

The association between FTO genotype and macronutrients' intake in overweight adults

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Abstract

Background Macro-nutrients can influence on body weight through their interactions with FTO gene polymorphisms. This study aimed to investigate the association between FTO gene rs9939609 polymorphism with macro-nutrients intake.

Methods This cross-sectional study was carried out on 196 overweight adults. The rs9939609 SNP in FTO was genotyped. Dietary intake was assessed by a valid 168-item semi-quantitative food frequency questionnaire (FFQ). The association between dietary macro-nutrients and the FTO genotype were assessed using linear regression after adjustments for sex, age, physical activity, triglycerides, fasting blood sugar (FBS), and low density lipoprotein (LDL).

Results The higher carbohydrates ($p=0.000$), fat intake ($p=0.009$) and calorie intake ($p=0.001$) were significantly associated with FTO gene risk allele ($P=0.001$). Carriers of the AA/AG genotype of rs9939609 had significantly higher calorie, fat, and carbohydrate intake than the carriers of the TT genotype ($p=0.019$, $p=0.010$, & $p=0.000$, respectively).

Conclusion The dietary carbohydrate and fat intake were associated with FTO genotype. Further studies are warranted to investigation of these interactions and the underlying mechanisms.

Introduction

Prevalence of obesity dramatically increased worldwide in developed and underdeveloped countries and today obesity is a global health-related problem (1, 2). More than 34.9% of adult's population of the United States are obese (3). Obesity is associated with other diseases such as cancer, hypertension, dyslipidemia cardiovascular disease, type 2 diabetes, and psychological disorders (4). Obesity is a multifactorial disorder caused by genetics, lifestyle and environmental factors (5) and recent studies reported that genetics may exert its effects by changing lifestyle. (4–6).

An important role of some genes in obesity has been reported in many studies (7–9). One of the most important gene is fat mass and obesity gene (FTO) that is found to be strongly associated with obesity (7–8). The FTO gene is located on the chromosome region 16q12.2, and it is widely expressed in several tissues such as brain, visceral fat, liver and hypothalamus. FTO genotype had a strong association with body mass index (BMI) and obesity (8–9).

FTO gene has an important role in regulation of food intake, energy balance, appetite and basal metabolic rate (BMR) (10). Recent studies reported an interaction between FTO genotypes and dietary intake (11–12). On the other hand, FTO genotypes may influence the effects of dietary macronutrients intake on BMI, body weight, food intake, energy balance, appetite, and hormone secretion (12–14). Dietary macronutrients including carbohydrate, fat, and protein, as the main source of energy, have key roles in regulation appetite, body weight, and BMI (14–15). In order to understand whether the intake of dietary macronutrients is associated with FTO gene, we conducted a study to investigate the interactions between changes in the amount of dietary carbohydrate, protein and fat, with the FTO genotype in overweight adults.

Methodology

This study was a cross-sectional study was carried out from September 2016 to October 2017 on 199 randomly selected participants referred to the Shohadaye Valfajr health center, Shiraz, Iran. In brief, participants were overweight adults with BMI between 24/9 to 29/9 kg/m² and aged 20 to 45 years. The inclusion criteria was defined as willingness to participate in the study, not participating in a weight management programs during two past months and no recent weight loss greater than 5%. We excluded participants with alcohol or drugs addiction (n=1), smoking, certain weight-related diseases (including specific psychological or neurological disorders, insulin resistance, thyroid disease, liver disease, renal failure, infectious and other specific diseases) (n=1), and pregnant or lactating women (n=1). All participants signed a consent form before participation in the study.

Anthropometric Measures

The height of the participants was measured with a calibrated tape line fastened to a wall and without shoes with a precision of 0.5 cm. A bio impedance analysis scale (BIA) (Tanita, Japan/BC-418) was used to measure anthropometric indices such as body weight, Body Mass Index (BMI), skeletal muscle percentage (SM%), body fat (BF), skeletal muscle (SM) and body fat percentage (BF%) after entering their height, age and gender.

Genotyping:

DNA was extracted from whole peripheral blood sample using the DNA extraction kit (SinaPure DNA Kit, PR881612/EX6001/CinnaGen/Iran). DNA samples were stored at -20 °C before genotyping. After DNA extraction, the concentration of the extract material was obtained by spectrophotometer NanoDrop device (ND1000,USA). *FTO* gene was genotyped for rs9939609 polymorphism via tetra primer amplification refractory mutation system polymerase chain reaction(ARMS-PCR)

Macronutrients' intake

Usual Macronutrients' intakes of participants were assessed by a validated 168-item semi-quantitative FFQ (16). The FFQ consisted of 168 food items with standard portion sizes commonly consumed by Iranian people. Face-to-face interviews were administered by a trained dietitian.

Macronutrients' consumption frequencies were converted to grams per day by using household measures. Daily intakes of energy were also measured for each person by using the modified US Department of Agriculture food consumption database, which was modified for Iranian foods.

Laboratory Measurement

Serum TG, TC, HDL, LDL, glucose and insulin levels were measured after 12 hours of an overnight fasting. leptin and adiponectin serum were measured using EDTA-anticoagulated tubes. Insulin, leptin and adiponectin level was determined by ELISA test (LDN, Germany).

Statistical Analysis

ANOVA test was used to compare anthropometric indices, plasma levels of hormones and lipid and sugar profile between different *FTO* genotypes. Tukey test was used for comparison the calorie and macronutrient intake between three genotypes. To adjust the effects of confounders, linear regression was used after that the assumptions of the linear regression model were confirmed. Statistical analyses were performed using SPSS version 23.0 (IBM SPSS Statistics for Windows, IBM Corp., Armonk, NY, USA). The results were considered statistically significant at $P < 0.05$.

Ethics approval and consent to participate

This study has been approved by Local ethics review boards at Shiraz University of medical sciences (Code: ir.sums.rec.1395.100).

Results

All data were normally distributed ($P > 0.05$). For the risk allele of *FTO rs9939609* genotype, about half of the subjects were heterozygote ($n=98$), 30% of them were TT wild type ($n=60$) and about 20% of them were AA homozygote ($n=38$). The BMI ($p=0.047$), fat mass ($p=0.001$), calorie intake ($p=0.001$), fat intake ($p=0.009$), and carbohydrate intake ($p=0.000$) were significantly different in three genotype groups (Table 1).

Tukey tests conducted to recognize differences between three genotypes identified for identified a significant difference between calorie, carbohydrate, fat intake and genotypes of *FTO*. Homozygotes for the *rs9939609* risk allele A had significantly higher calorie, fat, and carbohydrate intake than the carriers of the TT genotype ($p=0.019$, $p=0.010$, & $p=0.000$, respectively) but not significant for heterozygotes than the carriers of the TT genotype ($p=0.869$, $p=1.000$, & $p=0.966$, respectively) (Table 2).

To adjust the effects of confounders, linear association of *FTO rs9939609* different genotypes with the level of macronutrients' intake (carbohydrate, Fat, Protein) was assessed (Table 3). The level of calorie intake, carbohydrate, and fat intake were significantly different between *FTO* genotypes. This association remained significant for carbohydrate, calorie and fat intake after adjustment for age and sex ($p= 0.000$, $p=0.001$ and $p=0.009$ respectively) (model1). The results did not change after further adjustments for physical activity, TG, LDL, FBS ($p= 0.001$, $p=0.000$ and $p=0.019$ respectively) (model 2).

Discussion

In the present study, we evaluated the associations between *rs9939609 FTO* polymorphism with calorie, fat, carbohydrate and protein intake. The results identified that there was a significant difference between *FTO* genotype with calorie, carbohydrate, and fat intake, but not significant for protein intake. This association remained significant for calorie and macronutrients' intake after adjustments for sex, age, physical activity, LDL, HDL, and FBS. In AA carriers, dietary carbohydrate, fat, and calorie intake were higher than TT carriers. However, the results of recent studies about association between dietary macronutrients and *FTO* polymorphism were inconsistent. Timpson et al. reported higher energy intake and fat intake among *rs9939609* AA genotype carriers. They suggest that *FTO* polymorphism may influence on appetite and food

intake (17). Some studies reported that carriers of risk allele FTO received higher energy intake (17, 18). The AA carriers was reported to intake higher fat than TT genotype.

Consistent with our study, Daya et al. reported that carriers of AT/AA genotype had higher fat intake (1.40 times) and obesity risk than TT genotype (19). Fat intake may modify the effect of the FTO rs9939609 polymorphism on adiposity. It was observed that carriers of the A risk allele FTO rs9939609 had no significant influence on adiposity in subjects whose dietary fat intake was below 30% of total energy but fat intake higher than 30% increased central and total adipose tissues (20). Another study found that a high-fat diet in comparison with a high carbohydrate diet in rats did not change the FTO gene expression (21). Inconsistent with this study, Nowacka-Woszek et al. indicated that a high-fat diet could increase FTO genes expression in white adipose cells (22). Ronkainen et al. investigated the association between fat intake, the FTO expression and the IRX3 expression in rats. They found that the high-fat diet could influence on IRX3 expression and suppress FTO expression (30).

This study found that the AA carriers had higher carbohydrate intake than TT genotype. While Sonest et al found low carbohydrate intake associated with FTO genetic variants. In homozygous for alleles A, BMI higher than TT genotype but the increase in BMI was mainly restricted to subjects who reported low physical activity (15). Carbohydrate intake (especially glucose intake) increase FTO gene expression (24). Doaei et al. indicated that carbohydrates intake significantly increase FTO gene expression (25). In homozygous people for G allele of FTO gene, higher dietary carbohydrate intake had a positive association with FTO gene expression (25). Another study reported that higher sucrose administration decreased FTO gene expression (26) and sucrose feeding in rats did not change in in hypothalamic FTO expression (27).

This study found no association between protein intake and FTO genotype. While some studies indicated that protein intake was associated with FTO genotype (27–28) and leucine decreased FTO gene expression in the hypothalamus (27). However, another study reported that leucine intake increased FTO gene expression (28). Doaei et al found that higher protein intake up-regulated the FTO gene and also indicated that only in A allele carriers, protein intake was positively associated with FTO gene expression (25).

The FTO variants was associated with intake of energy-dense foods such as fat-rich foods (29). FTO gene variants played important roles in appetite regulation, food intake, tendency to choose energy-dense food (high fat and high carbohydrate diet) (30). The carriers of A allele FTO rs9939609 had Energy-dense food choices, higher body weight, and overeating behaviors (31).

Some studies suggested that FTO play a crucial role in regulating energy homeostasis. FTO gene is expressed in brain that controls feeding and energy expenditure (32). On the other hand, Fto expression level in hypothalamus is regulated by dietary intake. Interestingly, it was reported that a high-fat diet can down-regulate FTO expression in short-term and up regulate in long-term (33, 34).

On the other hand, the FTO gene is related with gut hormones such as orexigenic hormone, acyl-ghrelin, satiety hormone, peptide YY that regulate food intake and appetite (35). FTO gene polymorphism (AA genotype) influence on circulating PYY3-36 and acyl-ghrelin levels that lead to increased food intake especially energy-dense foods and reduced satiety(36,37).In rs9939609 AA carriers, suppression of acylated

ghrelin led to overeating and obesity (38). So, it is plausible that FTO gene polymorphisms could change appetite and food intake that may lead to weight gain and obesity.

Conclusion

FTO gene rs9939609 polymorphism is associated with dietary intake. The intake of calorie, carbohydrate, and fat intake were associated with FTO gene polymorphisms and this association remained significant for calorie and macronutrient intake after adjustments for sex, age, physical activity, LDL, HDL, and FBS. In AA carriers, dietary carbohydrate, fat, calorie was higher than TT carriers. Further studies are needed to increase our understanding of the underlying mechanisms of the association between FTO gene and dietary intake.

Declarations

Ethics approval and consent to participate

This study has been approved by Local ethics review boards at Shiraz University of medical sciences (ir.sums.rec.1395.100).

Availability of data and material:

Not applicable

Competing interests

The authors declare that they have no competing interests

Consent for publication

Not applicable.

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Authors' contributions

MM and MHE designed the study, involved in the data collection, analysis, and drafting of the manuscript. MM, MGh, SD were involved in the design of the study, analysis of the data, and critically reviewed the manuscript. All authors read and approved the final manuscript.

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Tables

Table1: characteristics of the subjects categorized by FTO rs9939609 genotypes (N=196)

Variables	TT (n=60)	AT (n=98)	AA (n=38)	P
Male sex (%)	15(49)	25(81.66)	10(3.26)	0.989
Age(years)	33.43(±6.461)	32.99(±6.488)	34.08(±5.961)	0.664
Weight(kg)	72.140(±9.8058)	72.618(±9.1667)	75.262(±9.3294)	0.241
height(m)	163.983(±9.8402)	163.980(±9.4112)	165.816(±9.0609)	0.564
BMI(kg/m2)	26.7086(±1.10977)	26.9072(±1.03883)	27.2864(±1.33132)	0.047*
FatMass (kg)	21.380(±3.9137)	22.160(±3.3318)	24.363(±4.2223)	0.001*
FM%	30.0847(±6.07727)	31.0358(±5.94178)	32.7175(±6.23811)	0.112
FFM (kg)	50.7600(±10.22795)	50.4586(±10.25310)	50.8989(±9.67006)	0.968
FFM%	69.9153(±6.07727)	68.9642(±5.94178)	67.2825(±6.23811)	0.112
IPAQ1(total counts per minute)	(±1391.611)1462.08	1134.34(±1580.308)	823.61(±1159.997)	0.100
Calorie intake(Kcal)	803.67 (±335.18753)	828.85(±284.16712)	976.77 (±309.66683)	0.001*
FBS(mg/dl)	86.95(±8.490)	89.18(±9.738)	91.42(±11.568)	0.084
LDL-C(mg/dl)	96.90(±20.755)	102.75(±16.100)	103.82(±18.475)	0.088
HDL-C (mg/dl)	47.20(±9.950)	42.82(±8.175)	40.87(±6.751)	0.088
TChol(mg/dl)	183.13(±29.514)	192.42(±23.446)	199.50(±25.438)	0.008
TG(mg/dl)	113.87(±48.315)	118.03(±27.235)	118.74(±29.388)	0.724
FAT(gr/day)	24.4433(±11.10069)	24.4573(±11.01026)	31.8353(±15.77593)	0.009*
CHO(gr/day)	115.63(±45.54972)	117.43(±41.17454)	152.35(±46.89251)	0.000*
Protein(gr/day)	228.32(±173.8147)	231.85(±158.10551)	273.97(±163.29332)	0.189
Fiber(gr/day)	8.0043(±3.60432)	7.6244(±3.15966)	8.4431(±2.50727)	0.621

*P-value <0.002

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein;; FFM, fat free mass; IPAQ, International Physical Activity Questionnaire; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceridess; FBS, fasting blood sugar;

Table 2. Tukey test for comparison the calorie and macronutrient intake between three genotypes

Variable	TT	AT	P value	AA	P value
Calorie	1	-25.17740	0.869	-173.09213*	0.019
FAT	1	-0.01397	1.000	-7.39193*	0.010
Protein	1	-3.52699	0.991	-45.65037	0.373
Carbohydrate	1	-1.80258	0.966	-36.72395*	0.000
Fiber	1	0.37984	0.748	-0.43883	0.785

*P-value <0.05

Table 3. Association of FTO genotypes with macronutrients' intake

variables	Model 1		Model 2	
	Beta	P	Beta	P
Calorie	0.149	0.001	0.162	0.000
FAT	0.186	0.009	0.172	0.019
Protein	0.092	0.189	0.090	0.219
Carbohydrate	0.250	0.000	0.246	0.001
Fiber	0.035	0.621	0.045	0.545

Model 1: adjusted for AGE& SEX; Model 2: Further adjustments for PA, TG, LDL, and FBS

*P-value <0.05