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Physiological Study of Lipoprotein Lipase Gene Pvu II Polymorphism in Cases of Obesity in Egypt

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ABSTRACT

Genetic predisposition has been implicated in obesity. Lipoprotein lipase (LPL) gene, the main lipase of chylomicrons and Low Density Lipoproteins (LDL), has a fundamental role in the transport and metabolism of plasma cholesterol. The present study was undertaken to test for the association of the LPL gene Pvu II polymorphism with obesity with or without hypertension and diabetes and dyslipidemia among affected Egyptian cases. This study has included 120 subjects affected with obesity; 57 of them were affected with metabolic syndrome (with diabetes, dyslipidemia and hypertension) while the other 63 cases were not complicated and were termed "simple obesity". These cases were compared to 83 healthy non-obese controls. Body Mass Index (BMI), Waist Hip Ration (WHR) and serum hpid levels were measured. The LPL gene polymorphic alleles were determined by PCR-RFLP that includes polymerase chain reaction for gene amplification followed by digestion with Pvu II enzyme and analysis according to the size of digested amplified DNA. Obesity cases had a significantly higher frequency of the homozygous mutated LPL Pvu II (+/+) genotype and also of the (+) allele particularly among metabolic syndrome cases compared to controls. Cases with the (+/+) homozygous genotype showed significantly higher frequency of diabetes, lower frequency of positive family history and lower values for waist hip ratio than those with the (+/-) and (-/-) genotypes. These cases have showed also higher levels of total cholesterol and LDL-C, yet not reaching statistical significance. This study showed a significant association between the LPL Pvu II gene polymorphism and obesity among Egyptian cases particularly when complicated with the metabolic syndrome.

Key words: LPL gene, obesity, diabetes mellitus, hypertension

INTRODUCTION

Obesity has become an extensive public health concern because its prevalence has increased to epidemic proportions. Many gene variants are involved in the development of obesity and body weight regulation (Rampersaud *et al*., 2008). The biological factors significantly associated with overweight and obesity were increasing age, being female and parental obesity. Also, non-biological factors including, physical inactivity, non-healthy diet, lower family monthly income and being non-smoker (Suleiman *et al*., 2009). The metabolic syndrome is a common multi-component

condition including abdominal obesity, dyslipidemia, hypertension and hyperglycemia. It is associated with an increased risk of cardiovascular disease and type 2 diabetes (Teran-Garcia and Bouchard, 2007).

Lipoprotein lipase (LPL) enter in the metabolism of the core triglycerides of circulating Very Low Density Lipoproteins (VLDL) by hydrolyzing them and chylomicrons, thereby delivering hpoprotein derived fatty acids to adipose tissues for storage or oxidation in muscle (Garfinkel and Schotz, 1987). Obesity in humans is a result of abnormal adipose tissue LPL activity (Lithell *et al*., 1978). LPL gene is located in chromosome 8p22 (Sparkes *et al*., 1987) and consist of 10 exons which is about 30 kbp (Monsalve *et al*.,1990). Taking into account that polymorphisms in a number of candidate genes have been reported to be associated with obesity; this study focused on LPL Pvu II gene polymorphism among Egyptian cases with simple and complicated obesity. This was done using the molecular biology techniques, utilizing the simple and rapid PCR (polymerase chain reaction) coupled with Restriction Fragment Length Polymorphism analysis (RFLP). Correlation of detected mutational types of LPL gene with the clinical severity of obesity and lipid profile was also attempted.

MATERIALS AND METHODS

This study has included 120 subjects affected with obesity with BMI (Body Mass Index) level being at least 30. They were selected from the Outpatient's Clinic, Department of Obesity and Diabetes, Specialized Internal Medicine Hospital, Mansoura University, Egypt between the times of January 2010 to January 2011. Their age Mean±SD was 31.5±11.2 years ranging from 13-61 years. They were in the form of 21 (17.5%) males and 99 (82.5%) females. Of them, 21 (17.5%) were positive for parental consanguinity, 73 (60.3%) had positive family history. Of these case, 57 (47.5%) had complications of diabetes, hypertension or dyslipidemia conforming with the definition of "metabolic syndrome" (Alberti and Zimmet, 1998; Grundy *et al*., 2005; Alberti *et al*., 2005) while the rest of cases (63; 52.5%) were not complicated and were termed "simple obesity". These cases were compared to 83 (9 males and 74 females) normal healthy controls from the same locality of an age Mean±SD of 29.62±9.73 years. They were taken from blood donors after confirming that they are free from obesity, hypertension or other cardiovascular disorders in addition to a negative family history of similar conditions.

Measurements of lipids: After obtaining informed consent, blood samples were obtained from all cases and controls in the morning after fasting for 12 h. Immediately following clotting, serum was separated by centrifugation for 15 min at 3000 rpm.. The levels of TC (Total cholestrol), TG (Triglyceride), HDL-C (High Density Lipoprotein Cholesterol) and LDL-C (Low Density Lipoprotein Cholesterol) in samples were determined by enzymatic methods with commercially available kits, Tcho-1, TG-LH (RANDOX Laboratories Ltd., Ardmore, Diamond Road, Crumlin Co. Antrim, United Kingdom, BT29 4QY), Cholestest N HDL. and Cholestest LDL (Daiichi Pure Chemicals Co., Ltd., Tokyo, Japan), respectively.

DNA extraction, purification and amplification: Another venous blood samples (3 mL) were collected on EDTA (ethylenediamine tetra acetate) containing tubes, DNA was extracted promptly using DNA extraction and purification Kit (Gentra Systems, USA) according to manufacturer's instructions and then stored at -20°C till use.

LPL gene amplification was carried out by PCR using the selected sequences for 5' and 3' primers: SB-75: 5'-ATG GCACCC ATG TGT AAG GTG-3' and SB-76: 5'GTG AAC TTC TGA TAA CAA TCT C-3' (Georges *et al*., 1996). Quality analysis of the PCR products (430 bp-long) was performed by electrophoresis with a 50 bp marker (Pharmacia Biotech, Uppsala, Sweden) on 1.5% agarose gel.

Restriction fragment polymorphism analysis (RFLP) of amplified DNA: Samples of PCR products (8 uL) were then incubated with Pvu II restriction endonuclease (Boehringer) overnight at 37°C. The 430 bp-long product was digested to 320 and 110 bp-long products if there was a Pvu II restriction site (+) and remain as it is if it is absent (-). The digested DNA was electrophoresed on a 2% agarose gel stained with ethidium bromide (90 V/1 h), visualized under UV light and photographed. The length of each amplified DNA fragment was determined by comparing migration of a sample with that of standard DNA marker (Fig. 1, 2).

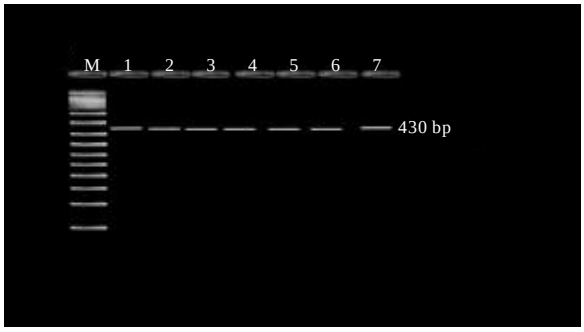

Fig. 1: Amplification product (430 bp) of LPL gene using Primer 1, Primer 2 M and molecular marker bp base pair. lane 1: -/- (no digestion) which include 2. lane 2: -/+ (digestion of one allele) which include 1,5, 7.lane 3: +/+ (digestion of both allele) which include 3,4,6. M molecular marker bp base pair

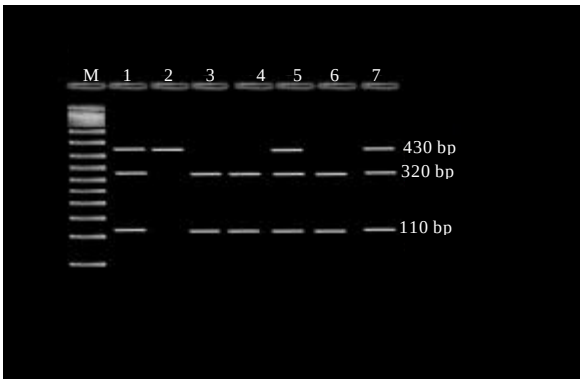

Fig. 2: Digestion products of amplified segment of LPL gene (430 bp) using PVU II restriction enzyme showing lane 1: -/- (no digestion) which include 2. lane 2: -/+ (digestion of one allele) which include 1,5, 7. lane 3: +/+ (digestion of both allele) which include 3,4,6. M molecular marker bp base pair

Statistical analysis: Statistical analysis of data was done using the software statistical package SPSS program version 17 (Chicago, USA). Student t-test was used to compare the numerical values related to lipid profile, body mass index and waist hip ratio, whereas Chi-square, Fisher exact and odds ratio with 95% confidence interval were used to compare frequencies of different genotypes and alleles among cases and controls.

RESULTS

Table 1 shows comparison between BMI, waist hip ratio and lipid profile among studied cases of obesity compared to controls. The BMI of total cases was significantly higher than that of the controls that was more obvious among metabolic syndrome cases. Similarly, the waist hip ratio of total cases was significantly higher that of the controls that was more obvious among simple obesity cases that were also significantly higher than metabolic syndrome cases. Lipid profile TC, TG, HDL-C and LDL-C of total cases was significantly higher than that of the controls. On the other hand, metabolic syndrome cases showed significantly higher TG with HDL-C levels than simple obesity cases.

Comparison between cases with obesity and healthy controls regarding their genotype and allelic distribution of LPL Gene Pvu II polymorphism is shown in Table 2. From this Table 2 it is noted that obesity cases had a significantly higher frequency of the homozygous mutated (+/+)genotype of LPL Gene Pvu II polymorphism particularly among cases with metabolic syndrome

Table 1: Body mass index, waist hip ratio and lipid profile among studied cases of obesity compared to controls

Parameter (M±SD)	Controls, n= 83	Total cases, n = 120	Metabolic syndrome, n = 57	Simple obesity, n = 63
BMI (kg m^{-2})	21.5±1.6	39.9±6.3**	40.1±7.1**	39.9±5.6**
WHR	0.77±0.03	0.96±0.14**	0.93±0.1**	0.99±0.16** #
TC (mg dL^{-1})	165.0±18.3	245.9±60.1**	242.7±57.3**	248.8±62.8**
TG (mg dL^{-1})	94.3±28.9	128.2±74.2**	152.3±87.9**	107.2±52.0* #
HDL-C (mg dL^{-1})	36.9±14.5	48.2±15.0**	44.7±13.3*	52.1±15.5** #
LDL-C (mg dL^{-1})	110.3±17.9	169.1±59.7**	160.2±60.5**	177.1±58.4**

*p<0.05 **p<0.001 significant compared to healthy controls, #: p<0.05 significant compared to metabolic syndrome

Table 2: Comparison between cases with obesity and healthy controls regarding their genotype and allelic distribution of LPL Gene Pvu II polymorphism

	Genotypes			Alleles	
LPL	(-/-)	(+/-)	(+/+)	(-)	(+)
Controls (n = 83)	43 (51.8)	37 (44.5)	3 (3.6)	123 (74)	43 (25.9)
Cases (n = 120)	49 (40.8)	47 (39.1)	24 (20)	145 (60.4)	95 (39.5)
p	0.15	0.47	0.001*	0.005*	0.005*
OR (95% CI)	0.64 (0.36-1.1)	0.8 (0.45-1.4)	6.6 (1.9-22.9)	0.53 (0.3-0.8)	1.8 (1.2-2. 8)
MetS (n = 57)	23 (40.3)	18 (31.5)	16 (28.7)	64 (56.1)	50 (43.8)
p	0.22	0.15	<0.0001**	<0.0001**	0.53
OR (95% CI)	0.62 (0.3-1.2)	0.58 (0.3-1.1)	10.4 (2.9-37.7)	0.34 (0.2-0.6)	1.17 (0.7-1.9)
Simple obesity (63)	26 (41.2)	29 (46)	8 (12.6)	81 (64.2)	45 (35)
p	0.24	0.86	0.05*	0.07	0.78
OR (95% CI)	0.65 (0.3-1.3)	1.1 (0.5-2.0)	3.9 (0.9-15.2)	0.6 (0.4-1.0)	1.1 (0.7-1.9)
MetS vs. simple obesity					
p	0.92	0.11	0.04*	0.2	0.2
OR (95 % CI)	0.96 (0.5-2.0)	0.5 (0.3-1.14)	2.7 (1.05-6.9)	0.7 (0.4-1.2)	1.4 (0.9-2.4)

*p significant = 0.05, **p significant <0.001 OR (95% CI) = Odds ratio (95% confidence interval)

Table 3: Body mass index (BMI), waist hip ratio, age of onset and lipid profile among cases of obesity related to their LPL genotypes

	LPL Genotypes			
Parameters	(-/-)	(+/-)	(+/+)	p
Age of Onset (M±SD)	25.4±11.4	26.1±10.7	25.9±9.9	>0.05
Gender n(%)				
Males	39 (39.3)	41 (41.1)	19 (19.1)	>0.05
Females	10 (47.6)	6 (28.5)	5 (23.8)	
Family History n (%)				
Positive	24 (32.8)	36 (49.3)	13 (17.8)	<0.05*
Negative	25 (53.1)	11 (23.4)	11 (23.4)	
Consangninity n (%)				
Positive	6 (28.5)	10 (47.6)	5 (23.8)	>0.05
Negative	43 (43.4)	37 (37.3)	19 (19.1)	
Hypertension n (%)				
Positive	9 (30.0)	12 (40.0)	9 (30.0)	>0.05
Negative	40 (44.4)	35 (38.9)	15 (16.7)	
Diabetes n (%)				
Positive	13 (33.3)	12 (30.8)	14 (35.9)	<0.05*
Negative	36 (44.4)	35 (43.2)	10 (12.3)	
BMI (M±SD)	40.3±6.1	39.96±7.6	39.3±3.7	>0.05
Waist hip ratio (M±SD)	0.98±0.2	0.97±0.1	0.90±0.1	<0.05*
Lipid profile (M±SD)				
TC	244.6±56.8	243.4±60.3	253.5±67.9	>0.05
TG	133.98±71.6	121.1±68.99	130.95±91.3	>0.05
HDL-C	47.3±14.8	50.2±16.3	47.7±12.8	>0.05
LDL-C	169.8±60.1	167.8±53.0	170.1±72.7	>0.05

*p significant = 0.05

compared to controls (p = 0.001, OR = 6.6 and p<0.0001, OR = 10.4 respectively). Cases of obesity had also a significantly higher frequency of (+) allele of LPL Pvu II gene polymorphism particularly also the metabolic syndrome cases compared to controls (p = 0.005, p<0.0001, respectively).

Also from this Table 2 it is noted that simple obesity cases showed also a higher frequency of the homozygous mutated (+/+) genotype of LPL Pvu II gene polymorphism yet this was statistically near significant (p = 0.05, OR = 3.9).

On other hand, by comparing metabolic syndrome cases to simple obesity cases it noted that metabolic syndrome cases had a significantly higher frequency of the homozygous mutated (+/+) genotype of LPL Gene Pvu II polymorphism (p= 0.04, OR = 2.7).

Table 3 shows a comparison between BMI, waist hip ratio, age of onset, Family History, Gender, Consanguinity, Hypertension, Diabetes and lipid profile among cases of obesity related to their LPL genotypes. From this Table 3, it is noted that Cases with the (+/+) homozygous genotype showed significantly higher frequency of diabetes, lower frequency of positive family history and lower values for waist hip ratio than those with the (+/-) and (-/-) genotypes. These cases have showed also higher levels of total cholesterol and LDL-C, yet not reaching statistical significance.

DISCUSSION

Excess adipose tissue lead to Obesity (Spiegelman and Flier, 2001). Obesity cause morbidity because of hypertension, type 2 diabetes mellitus, dyslipidemia, endocrinal abnormalities besides it can cause mortality due to some cancers like esophagus, colon, rectum and breast

(Spiegelman and Flier, 2001). Obesity can be combined with metabolic syndrome which includes a group of conditions as increased blood pressure, elevated insulin levels, excess body fat around the waist or abnormal cholesterol levels that stimulate the risk of heart disease, stroke and diabetes. Lipoprotein lipase (LPL) is a key enzyme in lipoprotein metabolism through hydrolysis of triglyceride-rich particles in muscles, adipose tissues and macrophages, thereby generating free fatty acids and glycerol for energy utilization and storage (Goldberg, 1996).

In this work, we explored the association of genetic polymorphisms of lipoprotein lipase gene Pvu II site with the development of either simple obesity or metabolic syndrome among Egyptian cases, correlating it to other clinical variables including gender, age of onset, Body Mass Index (BMI), waist hip ratio, diabetes, hypertension in addition to lipid profile and glucose. Our study results showed that the frequency of homozygous mutated (+/+) genotype and mutant (+) allele of LPL Pvu II gene polymorphism were significantly higher among cases of obesity associated with metabolic syndrome compared to controls. Thus (+/+) genotype and (+) allele may be considered as genetic risk factors for complicated obesity. This might support the autosomal recessive mode of the effect of this gene so that the homozygous mutant (+/+) is associated with the manifestation of complicated obesity.

These results are in agreement with results of (Sertic *et al*., 2009) who stated that LPL genetic polymer variants could represent predictive genetic risk markers for obesity-related metabolic disorders in young healthy subjects. Also these results are in agreement with results of Liu *et al*. (2005) who stated that, LPL Pvu II polymorphisms are determinants of plasma LPL concentration among Chinese population. These results are in agreement with results of with Zhu *et al*. (2003) who stated that the variants of LPL-Pvu II locus were important determinants of variation in serum cholesterol response to dietary change in hyperlipidemia population among Chinese population and in agreement with results of Wang *et al*. (1996) who stated that, Our patients with the Pvu II (+/+) genotype were significantly more likely to have diabetes. As far as we are aware, this has not been reported previously among Chinese population and with results of with Das *et al*. (2009) who stated that, LPL may have strong genetic association with hypertensive individuals among India population, and Wang *et al*. (2011) who studies LPL Pvu II polymorphism LPL gene and measured the serum lipid levels in a case-control study among preschool Chinese children. The variant genotypes of LPL Pvu II CC (+/+) were associated with a significantly increased risk of childhood obesity. These results are in agreement with results of Smart *et al*. (2010) who demonstrated that these common variants were apparently impacting the lipid levels in a healthy paediatric cohort, suggesting that even in these young children there may be potential in predicting their lifelong exposure to an adverse lipid profile. These results are in agreement with results of Voruganti *et al*. (2010) who stated there is strong genetic influence on plasma fatty acid distribution and that genetic variation in LPL that may play role in plasma fatty acid distribution among American studied subjects. Also, Kisfali *et al*. (2010) stated that, the number of candidate genes in metabolic syndrome and coronary heart disease susceptibility increases very rapidly from the growing spectrum of the genes influencing lipid metabolism like the LPL. Conversely, these results were in disagreement with results of Jemaa *et al*. (1995) who stated that, The Pvu II polymorphisms did not exhibit any significant association with the biochemical traits (total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein) among French population. Also, these results were in disagreement with the results of Shen *et al*. (2000), who stated that,: The LPL Pvu II is not significantly associated with type 2 diabetes mellitus in Chinese

population and Comparing cases-subgroups according to their family history as regard their studied genotypes, it is noted the cases with positive family history of obesity has a significantly higher frequency of the heterozygous mutant (+/-) genotype, whereas cases with negative family history showed a significantly higher frequency of the wild type or normal (-/-) genotype. This supports the familial nature of obesity particularly when associated with the (+) mutant allele. Interestingly, however, the (+/+) genotype was not significantly different when comparing cases with positive to that with negative family history. This may be due to the fact that most of our cases were taken from the outpatient ambulatory cases when it is expected that most of the cases with the (+/+) genotype will have a severe form of complicated obesity that requires inpatient or intensive unit (ICU) care. So, we recommend taking a wider scale sample of cases including inpatient and ICU cases to get a proper picture of the familial pattern of the disease.

BMI regarding their LPL genotypes, although, there are significant differences between cases and healthy controls ($p<0.001$) as being very high regardless of their genotypes, cases did not show a significant difference in between each other.

CONCLUSION

This study showed a significant association between the LPL Pvu II gene polymorphism and obesity particularly when complicated with metabolic syndrome among Egyptian cases. The genotype (+/+) was mostly associated with the risk of complicated obesity. Although, lipid profile was significantly higher among obesity cases compared to controls irrespective of the LPL genotype variants, it was non-significantly different between cases subgroups related to different LPL genotypes.

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