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Associations of the PPARα and Lipoprotein Lipase Enzyme Gene Polymorphisms with Dyslipidemia in Obese and Non-obese Males

Rithab Ibrahim Al-Samawi[1,*], Thekra A. Al-Kashwan[2], Abdul Hussein A. Algenabi[2]

[1]Department of Clinical Biochemistry, College of Pharmacy, University of Al-Ameed, Karbala; [2]Department of Clinical Biochemistry, College of Medicine, Kufa University, Najaf, Iraq

Background: Peroxisome proliferator-activated receptor α (PPARα) is a nuclear transcription factor responsible for gene expression, particularly those associated with lipid metabolism. The lipoprotein lipase enzyme (LPL) is considered a key enzyme in lipid metabolism and transport. The link between dyslipidemia and obesity is well understood. Dyslipidemia is also an established risk feature for cardiovascular disease. Thus, it becomes progressively essential to identify the role of genetic factors as risk markers for the development of dyslipidemia among obese males.

Methods: A case-control study was performed including 469 males. Anthropometric characteristics and serum lipid profiles such as triglycerides (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were evaluated. Genomic DNA extraction and purification were performed using whole blood samples. Restriction enzyme fragment length polymorphism was used to genotype PPARα and LPL single nucleotide polymorphisms. The associations between these polymorphisms and dyslipidemia were examined.

Results: The CC and CG genotypes of PPARα gene polymorphisms were significantly associated with higher TC and LDL-C levels ($P<0.05$). The TT genotype of the LPL gene polymorphism was significantly associated with higher TG levels and lower HDL-C levels ($P<0.05$). In contrast, the GG genotype may have a protective action against dyslipidemia.

Conclusion: The study reaches the interesting conclusion that there was a significant association between PPARα as well as LPL gene polymorphisms and dyslipidemia among obese and non-obese males.

Key words: Obesity, Dyslipidemia, Polymorphism, PPAR alpha, Lipoprotein lipase enzyme

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*Corresponding author
Rithab Ibrahim Al-Samawi

https://orcid.org/0000-0001-8112-7633

Department of Clinical Biochemistry, College of Pharmacy, University of Al-Ameed, PO Box 198, Karbala, Iraq
Tel: +964-7805773389
E-mail: risamawi@alameed.edu.iq

INTRODUCTION

Dyslipidemia is a metabolic abnormality characterized by alteration of the plasma lipids levels, represented by a decrease in the plasma high-density lipoprotein cholesterol (HDL-C) levels and increases in triglyceride (TG), total cholesterol (TC), and low-density lipoprotein cholesterol (LDL-C) levels.[1,2] Obesity is a complex disease involving an imbalance between food intake and energy dissipation.[3] The pathogenesis of obesity consists of both genetic and environmental factors. Obesity is widely prevalent and exhibits no sign of improvement, because weight loss is not only hard to achieve but also very difficult to maintain over time.[4] The association between dyslipidemia and obesity is an established risk factor of atherogenic cardiovascular diseases.[5] Many genes are involved in regulatory pathways for weight gain and obesity. Ligand-activated receptors called peroxisome proliferator-activated receptors (PPARs) participate in the lipid and glucose regulation of metabolism and also have a crucial role in the pathogenesis of obesity, diabetes (type

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2), adipocyte dysfunction, insulin resistance, fatty liver, and metabolic syndrome.[6] These functions indicate PPARs as candidate genes for obesity treatment, considering that any abnormality of these metabolic pathways due to single nucleotide polymorphisms (SNPs) may contribute to obesity and metabolic syndrome.[7] The PPARα has been described as a lipid sensor and is also associated with mitochondrial and microsomal ω-oxidation and peroxisomal β-oxidation of fatty acids, resulting in decreased fat storage and energy burning.[8] The SNP that has been differently related to dyslipidemia in various populations is PPARα (intron 7 G2467C) rs4253778.

Obesity changes lipoprotein metabolism, characterized by increases in TG and LDL-C and a decrease in HDL-C levels. Lipoprotein lipase enzyme (LPL) is considered an essential rate-limiting enzyme for degrading TG-rich lipoprotein into glycerol and free fatty acids. It enhances the hydrolysis of TG found in very low-density lipoprotein cholesterol (VLDL-C) and chylomicron particles. Therefore, it plays a vital role in plasma TG levels.[9] It was reported that the HindIII polymorphism of the LPL gene is considerably correlated with lipid metabolism.[10] Therefore, we focused on PPARα and LPL gene polymorphisms as genetic risk factors for the progression of dyslipidemia in obese and non-obese males.

METHODS

Participants and study design

A case-control study involving 469 apparently healthy males (including 217 obese and 252 non-obese) from the middle region of Iraq was established at the Department of Biochemistry in the College of Medicine, University of Kufa. Information regarding history of lipid abnormality, drug therapy, exercise, and smoking status was recorded based on face-to-face survey questions. The participants chosen for the study were categorized as non-obese and obese as defined by the World Health Organization criteria: body mass index (BMI) ≥ 30 kg/m^2 was considered obese, and BMI between 18.5 to 24.9 kg/m^2 was considered non-obese. The exclusion criteria were chronic illness (including hepatic, renal, or thyroid; heart failure; and diabetes), use of lipid-lowering agents, and use of alcohol and/or smoking. Females were not included due to sex variations in lipid parameters. Younger females have a more appropriate lipid profile, represented by higher HDL-C and lower LDL-C levels than do female after menopause.[11] Moreover, the obesity prevalence in males rapidly decreases after the age of 50 years, while the obesity prevalence in females immediately increases after the age of 30 years.[12] The Institutional Review Board of the Medical Ethical Committee at Kufa Medical College, University of Kufa approved this study (IRB no. 2253 on 2021-02-20). Written informed consent was obtained from all participants.

Anthropometric and biochemical examinations

Anthropometric measurements of body height, weight, and waist-to-hip ratio (W/H) were routinely performed in this study. The BMI was measured as weight (kg)/height (m^2). Furthermore, quantitative analyses of TG, TC, and HDL-C were performed from fasting venous blood samples using enzymatic colorimetric methods (Biolabo). The LDL-C concentration was calculated using the Friedewald equation.

Genomic DNA extraction

Genomic DNA was isolated from frozen whole blood samples of each participant in ethylenediaminetetraacetic acid disposable tubes using a DNA purification kit (Geneaid) according to the manufacturer's instructions and stored at –20 °C until use. The quantity and quality of the genomic DNA were measured using a photometer (IMPLEN NP 80).

Genotype detection analysis

The PPARα gene (rs4253778) was determined according to the method of Flavell et al.[13] A forward primer of 5′-ACAATCACTCCTTAAATATGGTGG-3′ and reverse primer of 5′-AAGTAGGGACAGACAGGACCAGTA-3′ were used. The amplification protocol was initial denaturation at 94 °C for 5 minutes, followed by 35 cycles of DNA denaturation at 95 °C (30 seconds), annealing at 53 °C (30 seconds), and extension at 72 °C (30 seconds); and final extension for 5 minutes at 75 °C. The amplification product was 266 bp in size. The LPL gene (rs320) was studied using a forward primer of 5′-TGA AGC TCA AAT GGA AGA GT-3′ and a reverse primer of 5′-TAC AAG CAA ATG ACT AAA-3′. The polymerase chain reaction (PCR) conditions were as follows: initial denaturation at 94 °C for 2 minutes, followed by 40 cycles of 94 °C for 15 seconds, 50 °C for 30 seconds, and 72 °C for 1 minute;

with a final extension at 72 °C for 2 minutes.[14] The PCR products of amplification were 770 bp in size.

To determine the PPARα G/C intron 7 gene polymorphisms, the TaqI restriction enzyme (Promega) was used to digest the PCR products, the resulting fragments were resolved by electrophoresis on 2% agarose gels, and the PPARα gene polymorphism was determined by substitution of guanine (G) with cytosine (C). The allele that exhibits the restriction site is described as the C allele, while the allele indicating absence of the site is the G allele. The CC genotype indicates homozygotes for the site (bands at 216 and 50 bp), while the GC genotype indicates heterozygotes for absence and presence of the site (bands at 266, 216, and 50 bp). Homozygotes for the absence of the site (band at 266 bp) are referred to as the GG genotype. For determination of the LPL gene (rs320), digestion of PCR products was achieved using the HindIII restriction enzyme (Promega), and the resulting fragments were resolved by electrophoresis on 2% agarose gels. The allele showing the restriction site is referred to as the thymine (T) allele, while the allele noting the absence of the site is the G allele. The TT genotype indicates homozygotes for presence of the site (600 and 170 bp), and the TG genotype indicates heterozygotes for the presence and absence of the site (770, 600, and 170 bp). Homozygotes for the absence of the site (770 bp) are referred to as the GG genotype.

Statistical analysis

Data were analyzed using IBM SPSS statistics version 26 (IBM Co.). All calculated data are presented as mean ± standard deviation. Two-sample t-test was used to compare the non-obese and obese groups. The one-way analysis of variance test was applied to distinguish mean lipid concentration in the genotype groups. A $P < 0.05$ was considered statistically significant. The distribution of genotypes was consistent with Hardy-Weinberg equilibrium. Multinominal logistic regression analysis was performed to test the associations between variables and the LPL and PPARα genotypes.

RESULTS

Characteristics of the study population

The demographic, anthropometric, and biochemical characteristics of the 217 obese and 252 non-obese males are shown in Table 1.

Table 1. Demographic, anthropometric, and biochemical properties of the obese and non-obese males

Variable	Obese (n=217)	Non-obese (n=252)	*P*
Age (yr)	42.26±6.88	40.96±7.44	NS
Height (cm)	173.86±3.75	174.95±3.15	NS
Weight (kg)	95.17±8.01	72.76±7.01	<0.001*
BMI (kg/m^2)	32.00±2.66	23.59±1.11	<0.001*
Waist circumference (cm)	108.86±7.23	89.16±8.23	<0.001*
Hip circumference (cm)	107.07±7.37	99.87±8.37	<0.001*
W/H	1.02±0.05	0.88±0.06	<0.001*
TC (mmol/L)	4.53±0.71	4.01±0.87	<0.001*
TG (mmol/L)	1.74±0.64	1.41±0.61	<0.001*
HDL-C (mmol/L)	0.82±0.18	0.90±0.15	<0.010*
LDL-C (mmol/L)	2.75±0.53	2.39±0.54	<0.001*
Types of obesity			<0.001*
Subcutaneous (W/H)	0.96±0.03	0.88±0.06	
Visceral (W/H)	1.04±0.04	-	
Subcutaneous	47 (21.66)	-	
Visceral	170 (78.34)	-	
Physical activity (n)			NS
Vigorous	7	8	
Moderate	210	244	
Educational status (n)			NS
Middle school	167	199	
College and above	50	53	

Values are presented as mean ± standard deviation or number (%).
*$P < 0.05$.
BMI, body mass index; W/H, waist-to-hip ratio; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NS, not significant.

The mean plasma lipids levels were significantly higher in the obese males ($P < 0.01$) than they were in the non-obese males. In contrast, the HDL-C level was significantly lower in the obese males than it was in the non-obese control group. Among the obese subjects, the number of subjects with visceral obesity was higher than that of those with subcutaneous obesity.

Interactions between LPL, PPARα genotypes, and parameters

In this study, within the non-obese group, the frequencies of the GG genotype of the PPARα gene polymorphism were higher than those in the obese group. In contrast, the frequencies of the GC and CC genotypes were lower in the non-obese group than they were in the obese group. For the LPL gene polymorphism, the frequencies of the GG and TG genotypes within the non-obese group

were higher than were those in the obese group (Table 2). In contrast, the frequencies of the TT allele were lower in the non-obese group than they were in the obese group (Table 2). Multinomial logistic regression analysis was performed to assess the interactions of LPL and PPARα genotypes with BMI; W/H; and TC, TG, HDL, and LDL levels (Table 3). The TT related to GG genotypes of the LPL gene polymorphisms revealed significant associations with TC and LDL ($P=0.01$ and $P=0.003$, respectively), while the TT related to TG genotypes exhibited significant associations with W/H and TG ($P=0.001$ and $P=0.001$, respectively). However, the GC related to GG genotypes of PPARα polymorphisms revealed significant associations with BMI and W/H ($P=0.0002$ and $P=0.025$, respectively).

Table 2. PPARα and LPL genotype distributions and allele frequencies

Variable	PPARα		LPL	
	Non-obese (n=252)	Obese (n=217)	Non-obese (n=252)	Obese (n=217)
Genotype, frequencies of allele				
CC	-	6 (2.77)	-	-
GC	53 (21.03)	74 (34.10)	-	-
GG	199 (78.97)	137 (63.13)	-	-
GG	-	-	66 (26.19)	44 (20.28)
TG	-	-	73 (28.97)	54 (24.88)
TT	-	-	113 (44.84)	119 (54.84)
Frequencies of allele total				
G	0.89	0.8	-	-
C	0.11	0.2	-	-
T	-	-	0.59	0.67
G	-	-	0.41	0.33

Values are presented as number (%).
PPARα, peroxisome proliferator-activated receptor α; LPL, lipoprotein lipase enzyme; C, cytosine; G, guanine; T, thymine.

Associations of PPARα and LPL genotypes with lipid concentrations

The association of PPARα genotypes with the plasma lipid concentration was analyzed. Subjects with GC and CC genotypes had higher TC and LDL-C levels than those with the GG genotype ($P<0.05$). Regarding the LPL gene polymorphism, subjects with the TT genotype had higher TG levels and lower HDL-C levels than those with the GG genotype ($P<0.05$) (Table 4).

Table 3. Associations between LPL and PPARα genotypes and laboratory parameters using multinominal logistic regression analysis

Genotype	Variable	Coefficient	SE	z-statistic	Lower	Upper	Exp(b)	*P*
LPL genotypes								
TT related to GG	BMI	0.04	0.02	1.80	−0.004	0.09	1.04	0.0717
	W/H	1.81	1.30	1.39	−0.73	4.36	6.14	0.1631
	TC	−0.36	0.14	−2.42	−0.65	−0.06	0.69	0.0154*
	TG	−0.11	0.18	−0.64	−0.47	0.24	0.88	0.5212
	HDL	1.55	0.81	1.91	−0.03	3.15	4.75	0.0555
	LDL	−0.66	0.22	−2.90	−1.10	−0.21	0.51	0.0036*
TT related to TG	BMI	−0.03	0.03	−1.08	−0.10	0.03	0.96	0.2777
	W/H	3.95	1.26	3.11	1.47	6.44	52.37	0.0018*
	TC	0.06	0.14	0.45	−0.21	0.34	1.06	0.6478
	TG	0.60	0.19	3.14	0.22	0.97	1.82	0.0016*
	HDL	−0.62	0.62	−0.99	−1.86	0.60	0.53	0.3196
	LDL	−0.08	0.20	−0.40	−0.48	0.32	0.92	0.6882
PPARα genotypes								
GC related to GG	BMI	0.08	0.02	3.68	0.03	0.12	1.08	0.0002*
	W/H	−6.62	2.95	−2.24	−12.42	−0.83	0.001	0.0250*
	TC	0.12	0.13	0.92	−0.14	0.39	1.13	0.3500
	TG	−0.07	0.17	−0.46	−0.41	0.25	0.92	0.6446
	HDL	−0.06	0.62	−0.10	−1.28	1.15	0.93	0.9139
	LDL	0.31	0.20	1.53	−0.08	0.71	1.36	0.1237

*$P<0.05$; 95% confidence interval.
LPL, lipoprotein lipase enzyme; PPARα, peroxisome proliferator-activated receptor α; SE, standard error; T, thymine; G, guanine; BMI, body mass index; W/H, waist-to-hip ratio; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; C, cytosine.

Table 4. Relationships of PPARα and LPL genotypes with lipid concentrations in the study population

Lipid	PPARα			LPL			
	GG	GC+CC	*P*	TT	TG	GG	*P*
TG (mmol/L)	1.58±0.67	1.41±0.61	0.013*	1.67±0.77	1.44±0.56	1.59±0.72	0.017*
HDL-C (mmol/L)	0.86±0.18	0.85±0.15	0.619	0.87±0.18	0.86±0.16	0.92±0.11	0.012*
TC (mmol/L)	4.30±0.76	4.45±0.65	0.042*	4.26±0.79	4.32±0.76	4.44±0.75	0.151
LDL-C (mmol/L)	2.58±0.61	2.74±0.53	0.014*	2.57±0.51	2.63±0.46	2.67±0.42	0.164

Values are presented as mean±standard deviation.
*$P<0.05$.
PPARα, peroxisome proliferator-activated receptor α; LPL, lipoprotein lipase enzyme; G, guanine; C, cytosine; T, thymine; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol.

DISCUSSION

In this study, we evaluated whether PPARα (intron 7 G/C) rs4253778 and LPL rs320 variants can be considered genetic risk factors for dyslipidemia among obese male subjects. Several previous studies have focused on the associations between PPARα and LPL gene polymorphisms and the progression of dyslipidemia in various diseases and populations.[15-17] Some of these studies analyzed the influence of PPARα gene polymorphisms on plasma lipid levels. Other studies investigated the effects of LPL gene polymorphism on the plasma lipid profile. However, the results are inconsistent.

Association of PPARα gene polymorphisms with dyslipidemia in obese and non-obese males

Various polymorphic regions have been detected within the PPARα gene, although many of these polymorphic sites are uncommon or functionally silent. In 2002, Flavell et al.[13] discovered a novel GC polymorphism site in intron 7 (rs4253778). This group also reported an increase in the progression of atherosclerosis among C allele carriers compared to that among G allele homozygotes.[13] In our study, the homozygote genotype of the C allele was pooled with the heterozygote genotype GC due to the low frequency of CC. Interestingly, none of the non-obese males had the CC homozygote genotype. Our results demonstrated that the genotype distribution and frequency of the C allele were higher than those in the Indian population,[18] similar to those in European populations[19] and the Chinese Han population,[20] but lower than those in the Brazilian elderly.[21] However, the data concerning the Iraqi population are limited. The PPARα gene is thought to be a candidate for assessment of dyslipidemia and atherosclerosis because of its important role in regulating lipids metabolism in response to fatty acids.[22] Therefore, it is crucial to confirm if polymorphisms in the PPARα gene are associated with alterations in the serum lipid concentration among obese and non-obese males. In the present study, significant associations were recognized between lipids parameters and PPARα genotypes in the study population. The CC and GC genotypes were significantly associated with increased TC and LDL-C levels compared with the GG genotype (Table 4). These findings suggest that the C allele significantly promotes dyslipidemia. Similarly, Purushothaman et al.[18] observed a positive association between the C allele and dyslipidemia that led to an increase in the risk of cardiovascular diseases. Likewise, Doney et al.[23] revealed that the presence of the C allele increases the risk for myocardial infarction in the Scottish population. Interestingly, Márkus et al.[24] indicated that the C allele is closely related to the concentration of serum fetuin-A, which is a hepatic glycoprotein that has been implicated in the progression of obesity. Furthermore, an earlier study showed that the C allele is associated with increased TC and LDL-C levels in diabetic patients.[25] It also has been reported that the C allele of the PPARα gene polymorphism plays an important role in the enhancement of atherosclerosis in obese individuals.[26] In our study, a significant interaction was noted between BMI, W/H, and PPARα gene polymorphisms in the GC related GG groups (Table 3). The intron 7 G/C (rs4253778) gene polymorphisms of the PPARα gene are associated with a G-to-C transversion; however, because of its intronic location, this polymorphism is unlikely to be functional. However, it may be associated with a functional variant located in a promoter region or in an enhancer element of the PPARα gene, which leads to a reduction in gene expression.[18]

Association of the LPL gene polymorphisms with dyslipidemia in obese and non-obese males

The lipoprotein lipase gene has several polymorphisms, approximately 80% of which occur in the coding regions and 20% in the noncoding regions.[27] The Hind III polymorphism of the LPL gene (rs320) arises from a substitution of the amino acid T with amino acid G; this polymorphism was considered of particular importance due to its common occurrence.[16] In this study, the TT genotype was positively associated with high serum TG and lower HDL-C concentration, while the GG genotype was significantly associated with lower serum TG and higher HDL-C concentrations (Table 4). The genotype distribution of the LPL gene shows that the TT frequencies were higher in obese males than they were in non-obese males. In contrast, the GG frequencies were higher in non-obese than in obese males (Table 2). These findings are in agreement with several previous studies.[16,28,29] Our results revealed that the G allele frequency was similar to that observed among the Saudi[16] and Kuwaiti populations[30] but higher than that in the Chinese population[31] and lower than that in the Indian population.[32] These findings suggest that the prevalence of the G allele may differ across the population and have an ethnic specificity. Polymorphisms of the LPL gene have been widely disseminated in humans, and the impact of an LPL gene polymorphism (rs320) on lipid metabolism and concentration, involving TG, TC, HDL-C, and LDL-C, have been described.[33,34] Several studies exhibit a relationship between the T allele and risk of progression of metabolic disorders.[33-35] He et al.[36] reported that the G allele has a protective role among Asian populations but not in Europe since the G allele exerts a reverse relationship in Europeans. Furthermore, our previous study revealed that the T allele was significantly linked with decreased serum HDL-C concentration and increased TG concentration among Iraqi males who smoke. In contrast, the G allele demonstrated protected effects against dyslipidemia.[29] However, Munshi et al.[37] revealed no variation in the levels of LDL or VLDL among the LPL genotypes in the Indian population. The activity of LPL is known to influence HDL-C levels through its hydrolysis of TG-rich lipoprotein; perhaps the T allele influences the LPL activity, which leads to hypertriglyceridemia and lowered HDL-C levels. In addition, a decrease in LPL activity may impair the hydrolysis of TG in TG-rich molecules (VLDL-C and chylomicron), decreasing the amount of surface material that is necessary to produce newly synthesized HDL-C.[36] Hence, it was suggested that the TT genotype is a risk factor for progression of atherosclerosis. In contrast, the G allele is thought to either reflect a polymorphism that changes the amino acid in the LPL (leading to an increase in the enzyme activity) or the efficiency of the lipid binding; alternatively, the alteration in the sequence within the gene promoter may lead to an increase in LPL expression.[38] The significant decrease in TG levels among individuals carrying the G allele could result from an increase in the clearance rate of TG-rich lipoproteins or due to increased lipid hydrolysis by the LPL enzyme. This increased hydrolysis leads to a decrease in the serum level of TG and increases in the transferred protein, phospholipid, and cholesterol from TG-rich lipoprotein to HDL particles; therefore, the production and concentration of HDL are both increased.[39] Interestingly, genetic polymorphisms in the LPL gene may affect the transfer of lipids and its metabolism and could modulate the subject's susceptibility to atherosclerosis. Since the Hind III polymorphism is present in an intron, the relationship is linked to a polymorphic locus that occurs in exon 9 (represented by Ser447Ter), to which it is fully connected.[40] In the present study, there was a significant interaction between TC, LDL, and LPL gene polymorphisms concerning the TT related GG genotypes, while there was considerable interaction between W/H, TG, and LPL gene polymorphisms concerning the TT related TG genotypes (Table 3). There are numerous target genes responsible for lipid metabolism that are regulated by PPARα. For example, PPARα activators can increase LPL activity, which influences TC and LDL-C levels through its hydrolysis of TG-rich lipoproteins. This suggests that the C allele of the PPARα gene may play a role in LPL activity that leads to increased TC and LDL-C concentrations.[21] However, the mechanisms by which the intron 7 polymorphism of the PPARα gene affects lipid levels remain unknown. Thus, the role of the C allele is yet to be detected.

In conclusion, the study revealed that the CC and CG genotypes of PPARα gene polymorphisms were significantly associated with obesity in the Iraqi population. The relationship between the intron 7 polymorphism of the PPARα gene with dyslipidemia suggests that the C allele is linked to increases in the TC and LDL-C serum concentrations. The study also demonstrates that the TT genotype of the LPL gene polymorphism was significantly related

to increased serum TG concentration and decreased HDL-C concentration among the study population. In contrast, the GG genotype may have protective action against dyslipidemia.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Study concept and design: RIAS; acquisition of data: RIAS; analysis and interpretation of data: RIAS, TAAK, and AHAA; drafting of the manuscript: RIAS, TAAK, and AHAA; critical revision of the manuscript: RIAS, TAAK, and AHAA; statistical analysis: RIAS; and study supervision: TAAK and AHAA.

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