Original Article

Interaction of Cry1 Gene Polymorphisms and Dominant Food Patterns on Obesity: A Cross-Sectional Study

Abstract

Background: Evidence suggests that there is some relationship between circadian clock gene variants and obesity. However, there are few examinations supporting this observation in human subjects. This study was aimed to investigate the interaction between Cry1 circadian gene polymorphism and major dietary patterns on obesity measurements. **Methods:** Healthy overweight and obese women aged 18–53 years old were recruited from health centers in Tehran, Iran by a multistage cluster random sampling method (n = 377). Major dietary patterns were elicited after assessing the intake of 16 food groups using a valid and reliable 147-item food frequency questionnaire (FFQ). Anthropometric measurements were performed for each and every participant. Body composition was analyzed using bioelectrical impedance analysis (BIA). Socio-demographic and physical activity data were also collected by a validated Farsi demographic questionnaire and the international physical activity questionnaire (IPAQ). The Cry1 rs2287161 polymorphism were genotyped using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). Generalized linear models were used for interaction analysis. **Results:** Two major dietary patterns, including healthy and unhealthy dietary pattern (HDP and UDP, respectively) were determined using factor analysis. Our study showed a significant higher weight (P = 0.003), body mass index (BMI) (P = 0.042), hip circumference (P = 0.052), and body fat mass (P = 0.028) in carriers of C allele compared with G allele. Moreover, a significant gene-diet interaction was observed between being a carrier of C allele and BMI (P = 0.099 for CC genotype; *P* = 0.1 for CG genotype) and fat mass (P = 0.1 for CG genotype). **Conclusions:** The current study suggests a significant interaction of Cry1 rs2287161 gene polymorphisms in people following a healthy dietary pattern on BMI and fat mass among carriers of C allele compared to carriers of G allele.

Keywords: *Circadian clocks, diet; dietary patterns and Cry1 gene polymorphisms, fat body, gene-environment interaction, obesity*

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Introduction

The prevalence of obesity, as a multifactorial metabolic disorder, is rapidly increasing worldwide, and particularly in the Middle East.[1,2] It is predictable that by 2030, half of the population will be obese.[3] The obesity epidemic is associated not only with increased mortality, but also with lower quality of life, increased needs of professional health care, and dramatically increased health care costs.[4,5] The causes of obesity are divided into two main categories of genetic and environmental factors, such as diet, physical activity, and so on; however, it may be more prudent to assume that a combination of both factors plays the major role.[6] Therefore, gene-environment interaction could be regarded as the most potent pathological exposure determining the risk of obesity in individuals.[7,8]

One of the factors affecting the body metabolism, and thus possibly obesity, is the body circadian clock. In mammals, the circadian rhythm affects almost all aspects of physiology and behavior, including sleep cycle, cardiovascular activity, endocrine system, body temperature, kidney activity, gastrointestinal physiology, and hepatic metabolism.[9,10] At the molecular level, the circadian clock is regulated by a network of transcription and translation factors; these factors, in turn, are regulated by positive and negative feedback pathways that exist in the suprachiasmatic nucleus of hypothalamus. The main components of the positive limb are Clock and Bmal1 and the major components of the negative limb are period (Per) and cryptochromes (Cry).[11]

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The cryptochromes family, including cry1 and cry2, play an important role in regulating the circadian rhythm.[12] Studies on mutant animals have linked the disruption of circadian clock rhythm to metabolic abnormalities and obesity.[11,13,14] Studies at the human level are very limited. One study on Chinese population have supported the association between some clock gene polymorphisms and abdominal obesity.[15]

Dietary modification is the major environmental factor worthy of note. Studies have suggested a connection between dietary intake, circadian preference (morning, intermediate, or evening-type) and obesity; it seems that individuals with late preference (evening-type) are more likely to pursue unhealthy dietary habits, including skipping the breakfast, lower consumption of fruits and vegetables, higher consumption of sugar and alcohol, and so on, as compared to individuals with morning preference.[16-18] However, the various interactions between different nutrients, the circadian rhythm, and the epigenetic factors involved cannot be understood thoroughly using a single foodstuff; thus, a complete dietary pattern is more reasonable to be taken into account.[19]

Findings have supported the relationship between circadian clock, diet, and obesity. To the best of our knowledge, there is no research to map out the interaction of clock gene polymorphism and dietary pattern on obesity. The current study aimed to examine the relationship between interaction of Cry1 gene polymorphism rs2287161 and dietary patterns on obesity.

Methods

Study protocol

A cross-sectional design was adopted and the study was conducted between Feb 2018 and May 2019. Study participants were recruited from overweight and obese women referred to 21 health centers of Tehran, Iran by a multistage cluster random sampling method. The inclusion criteria included: (1) having a body mass index (BMI) between 25 to 40 kg/m2, and (2) an age range of over 18 years. Participants were excluded if they (1) had entered the menopause, (2) were pregnant, (3) had a history of cardiovascular disease, diabetes, cancer, kidney disease, or thyroid disease, (4) used nutritional supplements over the last three mounts, or (5) had followed any kind of weight loss regimen over the past year. The sample size for this study was calculated according to Peduzzi method using a binary logistic regression model.[20] The research protocol was fully explained to study participants and after signing a written consent, 377 overweight and obese women entered the research. The measurements and evaluations were done in the laboratory of the Faculty of Nutritional Science and Dietetics, Tehran University of Medical Science (TUMS). The protocol of study was approved by the ethics committee of TUMS (IR.TUMS.VCR.REC.1398.051).

Outcome measurements

Anthropometric measurements

Weight was measured in minimal clothing without shoes using a digital scale (Seca 808; Hamburg, Germany) with a sensitivity of 0.1 kg. Height was determined by a stadiometer (Seca) with a sensitivity of 0.5 cm. BMI was calculated as weight in kilograms divided by the height squared in meters. Waist circumference was measured by an unstreached tape between the lowest gear and the iliac crest and in expiratory state. Then the waist to hip ratio (WHR) was calculated for each person.

Sociodemographic assessment

A validated Farsi demographic questionare,[21] including measures of education level, employment status, smoking, family size, economic situation, and income was used in order to obtain necessary demographic data.

Dietary assessment

A a valid and reliable semi-quantitative 147-item food frequency questionnaire (FFQ) was used to assess dietary intake. The participants were asked by a trained questioner to report their amount and frequency of food intake on a daily (e.g., bread), weekly (e.g., meat), monthly (e.g., fish), or yearly (e.g., some seasonal fruits) basis. The portion sizes reported by study subjects were converted to grams per day and were enterned in the Nutritionist IV software for further analysis (version 7; N-Squared Computing, Salem, OR, USA). The validity and reliability of the questionnaire were assessed in the Tehran Lipid and Glucose Cohort.[22]

Body composition analysis

Body composition analysis was assessed using bioelectrical impedance analysis (BIA) Inbody 770 Scanner (Inbody Co., Seoul, Korea). According to the implementation protocol, the study participants were asked to avoid wearing too many clothes, carrying metal jewelry, watch or electronic devices, and eating and exercising for at least four hours before the assessment. Moreover, they were asked to urinate before the measurements. Each participant stood on the device in bare feet and held the handles for some seconds until the device notified the end of the analysis.

Physical activity assessment

The International Physical Activity Questionnaire (IPAQ) was used to evaluate physical activity. The questionnaire has showed the acceptable validity and reliability in previous studies.[23,24] This questionnaire describes physical activity at three levels, including intense (e.g., football and running), moderate (e.g., cycling at medium speed), and low (e.g., walking). Study subjects were asked to answer the questions based on the duration and frequency of the activity during the previous week. The number obtained from the physical activity questionnaire

indicated the intensity of the activity: <600 (MET-h/wk), 600-3500 (MET-h/wk), and >3500 (MET-h/wk) which were interpreted as low, moderate, and severe physical activity levels; respectively.[25]

Laboratory investigations

Venous blood samples (10 mL) were obtained from each study participant fasting overnight for 10 to 12 hours at the Nutrition and Biochemistry laboratory of School of Nutritional Sciences and Dietetics, TUMS. Blood samples were collected in EDTA containing tubes. After resting for 30 minutes in room temperature, samples were stored in -20°C until the genotyping analysis.

DND extractionand genotyping

About 3 mL of prepheral blood samples were obtained from all study subjects. Genomic DNA was isolated from prepheral whole blood leukocytes using GeneAll Mini Columns Type kit (GeneAll, South Korea). The extracted DNA was used to determin the rs2287161 single-nucleotide polymorphism (SNP) located between cry1 and MTERF2 gene. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was conducted on the rs2287161 SNP using forward: 5′-GGAACAGTGATTGGCTCTATCT -3′ and reverse primer: 5′-GGTCCTCGGTCTCAAGAAG-3′. The amplication proccess was performed in 5 steps, including 4 minutes initial denaturation (94°C), 30 seconds denaturation (94°C), 30 seconds annealing (58°C), 30 seconds extension (72°C), and 5 minutes final extension (72°C); denaturation, annealing, and extension were done for 35 cycles. PCR products were digested using BseYI (New England Biolabs, Cataloge number: R0635S) which yielded two cuts and three fragments of 108, 50, and 226 base pairs (bps); and one cut and two fragments of 156 and 226 bps in the presence of G and C alleles, respectively.

Statistical analysis

Findings of the study were analyzed using the SPSS (version 20). Data were reported as means and standard deviations. Kolmogrov–Smirnov was used to verify the normality of data distribution. ANOVA test was used to compare the data related to anthropometric and body composition, based on dietary patterns and genotypes. In order to use this tset, participants that followed each dietary pattern were catogorized into three groups (tertiles), then the effect of each dietary pattern on the relevant variables was analyzed. We took advantage of the post hoc method (Tukey) to observe the differences in the variables of concern between groups. In the next step, anthropometric and body composition variables based on dietary patterns and genotypes were compared through ANCOVA test adjusted for age, BMI, calorie intake, and physical activity. *P* value <0.05 was considered as significant for all the tests mentioned above.

The interaction of Cry1 gene polymorphisms and major dietary patterns on anthropometric and body composition measurements were verified by Generalized Linear Models. In this model, the studied outcomes, including BMI and body fat mass, were considered as response variables (dependent variable); while Cry1 genotypes and each dietary pattern were regarded as factor variables, and age and calorie intake as covariates. In interaction models, *P* values <0.1 were considered as statistically significant.

Results

General charachteristics

The general charachteristics of study participants are listed in Table 1. Four hundred four overweight and obese women enterd the study, but due to lack of information, some participants were not included in the analysis. Three hundred seventy-seven overweight, obese, and apparently healthy women with an age range of 18 to 53 and mean (±SD) of 36.64 (±9.02) years participated in the study. The mean (±SD) of height, weight, BMI, body fat mass, and fat free mass of subjects were 161.05 (± 5.82) cm, 79.90 (± 10.73) kg, 30.81 (± 3.8) kg/m^2, 33.73 (± 7.47) kg, and 45.98 (± 5.2) kg, respectively.

Dietary pattern

Two major dietary patterns which were later entitled as healthy dietary pattern (HDP) and unhealthy dietary pattern (UDP), were determined by factor analysis based on eigenvalues greater than one. To extract these two dietary patterns based on 16 food groups, the principal component analysis (PCA) was done. HDP was charachterized as consuming higher amounts of vegetables, fruits, fruit juices, dried fruits, dairy, fish, poultry, red meat, eggs; and lower amounts of unhealthy fats, grains, high-energy drinks, sweets, desserts, and industrial juices.

Table 1: Characteristics of study participants

Variable	Min	Max	Mean	SD
Anthropometrics				
Age (ys)	18	53	36.64	9.02
Height (cm)	142	179	161.05	5.82
Weight (kg)	59.50	122.4	79.90	10.73
BMI (kg/m^2)	25.2	40.6	30.81	3.80
WC (cm)	74	121.5	96.82	9.65
HC (cm)	100	140	113.03	7.75
Body composition analysis				
PBF (%)	27.1	53	41.93	5.00
BFM (kg)	19.4	63.2	33.73	7.47
FFM (kg)	33.4	63	45.98	5.2
VFL	7	20	15.73	3.21
TBW (L)	24.6	46.3	33.88	3.96

y: Year; cm: Centimeter; kg: Kilogram; BMI: Body mass index; m: Meter; WC: Waist circumference; HC: Hip circumference; PBF: Percent body fat; BFM: Body fat mass; FFM: Fat free mass; VFL: Visceral fat level; TBW: Total body water

In UDP, participants were more likely to consume higher quantities of processed meats, organ meats, fast foods, sauces, high-energy drinks, sweets, desserts, industrial juices; and lower quantities of legumes. To simplify the reading of loading factor matrix, the values lower than 0.3 were discarded. Food groups and loading factors are presented in Table 2.

Each dietary pattern was divided into tertiles for further comparison in dietary adherence. Higher adherance to HDP was associated with lower percent body fat (P = 0.036), and higher free fat mass (P = 0.049); after adjusment for age, physical activity, and calorie intake. Moreover, significant differences across the tertiles of UDP were observed for age (P < 0.001), height (P = 0.058), fat free mass (P = 0.014), and total body water (P = 0.025) ; however, except for age (P = 0.004), these dicrepancies disappeared after being adjusted for age, physical activity, and calorie intake [Table 3].

Cry1 genotypes

Distribution of Cry1 rs2287161 polymorphism was GG (28.4%), CG (39.3%), and CC (32.4%); and overall 51.98% and 48.02% for C and G allele, respectively [Table 4]. Significant differences across Cry1 rs2287161 polymorphism were observed for weight (P < 0.001), BMI (P < 0.001), waist circumference (P = 0.013), hip circumference (P = 0.013), body fat mass (P = 0.002), visceral fat level (P = 0.04), and total body water (P = 0.014). After adjusting for age, physical activity, and calorie intake, significant associations between being a carrier of GG genotype and lower weight (P = 0.003), BMI (P = 0.042), hip circumference (P = 0.052), and body fat mass (P = 0.028) were observed.

Table 2: Food groups and loading factors for HDP and UDP

Food groups	Dietary patterns	
	HDP	UDP
Vegetables	0.733	
Unhealthy oils	-0.519	
Dairies	0.496	
Fruits, natural juices	0.495	
White meats	0.429	
Meat and egg	0.433	
Grains	-0.326	
Nuts and healthy oils	0.312	
Fast food and sauces		0.640
Organ and processed meats		0.633
Snacks		0.573
Legumes	0.306	-0.511
Sugar, sweets and deserts	-0.3	0.442
Salts		
Tea and coffee		
Spices		
Total variance	13.18	11.2

Gene-diet interaction

As the interaction of each dietary pattern (HDP and UDP) and Cry1 gene polymorphisms with body fat mass was verified, we found that in individuals carrying at least one risk allele (CC or CG genotype) with the highest adherence to the HDP, when compared with those with no risk allele (GG genotype) with the lowest adherence to HDP, body fat mass was significantly lower (P = 0.099 for CC; *P* = 0.1 for CG).

Similar gene-diet interactions were observed for BMI. BMI was significantly lower in those carrying the genotype CC (P = 0.15) when they had the highest adherence to a HDP. Also, BMI was significantly lower in highest adherence to HDP in the participants carrying CG (P = 0.1). When the interaction of UDP and Cry1 gene genotype on body fat mass and BMI was examined, we were not able to find any significant association. Table 5 presents the data regarding the interaction of HDP and UDP with Cry1 on BMI and body fat mass.

Discussion

The present study addressed the relationship between interaction of Cry1 gene polymorphism rs2287161 and dietary patterns on obesity and body composition. After adjusting for confounding variables, we were able to observe a significant positive association between being a carrier of CC genotype and having a higher weight, BMI, waist circumference, hip circumference, fat mass, and visceral fat. Additionally, the gene-diet interaction revealed, individuals with CC and CG genotypes who had significantly higher mean fat mass and other obesity-related measurements, while following HDP, had about 3.5 kg less fat mass, compared with GG carriers. The present study, for the first time, has investigated the association of the Cry1 rs2287161 polymorphism with fat mass and obesity-related components.

The circadian clock genes have already been studied in relation to diet and obesity. For example, some CLOCK gene SNPs, such as rs3749474, rs1554483, rs4864548, rs4580704, and rs1801260, were already associated with obesity, energy intake, and BMI.[26,27] In our study, carriers of risk allele C who were more obese, have less weight when adhering to HDP compared with people homozygous for G allele. This study showed that improving adherence to HDP might alter the effect of genetic polymorphisms on obesity in carriers of the risk allele more than in individuals having a lower-risk genetic background. Similar findings were observed in a cohort study in the population of Nurses' Health Study (n = 8828) and the Health Professionals Follow-up Study (n = 5218).[28] Also paralleled with our findings, a meta-analysis of ten studies has shown that in people predisposed to obesity carrying an FTO-gene polymorphism, diet and lifestyle interventions may cause greater weight loss compared with non-carriers.[29]

Table 3: Characteristics of study participants according to adherence to HDP and UDP

Variable	HDP			*P**	*P***	UDP			*P**	*P***
	T1	T2	T3			T1	T2	T3		
Anthropometrics										
Age (y)	35.86±9.44	36.49±8.79	37.75±9.05	0.235	0.303	37.72±8.26[a]	38.28±9.21[a]	34.09±9.31b	0.001>	0.004
Height (cm)	161.21±5.78	160.02±5.93	161.71±5.83	0.07	0.211	161.8±5.60[a]	160.04±6.14[b]	161.13±5.78[a,b]	0.058	0.445
Weight (kg)	79.66±11.28	79.68±9.69	80.17±10.96	0.914	0.213	81.54±10.78	78.50±10.86	79.46±10.13	0.069	0.365
BMI (kg/m^2)	30.73±4.22	31.13±3.57	30.65±3.60	0.573	0.410	31.12±3.56	30.70±3.98	30.67±3.89	0.576	0.497
WC (cm)	97.86±9.63	96.21±9.23	95.69±14.16	0.403	0.378	97.02±14.11	96.00±9.10	96.85±10.13	0.812	0.495
HC (cm)	112.93±8.45	112.77±7.42	113.63±7.71	0.824	0.734	112.85±7.56	114.38±6.67	111.88±8.29	0.262	0.092
Body composition analysis										
PBF (%)	42.16±5.17	42.39±4.90	41.29±4.97	0.196	0.036	41.74±4.94	41.89±5.12	42.20±5.05	0.769	0.679
BFM (kg)	33.89±8.04	33.94±6.84	33.42±7.52	0.831	0.423	34.28±7.58	33.25±7.45	33.71±7.41	0.548	0.616
FFM (kg)	45.62±5.00	45.49±5.10	46.82±5.56	0.089	0.049	47.09±5.11[a]	45.39±5.51[b]	45.45±4.97[b]	0.014	0.503
VFL	15.76±3.25	15.92±2.98	15.53±3.44	0.645	0.099	15.85±3.17	15.57±3.28	15.78±3.25	0.771	0.740
TBW (L)	33.72±3.99	33.56±3.89	34.37±4.08	0.243	0.331	34.67±3.91[a]	33.46±4.16b	33.51±3.81b	0.025	0.41

HDP: Healthy dietary pattern; UDP: Unhealthy dietary pattern; y: Year; cm: Centimeter; kg: Kilogram; BMI: Body mass index; m: Meter; WC: Waist circumference; HC: Hip circumference; PBF: Percent body fat; BFM: Body fat mass; FFM: Fat free mass; VFL: Visceral fat level; TBW: Total body water. **P* for ANOVA test. ***P* for ANCOVA test after adjustment for age, physical activity, and calorie intake

Table 4: Characteristics of study participants according to cry1 rs2287161 genotype

Variable	Genotypes (*n*/percent)			*P**	*P***
	GG (107/28.4)	CG (148/39.3)	CC (122/32.4)		
Anthropometrics					
Age (y)	35.03±8.3	36.83±9.29	37.77±9.3	0.07	0.081
Height (cm)	161.77±5.59	160.27±5.22	161.05±6.10	0.128	0.536
Weight (kg)	78.25±9.06[a]	77.49±9.38[a]	82.56±11.07[b]	0.001>	0.003
BMI (kg/m^2)	29.88±3.05[a]	30.30±3.33[a]	31.74±4.13[b]	0.001>	0.042
WC (cm)	94.98±8.84[a]	95.99±8.36[a]	99.12±10.76[b]	0.013	0.180
HC (cm)	111.37±6.39[a]	112.02±6.41[a]	115.38±8.45[b]	0.013	0.052
Body composition analysis					
PBF (%)	41.02±4.25	41.89±4.86	42.55±5.15	0.063	0.279
BFM (kg)	32.21±5.99[a]	32.86±6.78[a]	35.27±7.77[b]	0.002	0.028
FFM (kg)	45.95±5.11	45.05±5.10	46.50±4.82	0.068	0.225
VFL	15.24±3.02[a]	15.48±3.18[a]	16.25±3.12[a,b]	0.04	0.063
TBW (L)	33.72±3.71[a]	33.10±3.74[a]	34.51±3.98[a,b]	0.014	0.129

n: Number; y: Year; cm: Centimeter; kg: Kilogram; BMI: Body mass index; m: Meter; WC: Waist circumference; HC: Hip circumference; PBF: Percent body fat; BFM: Body fat mass; FFM: Fat free mass; VFL: Visceral fat level; TBW: Total body water. **P* for ANOVA test. ***P* for ANCOVA test after adjustment for age, physical activity, and calorie intake. *P*

Studies of the interaction of other genes associated with the circadian clock regulation and environmental factors are very limited. However, one study has been shown that CLOCK rs1801260 SNP was associated with greater weight loss and poor adherence to the Mediterranean diet; there was also an interaction between carrying this SNP with saturated fatty acids intake which in turn modified waist circumference and overnight feeding.[30] Animal studies have also shown that saturated fat alters the correlation between SNPs in clock genes and obesity. They have suggested that animals fed saturated fat faced circadian disruption, obesity, and metabolic syndrome.[31,32]

In the present study, we observed that the C allele in Cry1 rs2287161 SNP modifies the impact of an HDP, consisting lower saturated fat intake, which leads to lower BMI and fat mass. Although the mechanisms of this association are not well understood, some studies have suggested roles of circadian clock genes in regulation of lipid metabolism and adipogenesis.[33,34] Moreover, in animal models high-fat diet is shown to alter the clock gene expression and circadian oscillation balance.[35,36]

Many circadian clock genes were studied in relation to emotion, emotional feeding, and obesity.[31,37] Garaulet *et al*.[31] investigated the interaction between the CLOCK 3111T/C genotype and emotional eating behavior on the effectiveness of a weight loss program. The study found that among carriers of the minor C allele, individuals with "emotional eating" lost less weight than the "non-emotional

Table 5: Interaction of HDP and UDP with Cry1 on BMI and BFM

Interaction	BMI			BFM		
	β	95% CI	*P**	β	95% CI	*P**
HDP						
CC*T3	-3.48	-6.71--0.2	0.034	-3.71	-8.12-0.7	0.099
CC*T2	-0.46	-3.81-2.87	0.784	0.53	-4.03-5.11	0.817
CC*T1		Ref			Ref	
GC*T3	-2.26	-5.36-0.8	0.15	-3.57	-7.81-0.67	0.1
GC*T2	-1.21	-4.42-1.99	0.457	2.54	-1.84-6.93	0.25
GC*T1	Ref			Ref		
GG*T3	Ref			Ref		
GG*T2						
GG*T1						
UDP						
CC*T3	0.48	-1.77-2.74	0.674	-0.23	-4.67-4.19	0.917
CC*T2	0.86	-1.45-3.17	0.465	1.65	-2.89-6.18	0.474
CC*T1		Ref			Ref	
GC*T3	-1.07	-3.26-1.1	0.33	-2.53	-6.81-1.74	0.246
GC*T2	-0.85	-3.14-1.42	0.461	-1.31	-5.78-3.16	0.565
GC*T1		Ref			Ref	
GG*T3	Ref			Ref		
GG*T2						
GG*T1						

HDP: Healthy dietary pattern; UDP: Unhealthy dietary pattern; T: Tertile; BMI: Body mass index; BFM: body fat mass. **P* for generalized linear models. $P<0.1$ were considered as statistically significant

eating". Likewise, Soria *et al*.[38] showed that there was a significant association between different circadian clock gene SNPs and mental disorders, such as depression and bipolar disorder. They found that in the carriers of the C allele of the Cry1 rs2287161 gene, the risk of mental disorders is up to three times higher than homozygous carriers for the G allele. On the other hand, many studies have found positive and significant relationships between mental disorders, such as depression and obesity,[39,40] which may be one of the probable hypotheses explaining the association between clock and obesity genes. Moreover, studies on animals have revealed that higher transcription of orexigenic hormones and polyphagia, like orexin and ghrelin, which may in turn result in obesity, are observed more frequently in CLOCK-mutant mice.[41,42] Based on these observations, the hormonal pathway could also be one of the regulatory pathways that may explain the association between CLOCK gene polymorphisms, obesity-related genotypes, and obesity.

This study has some limitations. First, the cross-sectional design of the study does not allow us to derive a causal relationship between the studied variables. Second, we were not able to assure the health status of the study participants, in part due to lack of a screening method. Third, the gender specificity of the study population does not permit an extrapolation to the whole society. Fourth, the use of FFQ is mostly associated with various biases.[43] For example, misclassification bias may occur with regard to the classification of food items into groups according to the researcher's idea. However, it is the first study determines the frequency of Cry1 rs2287161 gene genotype in Iranian population. Moreover, to our best of knowledge, this is the first study investigating the interaction of major dietary patterns and Cry1 rs2287161 polymorphism on obesity-related parameters paving the way for other studies with larger populations or interventional designs.

Conclusion

Our study showed significant differences between Cry1 rs2287161 variants and obesity-related measurements. We found that Cry1 rs2287161 gene polymorphisms interact with an HDP probably resulting to a lower BMI and fat mass among carriers of C allele compared to G allele. From another point of view, the current study indicated that improving adherence to HDP may be more beneficial to women with higher risk for obesity compared with those having a lower-risk genetic profile.

Abbreviations: Cry: Cryptochromes, Per: period, BMI: body mass index, WHR: Waist to hip ratio, FFQ: food frequency questionnaire, IPAQ: International Physical Activity Questionnaire, PCR-RFLP: Polymerase chain reaction-restriction fragment length polymorphism, HDP: healthy dietary pattern, UDP: unhealthy dietary pattern, SNP: single-nucleotide polymorphism.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have

given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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