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RESEARCH PAPER

Association of LXRα polymorphisms with obesity and obesity-related phenotypes in an Iranian population

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Abstract

Background: Obesity is a multifactorial disorder due to the complex interaction between genetic and environmental factors. Liver X receptor alpha (LXRα), encoded by the gene *NR1H3*, is involved in lipoprotein metabolism and its genetic variations may also play a role in the aetiology of obesity.
Aim: To assess the association of two *NR1H3* polymorphisms (rs11039155 and rs2279238) and their haplotypes with obesity in an Iranian population.
Subjects and methods: A total of 447 unrelated subjects (including 206 overweight, 162 obese and 79 controls) were enrolled in the study and were genotyped by TaqMan assay using DNA from peripheral blood. The association of these two LXRα polymorphisms with the presence of obesity and overweight was assessed.
Results: There was no significant association between the two SNPs and obesity, even after adjustment for age and sex. By logistic regression using a dominant model, the odds ratios for obesity were: 1.32 (0.85–2.74) for rs11039155 and 0.77 (0.30–1.99) for rs2279238. Haplotype analyses identified three common haplotypes GC, GT and AC with frequency greater than 1%, but none of the haplotypes was associated with the risk of obesity.
Conclusions: This study revealed that there was no significant association between LXRα polymorphisms and the presence of obesity in an Iranian population and suggests that these two SNPs are not major contributors to obesity risk in this population.

Keywords

Liver X receptor-α gene, obesity, single nucleotide polymorphism

History

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Introduction

Obesity is characterized by excessive accumulation of body fat and is a major global epidemic in the developed world and increasingly in the developing world (Kopelman, 2000; Cheung & Mao, 2012). The prevalence of obesity is increasing at an alarming rate worldwide (Ogden et al. 2007). Obesity is a multifactorial condition resulting from an interaction of genetic and environmental factors; and is associated with an increased risk of type 2 diabetes, cardiovascular disease, metabolic syndrome, high blood pressure, stroke and certain forms of cancer (Borecki et al., 1998; Bergstrom et al., 2001). About 50–70% of variation in body weight can be explained by genetic factors and identification of genes associated with obesity may be helpful to design prevention strategies.

A variety of genes involved in the regulation of food intake, energy expenditure and body weight have been suggested to contribute in a polygenic manner in predisposing to obesity. Genome-wide association studies (GWAS) in several populations have identified at least 52 genetic loci (over 600 genes, gene markers and chromosomal regions) associated with obesity (Loos, 2012). The liver X receptor alpha (LXRα) is a ligand dependent transcription factor expressed in the liver, kidney, small intestine, macrophages, adipose tissue, spleen and adrenal glands and is encoded by the *NR1H3* gene located on chromosome 11p11.2 (Kohro et al., 2000).

After its activation by cholesterol-derived oxysterols and forming heterodimers with retinoid X receptors (RXRs), LXRα induces the expression of a number of genes involved in cholesterol homeostasis, lipid and glucose metabolism and lipogenesis (Tobin et al., 2000; Chawla et al., 2001; Juvet et al., 2003; Laffitte et al., 2003). LXRα has pivotal roles in the synthesis and accumulation of lipids in adipocytes, by its induction of SREBP1c, and is responsible for lipogenic effects (Lund et al., 2006). Although genetic linkage analysis has

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previously revealed that *NR1H3* is not located in a region susceptible to obesity or related traits [the 2005 Obesity Gene Map (Rankinen et al., 2006)], recent epidemiological studies have reported significant association between *NR1H3* polymorphisms and body mass index (Dahlman et al., 2006), cholesterol concentrations (Robitaille et al., 2007; Sabatti et al., 2009) and the presence of metabolic phenotypes (Legry et al., 2008).

Because of the proposed involvement of LXRα in lipid and carbohydrate metabolism, we hypothesized that *NR1H3* gene polymorphisms and haplotypes may be associated with obesity phenotypes in human population samples. Based on previous studies, we selected two potentially functional SNPs (rs11039155G > A and rs2279238C > T) of *NR1H3* gene with a minor allele frequency (MAF) ≥ 0.05 to investigate the association with susceptibility to obesity or related phenotypes in an Iranian population.

Material and methods

Four hundred and forty-seven genetically unrelated adult subjects between 18–60 years of age were randomly selected using a population-based cluster sampling from Mashhad, the second largest city in Iran. The population sample was divided into three groups by adiposity: 206 subjects were classified as overweight with a body mass index (BMI) between $\geq 25\,kg/m^2$ and $<30\,kg/m^2$, 162 as obese with a BMI $\geq 30\,kg/m^2$ and 79 as normal weight with BMI $< 25\,kg/m^2$. All participants voluntarily attended a complete clinical examination that included standardized anthropometric measurements and fasting plasma samples collection and completed a standardized questionnaire including questions such as name, ethnicity and family history, past medical history, age, sex and dietary habits. Subjects were excluded if they had a medical history of myocardial infarction (MI), stroke, diabetes mellitus, endocrinological abnormalities, congestive heart disease, liver and/or renal disease and alcohol consumption or were taking medications that altered blood pressure, lipid or glucose metabolism. Informed consent was obtained from all participants using protocols approved by the Ethics Committee of the Mashhad University of Medical Science (MUMS).

Anthropometric and biochemical measurements

Anthropometric measurements included weight, height, waist circumference, hip circumference, waist/hip ratio, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by the trained investigators using standard methods of measurement in accordance with WHO standards (Europe WHO, 1989). All measurements were taken after an overnight fast while the participants dressed in lightweight clothing without shoes. BMI (kg/m^2) was calculated as body weight/height and a BMI of 20–25 was considered normal, 25–30 was categorized as over-weight and ≥30 obese. Blood samples were taken in the morning after an overnight fast. Fasting plasma glucose was determined by the glucose oxidase method. Serum lipid profile including total cholesterol (TC), high density lipoprotein cholesterol (HDL), low density lipoprotein cholesterol (LDL) and triglyceride (TG) were determined by routine enzymatic methods.

Genotyping

Genomic DNA was extracted from EDTA whole blood using the FlexiGene DNA isolation Kit (FlexiGene DNA isolation Kit, Qiagen) according to the manufacturer's protocol. The quality of genomic DNA was assessed by agarose gel-electrophoresis and the concentration quantitated by NanoDrop1000, which is based on the optical density measurement. Samples were genotyped for the two *NR1H3* SNPs by allelic discrimination assays using TaqMan probes (C_25605618_10 and C_15967384_10; Applied Biosystems, Foster City, CA). The reaction was performed on an ABI 7500 Real Time PCR System (Applied Biosystems). The conditions for the polymerase chain reaction were 95 °C for 10 minutes and 40 cycles of 92 °C for 15 seconds and 60 °C for 1 minute. Individual genotypes identification was analysed by SDS software version 1.3 (Applied Biosystems). To assess genotyping quality control, a selection of 5% random samples was regenotyped for two SNPs and nuclease-free water was used as negative control.

Statistical analysis

The allele and genotype frequencies and the association between genotypes and clinical groups and analysis of deviation from Hardy–Weinberg equilibrium were assessed using the chi-square or Fisher's exact tests. The quantitative variables were expressed as mean ± standard deviation (SD). Continuous variables without normal distribution such as TG and LDL were logarithmically transformed before inclusion in the analysis. Differences among groups were tested using *t* test for unpaired data. One-way analyses of variance (ANOVA), followed by post-hoc Bonferroni test, was used to compare mean differences for anthropometric traits between genotype groups. cubeX software was used to calculate haplotype frequencies and D' and r^2 values for linkage disequilibrium (LD) (Gaunt et al., 2007). Logistic regression analysis, adjusted for age and sex as confounding variables, was performed to calculate odds ratio (OR) and its 95% confidence intervals (CI) for each SNP and haplotypes. All statistical analysis was performed using the Statistical Package for Social Science (SPSS for windows, version 16) (SPSS Inc., Chicago, IL). Statistical significance was defined as *p* values ≤ 0.05 for all comparisons (two-sided).

Results

Characteristics of subjects

The clinical and biometrical characteristics of the total population sample, stratified by phenotype distribution, are listed in Table 1. Anthropometric parameters including weight, BMI, waist circumference, hip circumference and waist/hip ratio and biochemical parameters including fasting glucose, TG, SBP, DBP and the ratio of female-to-male were higher in overweight-obese than in normal weight subjects ($p < 0.05$), whereas the serum concentration of HDL-C was lower in obese than in normal weight subjects ($p = 0.009$). There were no significant differences between the three groups with respect to age and serum concentrations of TC and LDL-C ($p > 0.05$ for all).

Table 1. Anthropometric and clinical characteristics of the study population.

Characteristics	Normal ($n=79$)	Overweight ($n=206$)	Obese ($n=162$)	p Value
Sex (M/F)	28/51	83/123	41/121	0.009
Age (years)	48 ± 7.76	47 ± 7.23	48 ± 6.83	NS
Weight (kg)	59.57 ± 7.55	72.38 ± 8.93	82.75 ± 10.08	<0.001
Height (cm)	161 ± 9	162 ± 10	159 ± 9	0.004
BMI (kg/m^2)	23.04 ± 1.56	27.56 ± 1.37	32.81 ± 2.68	<0.001
Waist circumference (cm)	83.19 ± 9.4	92.38 ± 8.7	102.65 ± 8.8	<0.001
Hip circumference (cm)	95.3 ± 5.1	101.7 ± 5.1	110.7 ± 7.4	<0.001
W/H ratio	0.87 ± 0.08	0.91 ± 0.08	0.93 ± 0.07	<0.001
Glucose (mmol/l)	4.40 ± 0.77	4.55 ± 0.69	4.71 ± 0.81	0.006
HDL-C (mmol/l)	1.11 ± 0.28	1.02 ± 0.22	1.03 ± 0.22	0.009
LDL-C (mmol/l)	3.12 ± 1.03	3.19 ± 0.84	3.20 ± 0.81	NS
TC (mmol/l)	4.73 ± 1.08	5.01 ± .98	5.02 ± 0.96	0.072
TG (mmol/l)	1.40 ± 0.76	1.68 ± 0.81	1.78 ± 0.77	0.002
SBP (mmHg)	115.5 ± 14.1	121.3 ± 17.2	124.1 ± 19.9	0.003
DBP (mmHg)	74.2 ± 10.3	80.0 ± 11.2	81.4 ± 11.4	<0.001

BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; W/H, waist/hip; TC, total cholesterol; HDL-C, high density lipoprotein; LDL-C, low density lipoprotein cholesterol; TG, triglycerides; NS, non-significant. Values were expressed as mean ± SD.

Table 2. Genotype distributions and allele frequencies in three groups.

Genotype	Normal	Overweight	Obese	OR* (95% CI) Overweight vs normal	p	OR* (95% CI) Obese vs normal	p
rs11039155	79	206	162				
GG	57 (72.2)	138 (67.0)	102 (63.0)	1.00	—	1.00	—
GA + AA	22 (27.8)	68 (33.0)	60 (37.0)	1.28 (0.72–2.26)	0.402	1.32 (0.85–2.74)	0.159
G allele	135 (85.4)	338 (82.0)	253 (78.1)	1.00	—	1.00	—
A allele	23 (14.6)	74 (18.0)	71 (21.9)	1.30 (0.77–2.14)	0.334	1.65 (1.00–2.76)	0.057
rs2279238	70	198	155				
CC	40 (57.1)	111 (56.1)	90 (58.1)	1.00	—	1.00	—
CT	22 (31.4)	68 (34.3)	51 (32.9)	1.13 (0.62–2.06)	0.696	1.04 (0.55–1.94)	0.914
TT	8 (11.4)	19 (9.6)	14 (9.0)	0.87 (0.35–2.16)	0.767	0.77 (0.30–1.99)	0.586
C allele	102 (72.9)	290 (73.2)	231 (74.5)	1.00	—	1.00	—
T allele	38 (27.1)	106 (26.8)	79 (25.3)	0.98 (0.64–1.51)	0.931	0.92 (0.58–1.44)	0.710

χ^2-test and logistic regression were used.
OR, odds ratio; CI, confidence interval.
*Adjusted for age and sex.

Genotypic and allelic frequencies

The genotypic and allelic frequencies of the two SNPs in the entire study groups are summarized in Table 2. Genotype frequencies of two SNPs for the total sampled population and for each group separately were in accordance with Hardy–Weinberg equilibrium ($p>0.05$ for all). For the rs11039155 polymorphism, frequency of the AA genotype was very low and so the GA and AA genotypes were combined. There were no significant differences in genotype and allele distributions of two polymorphisms between normal weight and overweight or obese subjects. The crude odds ratios (OR) for the overweight or obesity in subjects carrying the rare alleles of these polymorphisms were assessed by logistic regression in a dominant model using homozygous for the common allele as reference and results showed no evidence for any significant increased or decreased risk for obesity or overweight with either of the two polymorphisms (Table 2). Similar values were obtained after adjusting for age and sex and further association analysis based on sex discrimination did not modify these results (data not shown). We also analysed anthropometric and obesity-related metabolic traits among different genotypes of *LXRα* SNPs and found no statistically significant differences in their mean scores except TC for rs11039155 and SBP for rs2279238 ($p=0.031$, $p=0.049$, respectively) (Table 3).

To evaluate the combined effect of two polymorphisms on mean values of biometric and clinical characteristics among the groups, subjects were divided into four groups according to the combination of the two genotypes from each SNP (GG-CC, GG-XT, XA-CC and XA-XT) (Table 4). None of the subjects showed XA-CC diplotype and there were no differences in the variables among the three combination groups of the polymorphisms, except that the body weight of the G/G-X/T group was significantly lower than the other groups ($p=0.036$). We also computed haplotype frequencies and degree of linkage disequilibrium by D' and r^2 according to the combination of the two SNPs (Table 5). Results showed that the two polymorphisms were in linkage disequilibrium ($D'=0.981$, $r^2=0.812$ in the obese group and $D'=1.00$, $r^2=0.502$ in controls). Haplotype analysis associating the two studied LXRα SNPs (rs11039155-rs2279238) revealed three possible haplotypes with an estimated frequency of more than 1%.

Table 3. Biometric and clinical characteristics according to the genotypes of LXRα variants.

	rs11039155			rs2279238			
Characteristics	GG	GA + AA	*p*	CC	CT	TT	*p*
n (%)	297 (66.4)	150 (33.6)	–	241 (57.0)	141 (33.3)	41 (9.7)	–
Weight (kg)	73.6 ± 12.3	74.3 ± 11.9	0.579	74.0 ± 12.5	73.4 ± 11.7	73.0 ± 11.9	0.814
Height (cm)	160.6 ± 8.6	160.1 ± 9.3	0.534	160.3 ± 8.6	159.9 ± 9.2	160.2 ± 9.4	0.900
BMI (kg/m^2)	28.5 ± 4.1	29.0 ± 4.0	0.235	28.8 ± 4.1	28.7 ± 3.9	28.5 ± 4.0	0.906
WC (cm)	94.0 ± 11.6	95.3 ± 10.5	0.252	94.5 ± 11.6	94.9 ± 11.4	94.2 ± 9.3	0.913
HC (cm)	103.4 ± 8.5	104.5 ± 7.6	0.208	103.6 ± 8.8	104.3 ± 8.1	103.6 ± 7.2	0.732
W/H ratio	0.91 ± 0.08	0.91 ± 0.07	0.741	0.91 ± 0.07	0.01 ± 0.08	0.91 ± 0.07	0.882
Glucose (mmol/l)	4.57 ± 0.78	4.59 ± 0.74	0.788	4.57 ± 0.78	4.59 ± 0.75	4.65 ± 0.65	0.827
HDL-C (mmol/l)	1.04 ± 0.23	1.04 ± 0.24	0.965	1.04 ± 0.23	1.06 ± 0.25	1.02 ± 0.19	0.545
LDL-C (mmol/l)	3.12 ± 0.83	3.29 ± 0.90	0.055	3.09 ± 0.80	3.31 ± 0.91	3.17 ± 0.90	0.079
TC (mmol/l)	4.87 ± 0.94	5.08 ± 1.09	0.031	4.85 ± 0.93	5.09 ± 1.08	4.93 ± 0.97	0.07
TG (mmol/l)	1.72 ± 0.91	1.71 ± 0.88	0.852	1.72 ± 0.91	1.70 ± 0.93	1.70 ± 0.74	0.982
SBP (mmHg)	121.5 ± 17.5	120.9 ± 18.6	0.753	121.6 ± 17.8	122.4 ± 18.5	114.8 ± 14.3	0.049
DBP (mmHg)	79.7 ± 11.5	79.2 ± 10.9	0.615	79.8 ± 11.4	79.8 ± 11.2	75.9 ± 10.5	0.105

BMI, body mass index; WC, Waist circumference, HC, Hip circumference, W/H, waist/hip HDL-C, high density lipoprotein; LDL-C, low density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides, SBP, systolic blood pressure; DBP, diastolic blood pressure. Values are expressed as number (%).

Table 4. Comparisons of the variables among different groups according to the combination of the different genotypes of two rs11039155 and rs2279238 polymorphisms in the LXRα gene.

Characteristics	G/G – C/C (*n* = 234)	G/G – X/T (*n* = 32)	X/A – X/T (*n* = 141)	*p* Value
BMI (kg/m^2)	28.86 ± 4.15	27.26 ± 3.96	28.99 ± 3.83	0.081
Body Weight (kg)	74.29 ± 12.5	68.66 ± 10.1	74.61 ± 11.8	0.036
Height (cm)	160.3 ± 8.5	158.9 ± 7.9	160.4 ± 9.4	0.665
WC (cm)	93.1 ± 11.6	96.7 ± 10.9	92.4 ± 14.1	0.380
HC (cm)	103.7 ± 8.8	102.23 ± 8.5	104.64 ± 7.8	0.295
W/H ratio	0.91 ± 0.07	0.90 ± 0.09	0.91 ± 0.08	0.740
Glucose (mmol/l)	4.57 ± 0.78	4.67 ± 0.75	4.56 ± 0.71	0.736
TC (mmol/l)	4.84 ± 0.92	5.11 ± 1.06	5.02 ± 1.05	0.131
TG (mmol/l)	1.66 ± 0.70	1.78 ± 0.82	1.64 ± 0.76	0.664
HDL-C (mmol/l)	1.04 ± 0.23	1.11 ± 0.25	1.04 ± 0.24	0.282
LDL-C (mmol/l)	3.10 ± 0.80	3.35 ± 1.07	3.24 ± 0.86	0.185
SBP (mmHg)	121.6 ± 17.9	122. 1 ± 16.4	121.0 ± 18.4	0.822
DBP (mmHg)	79.84 ± 11.5	79.18 ± 12.9	78.95 ± 10.8	0.754

BMI, body mass index; WC, Waist circumference, HC Hip circumference, W/H, waist/hip, TC, total cholesterol; TG, triglycerides, HDL-C, high density lipoprotein; LDL-C, low density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure. Values are expressed as number (%).

Table 5. Haplotype frequencies associating LXRα rs11039155–rs2279238 polymorphisms in the study population and linkage disequilibrium statistics.

Gene	Haplotype	Frequency among controls	Frequency among obese	*p* Value	Diplotype	*n*
LXRα	GC	0.73	0.75		G/G – C/C	234
	GT	0.11	0.04		G/G – X/T	32
	AC	0.00	0.00	0.085	X/A – C/C	0
	AT	0.15	0.23		X/A – X/T	141
LD	D'	1.00	0.981			
	r^2	0.502	0.812			

The degree of linkage disequilibrium (LD) between the two variants is shown as D′ and r^2 for each group.

Compared with the most common and non-risk haplotype (GC), none of the haplotypes were associated with any significant increased or decreased risk of obesity. These analyses revealed no further association between the SNPs and obesity.

Discussion

Obesity is a specific phenotype that results from multiple and complex interactions between genetic and environmental factors. Prevalence of obesity has increased worldwide during recent years (James, 2004). Environmental factors including excessive dietary calories, physical inactivity and metabolic or endocrine abnormalities are important factors in the aetiology of obesity. However, recent genome-wide association studies have clearly revealed that there is a strong genetic contribution to obesity (Loos, 2012). These may vary with ethnicity. Several candidate genes have been proposed and LXRα is one of these candidates. The present study is the

first to test the relationship between two common LXRα gene SNPs (rs11039155G > A and rs2279238C > T) and obesity/overweight or its related traits in Iranian adults.

Our results showed no significant genetic association between the rs11039155G > A and rs2279238C > T SNPs with obesity or overweight. The genotypic distributions and allele frequencies of these two polymorphisms did not show any significant disease association, nor was there any convincing evidence for a significant association between obesity and LXRα diplotypes and haplotypes. There were no significant differences in the means of the anthropometric and clinical variables between genotype groups (Table 3). These results suggest that these two SNPs are not major risk factors for obesity and related phenotypes in our population from Northeastern Iran.

There have been few previous studies on the association between the LXRα gene variants and obesity or obesity-related phenotypes. In one population-based study comprised of 559 Swedish women, Dahlman et al. (2006) demonstrated that LXRα mRNA expression levels in adipose tissue were higher in obese woman compared to non-obese women. They also observed associations between the LXRα SNP rs2279238, but not the rs11039155 and BMI, and between the LXRα haplotype CAAGCC (constituted by the LA5884G > C, LA9299G > A, rs12221497G > A, rs11039155G > A, rs2279239T > C, rs2279238C > T alleles) with obesity. They reported that rs2279238 CT carriers had the highest BMI; assuming a recessive, but not dominant model, suggesting a protective impact of the common C allele on BMI. Although our results appear inconsistent with those of Dahlman et al. with respect to the rs2279238 polymorphism, our results have a similar trend in the case of the rs11039155 polymorphism. Legry et al. (2008) reported no significant association between the *NR1H3* SNPs and plasma triglyceride concentrations, but rs11039155 AA carriers displayed an increased plasma HDL-cholesterol concentration and a 30% decrease in risk of having metabolic syndrome in a French population. With respect to the rs2279238 polymorphism, the findings of the present study are similar to those of Legry et al.

Legry et al. (2008) also reported that NR1H3 mRNA levels in macrophages were not affected by the rs11039155 SNP. Kozak (1987) have proposed that a nucleotide located six base pairs upstream from the ATG site can affect recognition of the AUG codon, so the rs11039155 (-6G > A) polymorphism located at this position in the 5′ region of NR1H3 may affect recognition of the AUG codon, making it more likely that it influences translational efficiency. The rs2279238 SNP is located in the coding region at an exon splicing enhancer (ESE) site in *NR1H3* exon 5, where splicing factor SRp55 binds. The nucleotide C to T substitution is, however, synonymous, resulting in no change in protein sequence (Price et al., 2011). Hence, the mechanism by which this splice variant may affect physiology or disease pathogenesis remains to be determined. A further possible explanation for these inconsistent findings could be that another disease associated variant is in linkage disequilibrium with these two SNPs in other populations. Ethnic and lifestyle differences between populations may affect the results of disease association studies.

According to Luan et al. (2001) the effects of genetic polymorphism on obesity phenotypes may be altered by the nutritional characteristics of populations. It is possible that different dietary patterns between Iranian and European populations could modulate the effect of genetic polymorphism on obesity phenotypes. On the other hand, study of lifestyle influences and other circumstances may reveal the effects of a given gene variant.

Our study was conducted in a well-defined and ethnically homogenous population sample, although randomized cluster sampling avoided possible bias due to selection of obese/overweight and normal subjects. However, only two SNPs in *NR1H3* gene locus were studied, so it is not possible to conclude that genetic variability in LXRα is not associated with obesity or its related phenotypes. The relatively small sample size is also an important limitation of the present study and its statistical power may be insufficient to detect a weak genotype–phenotype association. Furthermore, it would be important to take into account lifestyle factors such as physical activity and dietary intake.

Conclusion

To our knowledge, this is the first study to investigate the association between two SNPs in LXRα and obesity in an Iranian population. Based on the present results, there was no association between LXRα gene rs11039155G > A and rs2279238C > T polymorphisms and obesity/overweight or related traits. With this in mind, it is clear that the obtained results here should be interpreted within the context of its limitations and given the relatively small size of the study sample; further studies in other groups of subjects may be helpful to investigate a more subtle effect of this gene in this serious phenotype.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. This work was supported financially by the Gastroenterology and Liver Disease Research Center, Shahid Beheshti University of Medical Sciences (Research Project Number: 648, as a PhD student dissertation).

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