Int J Mol Epidemiol Genet 2016;7(1):67-73
www.ijmeg.org /ISSN:1948-1756/IJMEG0010532

Original Article

Dyslipidemia, insulin resistance and dietary fat intake in obese and normal weight adolescents: the role of uncoupling protein 2 -866G/A gene polymorphism

Emy Huriyati[1*], Harry F Luglio[1*], Prima D Ratrikaningtyas[2*], Ahmad F A Tsani[1*], Ahmad H Sadewa[3*], Mohammad Juffrie[4*]

Departments of [1]Nutrition and Health, [2]Public Health, [3]Biochemistry, [4]Child Health, Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia. [*]Equal contributors.

Received May 22, 2015; Accepted February 28, 2016; Epub March 23, 2016; Published March 30, 2016

Abstract: Obesity in adolescents has been associated with increased cardiovascular risk factors such as dyslipidemia and insulin resistance. Several factors have been proposed to be associated with cardiovascular risk factors in adolescents including dietary habit, physical activity and genetic. This study was aimed to evaluate the interaction between genetic variation and dietary intake on cardiovascular metabolic risk factors in obese and normal weight adolescents. The UCP2 gene was chosen because it was previously correlated with dietary intake and cardiovascular risk factors. This study is a case control study done in 10 senior high school in Yogyakarta. Subjects were obese and normal weight adolescents taken from an obesity screening with age ranged between 16 and 18 years old. Dyslipidemia was observed by measuring total cholesterol, triglyceride, LDL dan HDL level while insulin resistance was determined by calculating fasting glucose and insulin level. Lipid profile, glucose and insulin level were measured after 8 hours of fasting. UCP2 -866G/A gene polymorphism were determined using *polymerase chain reaction-restriction fragment length polymorphism* (PCR-RFLP). The results show that obese adolescents had significantly higher blood pressure, total cholesterol, LDL, triglyceride, insulin level and lower HDL level than their normal weight counterparts (all $p<0.001$). In obese adolescents, UCP2 -866G/A was associated with blood pressure ($p=0.025$), total cholesterol level ($p=0.025$), LDL ($p=0.024$) level and HOMA IR ($p<0.001$) but not with dietary fat intake ($p=0.386$). Additionally, subjects with UCP2 -866G/A gene polymorphism and high dietary fat intake had lower risk on obesity compared to those without UCP2 -866G/A gene polymorphism and low dietary fat intake. We conclude that the UCP2 -866G/A was associated with dyslipidemia, insulin resistance in obese adolescents. Additionally, we also observed the interaction between UCP2 -866G/A gene polymorphism and dietary intake on the risk of obesity.

Keywords: Adolescent obesity, UCP2, dyslipidemia, insulin resistance, dietary fat

Introduction

The worldwide prevalence of obesity in childhood and adolescent has been increasing in the recent decades. This is not only a problem for developed countries such as United States and Europe [1], but also a problem for developing countries such as Indonesia. Based on National Health Survey in 2013 [2], the current prevalence of overweight and obesity for adolescents aged 16-18 years old is 7.3%. This number was dramatically increased from data in 2007 which showed only 1.4% of adolescents aged 16-18 years old were overweight or obese.

Childhood and adolescent obesity has become an important risk factor for cardio metabolic disorder such as dyslipidemia, insulin resistance, and inflammation [1]. In our previous study, we found that 55.7% of obese adolescent girls were insulin resistant [3]. It has been previously showed before that obese adolescent had abnormal atherogenic lipid profile consisted by increased LDL and triglyceride level as well as reduced HDL level [4-6]. Although the exact mechanism is still remain unclear, it is suspected that dyslipidemia occurred in obese adolescents was due to insulin resistance [1]. Additionally, a consecutive increment in dietary

Table 1. Characteristics of subjects

Characteristics	Obese* (n=106)	Normal Weight* (n=155)	*p*
Age (years)	16.87±0.64	16.79±0.64	0.1367
Height (cm)	163.69±9.09	162.69±8.86	0.1865
Weight (kg)	90.73±13.95	56.37±10.34	<0.0001
BMI/age (z-score)	2.50±0.05	-0.41±0.07	<0.0001
Waist circumference (cm)	96.11±10.86	72.28±9.92	<0.0001
Neck circumference (cm)	36.44±4.28	31.90±3.17	<0.0001
Systolic Blood Pressure (mmHg)	120.67±11.46	112.88±13.74	<0.0001
Diastolic Blood Pressure (mmHg)	82.15±9.44	77.10±9.67	<0.0001
Fasting blood glucose (mg/dl)	84.00±10.21	82.76±9.76	0.1621
Fasting insulin (µl/dl)	22.26±9.67	11.75±5.63	<0.0001
HOMA IR	2.75±0.25	1.38±0.59	<0.0001
HOMA % S	47.39±2.08	85.10±3.51	<0.0001
HOMA β	216.58±7.62	143.73±4.13	<0.0001
Total cholesterol (mg/dl)	178.23±37.017	159.87±29.54	<0.0001
LDL (mg/dl)	102.74±39.19	83.23±29.28	<0.0001
HDL (mg/dl)	45.78±9.40	52.45±11.04	<0.0001
Triglyceride (mg/dl)	117.77±63.37	79.38±32.20	<0.0001
Fat intake (gr)	71.67±39.35	78.13±36.81	0.0084
Proportion of energy from fat (%)	23.95±5.99	24.29±5.93	0.3237

**mean ± SD.*

fat intake was also related to elevated lipid in blood [7].

One of the important regulators of lipid metabolism is Uncoupling Protein 2 (UCP2). This protein is expressed in wide variety of tissues such as spleen, immune system, pancreas and central nervous system; therefore studies suggested that UCP2 is an important regulator of dietary intake, insulin and immune response [8]. Due to its ability to control dietary intake and energy metabolism, it has been suggested that UCP2 gene polymorphism is associated with obesity. A meta-analysis study showed that A allele of UCP2 -866G/A polymorphism had a protective effect on overweight and obesity, especially for European populations [9]. Additionally, a cross sectional study in Balinese population suggested that environment factor is an important component to be address when analyzing the effect of UCP2 -866G/A polymorphism on obesity and cardio-metabolic risk factors [10]. Therefore this study was aimed to analyze the interaction of UCP2 -866G/A gene polymorphism with dietary fat intake on obesity, dyslipidemia, and insulin resistance in adolescents.

Material and methods

This is an observational study with case control design done in Yogyakarta, Indonesia. Obese adolescent boys and girls aged between 16-18 years old were in the case group and their normal weight counterparts were in control group. Obese subjects were randomly selected based on obesity screening on more than 3918 students in 10 senior high schools in Yogyakarta. Meanwhile their normal-weight counterparts were matched based on gender age and area of high school. This study has been approved by the ethical committee of Faculty of Medicine, Universitas Gadjah Mada. After selected, the parents of subjects were given the informed consent regarding the study design, what will be measured and what is the purpose of the study. The inclusion criteria includes age between 15-21 years old, their parents agreed to sign the informed consent, not having chronic diseases. The exclusion criteria of this study were having a medication during test days.

All measurements include anthropometric, dietary intake and blood pressure measurement were done by trained enumerators. Body weight was measured using a digital scale with 0.1 kg precision. Height was measured using a microtoise with 0.1 cm precision. BMI (body mass index) was calculated by dividing weight in kg by the square of height in meter. The status of obesity and normal weight were determined by calculating Z score using BMI for age based on WHO standard. Waist circumference and neck circumference were measured using plastic tape with 0.05 mm precision. For the neck circumference, the tape was placed below laryngeal prominence and applied perpendicular to the long axis of the neck [11]. For the waist circumference, tape was placed in line with umbilical cord and circular around the waist. Before the measurement preformed,

Table 2. The association between obesity, blood pressure, biochemical measurements and fat intake

Variable	Obese n (%)	Normal Weight n (%)	*p*	OR	CI 95%
Gender					
Male	59 (55.66)	86 (55.48)	0.978	1.01	0.59-1.708
Female	47 (44.34)	69 (44.52)			
Waist Circumference					
>80 (female) and >90 (male)	93 (87.74)	17 (10.97)	0.0001	58.07	25.4-135.6
≤80 (female) and ≤90 (male)	13 (12.26)	138 (89.03)			
Neck Circumference					
High	121 (91.66)	62 (48.07)	<0.0001	12.1	5.8-27.1
Normal	11 (8.34)	67 (51.93)			
Systolic Blood Pressure					
High	77 (72.64)	71 (45.81)	0.0002	3.14	1.79-5.55
Normal	29 (27.36)	84 (54.19)			
Diastolic Blood Pressure					
High	82 (77.36)	80 (51.61)	0.0001	3.20	1.78-5.83
Normal	24 (22.64)	75 (48.39)			
Fasting blood glucose					
Normal	102 (96.23)	147 (94.84)	0.599	0.72	0.15-2.77
Low	4 (3.77)	8 (5.16)			
Fasting insulin					
High	33 (31.13)	3 (1.94)	<0.0001	22.9	6.76-119.15
Normal	73 (68.87)	152 (98.06)			
HOMA IR					
High	54 (50.94)	7 (4.52)	0.226	21.95	9.08-60.1
Normal	52 (49.06)	148 (95.48)			
HOMA % S					
Abnormal	98 (92.45)	97 (62.58)	<0.0001	7.3	3.23-18.59
Normal	8 (7.55)	58 (37.42)			
HOMA β					
High	85 (80.19)	84 (54.19)	<0.0001	3.42	1.87-6.38
Normal	21 (19.81)	71 (45.81)			
Total cholesterol					
High	20 (18.87)	13 (8.39)	0.012	2.54	1.13-5.84
Normal	86 (81.13)	142 (91.61)			
LDL					
High	20 (18.87)	11 (7.10)	0.004	3.04	1.31-7.36
Normal	86 (81.13)	144 (92.90)			
HDL					
Low	25 (23.58)	19 (12.26)	0.016	2.20	1.08-4.52
Normal	81 (76.42)	136 (87.74)			
Triglyceride					
High	24 (22.64)	5 (3.23)	<0.0001	8.78	3.10-30.3
Normal	82 (77.36)	150 (96.77)			
Genotype UCP2					
AA+GA	61 (57.55)	102 (65.81)	0.176	0.70	0.41-1.21
GG	45 (42.45)	53 (34.19)			
Dietary fat intake					
High	44 (41.51)	66 (42.58)	0.863	0.95	0.56-1.62
Normal	62 (58.49)	89 (57.42)			

Table 3. Characteristics of subjects

Characteristics	n	Obese (mean ± SD)			*p*	Normal Weight (mean ± SD)			*p*
		GG	GA	AA		GG	GA	AA	
N	261	45 (25/20)	49 (27/22)	12 (7/5)		53 (27/26)	81 (48/33)	21 (11/10)	
Age (years)	261	16.87±0.63	16.88±0.64	16.85±0.68	0.947	16.92±0.68	16.68±0.61	16.89±0.56	0.564
BMI/Age (kg/m^2) per Age	261	2.77±0.42	2.69±0.44	2.69±0.42	0.921	-0.04±0.99	-0.16±1.08	0.15±1.17	0.623
Waist Circ. (cm)	261	96.3±11.3	96.7±10.5	92.8±10.6	0.879	72.07±11.2	72.02±9.21	73.8±9.37	0.259
Neck Circ. (cm)	261	36.4±3.74	36.5±5.11	36.1±2.05	0.002	31.57±3.28	32.16±3.12	31.74±3.15	0.921
Blood Pressure (mmHg)									
Systolic blood pressure	261	121.5±12.1	120.2±10.5	119.6±13.0	0.504	114.3±10.9	111.9±15.8	113.2±11.6	0.009
Diastole blood pressure	261	83.6±11.5	80.8±6.7	82.3±10.6	0.002	79.1±8.6	76.7±10.3	73.5±8.9	0.323
Fasting glucose (mg/dl)	261	83.6±9.8	84.4±10.9	83.7±8.9	0.633	81.2±9.3	82.3±8.9	88.57±12.2	0.169
Fasting insulin (μmol/dl)	261	23.2±8.5	21.5±10.8	21.6±9.1	0.266	11.7±7.1	11.6±4.4	12.6±5.5	0.001
HOMA IR	261	2.9±1.0	3.2±4.4	2.7±1.1	<0.001	1.44±0.88	1.44±0.54	1.55±0.68	<0.001
HOMA β	261	239±81	217±97	223±70	0.310	154±58	152±49.7	136±45	0.310
HOMA % S	261	40.5±17.6	46.7±22	42.7±15.7	0.165	87±44	80.6±37	76.2±29.7	0.100
Total cholesterol (mg/dl)	261	184.1±43.2	172.4±29.7	179.9±38.2	0.045	160.7±30.3	160.5±30.6	155.5±23.6	0.376
HDL (mg/dl)	261	44.1±8.2	47.2±10.0	45.9±10.5	0.312	53.4±9.9	52.1±11.9	51.4±10.5	0.357
Triglyceride (mg/dl)	261	119.3±67	116.97±63	115.3±46.6	0.358	80.8±34.1	82.6±31.8	63.4±24.2	0.220
LDL (mg/dl)	261	103±43.8	96.6±30.8	126.7±45.1	0.0575	84.5±31.5	84.1±28.6	76.5±26.3	0.583
Fat intake (g)	261	69.1±35	73.7±38	72.6±59	0.041	75.6±37	80.9±36	73.8±39	0.922
% fat to energy	261	24.4±6.6	23.7±5.7	23±5.03	0.402	23.3±5.9	24.9±5.8	24.3±6.2	0.949

Data are presented as mean ± SD. If it is normally distributed, then they are presented as median ± 95% CI. Data were analyzed using STATA.

participants were asked to stand with their head positioned in the Frankfurt horizontal plane. All measurement tools were calibrated in the Department of Metrology, Yogyakarta.

Blood pressure was measured from subject's left hand or right hand for left handed subjects, while sitting on the chair for at least 5 minutes using a calibrated sphygmomanometer. Status of hypertension for our subjects was based on gender, age and height [12]. Percentile blood pressures are classified into 50th, 90th, 95th, and 99th. And the categories are: normal blood pressure is less than 90th percentile, pre-hypertension is between 90th-95th percentile and hypertension is more than 95th percentiles. Data on dietary fat intake was collected using a semi-quantitative food frequency questionnaire. This data is showed as an absolute fat intake (gram), and proportion of energy from fat to total energy intake. High fat intake was determined when subjects had fat intake more than 30% on their total energy intake.

Analysis on lipid profile, glucose and insulin level were done using a sample blood from subjects after 8 hours fasting. A 10 mL blood was collected using plain tube, and serum was separated from whole blood using a centrifuge. Total cholesterol, LDL, HDL and triglyceride were measured from plasma using Diasys. Glucose level was analysed using GOD-PAP. Insulin level was measured using an enzyme linked immunosorbent assay or ELISA. Insulin resistance was determined based on HOMA IR which calculated based on this equation HOMA IR = (fasting insulin [mg/dL] × fasting glucose [mU/mL])/405 [13].

After the serum was separated, the buffy coat was taken and DNA was extracted using salting out method. A total 100 μg DNA then being analyzed using polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) with forward primer: 5'-CACGCTGCTTCTGCCAGGAC-3' and reverse primer: 5'-AGGCTCAGGAGATGGACCG-3'. PCR conditions are, 8 minutes of denaturation in 95°C followed by 35 cycles of 95°C for 1 minute (denaturation), 55°C for 1 minute (annealing), 72°C for 1 minute (extension) and 72°C for 7 minutes (final extension). After being amplified, the PCR product then digested using BST UI enzyme digestion. Restriction fragments were resolved on a 3% agarose gel.

Statistical analysis was done using STATA (Stata corp). Initially, all parameters were compared between obese and normal weight subjects using independent t-test. A Chi-square test was performed to measure the relationship between obesity and abnormality of lipid profile, glucose and insulin resistance as well as dietary fat intake. Subjects then grouped

Table 4. Obesity according to UCP2 -866G/A gene polymorphism

Polymorphism -866G/A	Obese (%)	Normal Weight (%)	OR	95% CI	*p*
GA/AA	61 (57.55)	102 (65.81)	0.70	0.41-1.21	0.176
GG	45 (42.45)	53 (34.19)	1.00		
Allele A	97 (36.74)	99 (38.37)	0.932	0.64-1.35	0.701
Allele G	167 (63.26)	159 (61.63)	1.00		

Data are presented as n (%). If it is normally distributed, then they are presented as median ± 95% CI. Data were analyzed using STATA.

Table 5. Obesity, UCP2 -866G/A gene polymorphism, and dietary fat intake

UCP2	Fat intake	Obese (%)	Normal Weight (%)	OR	95% CI	*p*
+	High	3 (2.83)	20 (12.90)	0.19	0.03-0.72	0.006
+	Low	58 (54.72)	82 (52.90)	0.90	0.50-1.61	0.701
-	High	8 (7.55)	6 (3.87)	1.69	0.47-6.45	0.363
-	Low	37 (34.90)	47 (30.23)	1.00		
Total		106	155			

based on their genotype and Chi-square test was used to analyze the differences in lipid profile, glucose and insulin resistance between genotypes. The analysis was done separately based on obesity status. Finally, an analysis on gene-environment interaction were done using Fisher exact test in several stages. Significance level is based on *p* value less than 0.05.

Results

A total of 263 adolescents were agreed to participate in this study and only 261 were completed all the measurements. This number was consisted by 106 obese adolescents and 155 normal-weight counterparts. The characteristics of both groups are presented in **Table 1**. In this study, we found that obese adolescents had higher fasting insulin level but not fasting plasma glucose. Fasting total cholesterol, LDL, triglyceride were higher and HDL level was lower in obese adolescents. Although obese and normal weight subjects have similar glucose level, obese adolescents had higher insulin level. In addition, blood pressures in obese adolescents were also higher. There were differences in dietary intake between obese and normal weight adolescents. Obese adolescents had less fat intake but no differences were seen in proportion of energy from fat to total calorie intake (**Table 1**). In line with results from **Table 1**, the odds ratio of high blood pressure, dyslipidemia and insulin resistance were higher in obese adolescent group (**Table 2**). In this study, high fat intake and A allele were not associated with obesity.

As shown in **Table 3**, UCP2 -866G/A gene polymorphism was associated with several metabolic profiles in obese and normal-weight adolescents. In obese adolescents, the differences in blood pressure, HOMA IR, total cholesterol and neck circumference level were seen between genotypes (all $p<0.05$). In normal-weight adolescents differences in blood pressure, HOMA IR and fasting insulin were also seen between genotypes (all $p<0.05$).

The interaction between dietary fat intake, obesity, and UCP2 -866G/A gene polymorphism were evaluated in this study. There is no association between UCP2 -866G/A gene polymorphism and obesity in this study (**Table 4**). Additionally, we showed that there was an interaction between dietary intake and UCP2 -866G/A gene polymorphism and obesity. (**Table 5**). Interestingly, subjects with high dietary fat intake and had UCP2 -866G/A gene polymorphism were less likely to become obese (OR: 0.19, $p=0.006$) compared to those with normal dietary fat intake and had no UCP2 -866G/A gene polymorphism.

Discussion

In this study, we highlighted that obesity in adolescents was associated with insulin resistance and dyslipidemia. Although UCP2 -866G/A gene polymorphism is not associated with obesity, this SNP was associated with high blood pressure, dyslipidemia and insulin resistance. In the gene-environment model, this genetic polymorphism interacted with dietary fat intake to induce obesity in adolescents. To our knowledge, this is the first study that evaluates the interaction between UCP2 -866G/A gene polymorphism and dietary fat intake on obesity in adolescent.

In this study, we confirmed that obesity in adolescents is associated with metabolic disturbance such as dyslipidemia and insulin resistance. As seen in our study, although obese adolescent had similar glucose level with their

normal-weight counterparts the insulin level is significantly high showing the degree of lack of sensitivity to insulin. This result is analogous to what we found in obese female adolescents [3]. It has been reported before that children with obesity often endure several lipid abnormalities including elevated triglyceride and LDL as well as decreased HDL [14]. One of the prominent feature of obesity in children is insulin resistance which also seen in our study. Insulin resistance induces dyslipidemia by increasing hepatic delivery of non-esterified free fatty acids to form triglyceride which in turn will increase triglyceride-rich lipoprotein. The high triglyceride level are processed into LDL less stable HDL, this will lead to increasing LDL level and decreasing HDL level [15].

In this study, we found that UCP2 -866G/A gene polymorphism was not associated with obesity in adolescents. Interestingly, we showed that UCP2 -866G/A gene polymorphism was interacted to dietary fat intake on the risk of obesity. Subjects with UCP2 -866G/A gene polymorphism and high dietary fat intake had lower risk on obesity compared to those without UCP2 -866G/A gene polymorphism and low dietary fat intake. This protection of A allele has also been reported elsewhere [9]. However, to our knowledge this is the first study that evaluates the interaction between UCP2 -866G/A gene polymorphism and dietary fat intake on obesity in adolescent.

UCP2 -866G/A gene polymorphism was associated with insulin resistance and dyslipidemia in obese adolescents. The associations between UCP2 with insulin resistance and dyslipidemia have already been reported before. The variant was associated with increased risk of dyslipidemia among French type2 diabetic patients [16]. However, the contradiction is also found as previous study reported that UCP2 -866G/A gene polymorphism was not associated with lipid profile and fasting blood level [10].

The mechanism on how UCP2 influenced obesity and metabolic disorder has been reviewed before [17]. UCP2 is up-regulated by nutrients and affect metabolic activity and ATP generation. It has recently reported that UCP2 prevents pyruvate efflux from mitochondria thus affect the citric acid process and promote glucose oxidation compared to lipid metabolism [18]. This protein is also important for glucose-stimulated insulin secretion [19]. The UCP2 -866G>A polymorphism is located at the proximal promoter of UCP2, the changes of nucleotide base affect its transcription factor binding sites [20, 21]. Previous study showed that human islets with GA-genotype have decreased glucose-stimulated insulin secretion compared to GG-genotype islets. The results suggested that A allele increase mRNA UCP2 expression thus induced UCP2 protein production and in turn decreased glucose stimulated insulin secretion [22]. Those finding support our finding on how obese subjects with AA genotype had less HOMA IR than the GG or GA genotype.

We concluded that UCP2 -866G>A polymorphism was not associated with obesity in adolescents. Additionally the polymorphism was associated with changes insulin resistance and dyslipidemia in obese and normal-weight adolescents. In obese adolescents subjects with AA genotype have lower HOMA IR but in normal-weight adolescents subjects AA genotypes have higher HOMA IR. We also found that UCP2 -866G>A polymorphism was interacted dietary fat intake and their combination is associated with reduced prevalence of obesity. From this study, it seems that subjects with A allele were more protected from insulin resistance and dyslipidemia.

Acknowledgements

Supported by Risbin Iptekdok, Indonesian Ministry of Health: HK.05.01/1.1/2184/2014.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Emy Huriyati, Department Nutrition and Health, Faculty of Medicine, Universitas Gadjah Mada, Yogyakarta, Indonesia. Jl. Farmako, Sekip Utara, Yogyakarta, Indonesia. Tel: +62274 547775; Fax: +62274 547775; E-mail: emyhuriyati@ugm.ac.id

References

[1] Sypniewska G. Laboratory assessment of cardiometabolic risk in overweight and obese children. Clinical Biochemistry 2015; 48: 370-376.

[2] Badan Penelitian dan Pengembangan Kesehatan RI. Riset Kesehatan Dasar 2013. 2013;

[3] Muhammad HFL, Huriyati E, Susilowati R and Julia M. Magnesium intake and insulin resistance in obese adolescent girls. Paediatrica Indonesiana 2009; 49: 200-204.

[4] Ahrens W, Pigeot I, Pohlabeln H, De Henauw S, Lissner L, Molnár D, Moreno LA, Tornaritis M, Veidebaum T, Siani A; IDEFICS consortium. Prevalence of overweight and obesity in European children below the age of 10. Int J Obes (Lond) 2014; 38 Suppl 2: S99-107.

[5] Freedman DS, Dietz WH, Srinivasan SR and Berenson GS. The Relation of Overweight to Cardiovascular Risk Factors Among Children and Adolescents: The Bogalusa Heart Study. Pediatrics 1999; 103: 1175-1182.

[6] Steinberger J and Daniels SR. Obesity, Insulin Resistance, Diabetes, and Cardiovascular Risk in Children An American Heart Association Scientific Statement From the Atherosclerosis, Hypertension, and Obesity in the Young Committee (Council on Cardiovascular Disease in the Young) and the Diabetes Committee (Council on Nutrition, Physical Activity, and Metabolism). Circulation 2003; 107: 1448-1453.

[7] Lopez-Miranda J, Williams C and Lairon D. Dietary, physiological, genetic and pathological influences on postprandial lipid metabolism. Br J Nutr 2007; 98: 458-73.

[8] Diano S and Horvath TL. Mitochondrial uncoupling protein 2 (UCP2) in glucose and lipid metabolism. Trends in Molecular Medicine 2012; 18: 52-58.

[9] Zhang M, Wang M and Zhao ZT. Uncoupling protein 2 gene polymorphisms in association with overweight and obesity susceptibility: A meta-analysis. Meta Gene 2014; 2: 143-159.

[10] Oktavianthi S, Trimarsanto H, Febinia CA, Suastika K, Saraswati MR, Dwipayana P, Arindrarto W, Sudoyo H and Malik SG. Uncoupling protein 2 gene polymorphisms are associated with obesity. Cardiovasc Diabetol 2012; 11: 41.

[11] Ben-Noun LL, Sohar E and Laor A. Neck Circumference as a Simple Screening Measure for Identifying Overweight and Obese Patients. Obes Res 2001; 9: 470-7.

[12] Falkner B and Daniels SR. Summary of the Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents. Hypertension 2004; 44: 387-388.

[13] Keskin M, Kurtoglu S, Kendirci M, Atabek ME and Yazici C. Homeostasis Model Assessment Is More Reliable Than the Fasting Glucose/Insulin Ratio and Quantitative Insulin Sensitivity Check Index for Assessing Insulin Resistance Among Obese Children and Adolescents. Pediatrics 2005; 115: e500-e503.

[14] Kwiterovich PO Jr. Recognition and Management of Dyslipidemia in Children and Adolescents. J Clin Endocrinol Metab 2008; 93: 4200-9.

[15] Laakso M, Sarlund H and Mykkänen L. Insulin resistance is associated with lipid and lipoprotein abnormalities in subjects with varying degrees of glucose tolerance. Arteriosclerosis 1990; 10: 223-31.

[16] Reis AF, Dubois-Laforgue D, Bellanné-Chantelot C, Timsit J and Velho G. A polymorphism in the promoter of UCP2 gene modulates lipid levels in patients with type 2 diabetes. Mol Genet Metab 2004; 82: 339-44.

[17] Dalgaard LT. Genetic Variance in Uncoupling Protein 2 in Relation to Obesity, Type 2 Diabetes, and Related Metabolic Traits: Focus on the Functional -866G>A Promoter Variant (rs-659366). J Obes 2011; 2011: 340241.

[18] Pecqueur C, Alves-Guerra C, Ricquier D and Bouillaud F. UCP2, a metabolic sensor coupling glucose oxidation to mitochondrial metabolism? IUBMB Life 2009; 61: 762-767.

[19] Chan CB, MacDonald PE, Saleh MC, Johns DC, Marbàn E and Wheeler MB. Overexpression of uncoupling protein 2 inhibits glucose-stimulated insulin secretion from rat islets. Diabetes 1999; 48: 1482-1486.

[20] Dalgaard LT, Andersen G, Larsen LH, Sørensen TI, Andersen T, Drivsholm T, Borch-Johnsen K, Fleckner J, Hansen T, Din N, Pedersen O. Mutational Analysis of the UCP2 Core Promoter and Relationships of Variants with Obesity. Obesity Research 2003; 11: 1420-1427.

[21] Krempler F, Esterbauer H, Weitgasser R, Ebenbichler C, Patsch JR, Miller K, Xie M, Linnemayr V, Oberkofler H and Patsch W. A Functional Polymorphism in the Promoter of UCP2 Enhances Obesity Risk but Reduces Type 2 Diabetes Risk in Obese Middle-Aged Humans. Diabetes 2002; 51: 3331-3335.

[22] Sesti G, Cardellini M, Marini MA, Frontoni S, D'Adamo M, Guerra SD, Lauro D, Nicolais PD, Sbraccia P, Prato SD, Gambardella S, Federici M, Marchetti P and Lauro R. A Common Polymorphism in the Promoter of UCP2 Contributes to the Variation in Insulin Secretion in Glucose-Tolerant Subjects. Diabetes 2003; 52: 1280-1283.