of polymorphism rs17818902 in the FTO gene in impacts of lifestyle interventions on obesity. In this study, 107 overweight females (BMI < 27) were studied. The intervention consisted of 10 weeks low-calorie diet (based on age) and physical activity (aerobic exercise 4 times/week, each time: 60 minutes). Genetic polymorphisms were studied using PCR and restriction enzymes on blood samples. The results showed that the change in BMI and other anthropometric (such as percentage of body fat, body water percentage, waist-to-hip ratio) and biochemical (lipid and blood sugar) indicators hove no relationship with the rs17818902 FTO gene variant.

In general, the studies on the effect of FTO on the success of lifestyle interventions represent the FTO genotype influence on the success of lifestyle interventions, while other studies did not report it. This difference in the results may be due to differences in lifestyle interventions, different target groups (for example in terms of age group), surveying various polymorphisms in various studies and due to ignore other genetic factors that influence on obesity (such as the impact of lifestyle interventions on IRX3 gene expression mediating FTO gene polymorphisms).[45]

Conclusion

The results of the studies on the FTO interaction with environmental factors show that the impact of FTO genotype on obesity may be affected by lifestyle. In most studies, the role of FTO polymorphisms in increased risk of obesity is significantly intensified by reduced physical activity and high calorie diet.

In the other hand, the results of the studies on the effect of FTO gene on the success of lifestyle interventions have been controversial. Future studies are crucial to further elucidate relationships between FTO gene and lifestyle interventions.

Acknowledgments

This study was funded by Shahid Beheshti University of Medical Sciences (code 2842) and Health Education and Promotion, Tehran, Iran, Department of Ministry of Health (code 642). We

acknowledge all the university staff for their excellent cooperation.

Conflict of Interests

Authors have no conflict of interests.

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How to cite this article: Kalantari N, Doaei S, Keshavarz-Mohammadi N, Gholamalizadeh M, Pazan N. **Review of studies on the fat mass and obesity-associated (FTO) gene interactions with environmental factors affecting on obesity and its impact on lifestyle interventions.** ARYA Atheroscler 2016; 12(6): 281-90.