

# 4G polymorphism of plasminogen activator inhibitor-1 (PAI-1), PAI-1 plasma levels, and lipid profiles in overweight/obese children and adolescents

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**Topic: Fat metabolism and Obesity**

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## Objectives:

Association studies have shown that PAI-1 4G polymorphisms are related with increased plasma PAI-1 levels, obesity, dyslipidaemia and cardiovascular disease (CVD) in adults. However, few studies, have explored that relation in overweight/obese (ov/ob) children/adolescents. We investigated the relationship between plasma PAI-1 levels, PAI-1 4g polymorphisms and lipid profiles in a group of greek ov/ob children/adolescents compared with healthy normal BMI controls.

## Methods:

193 children/adolescents aged 2.2-17.4 years old (99 ov/ob-group 1, 93 controls-group 2) participated in the study. Anthropometry, body mass index (BMI), PAI-1 plasma levels, total Cholesterol (TC), low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C), triglycerides (Tg), Apolipoproteins A and B (ApoA, ApoB) and lipoprotein (a) (Lp(a)) were measured. PCR-restriction fragment length polymorphism was performed for the 4G/4G, 4G/5G και 5G/5G PAI-1 polymorphisms. IBM Statistics SPSS 20.0, p<0.05 were used.

Table 1. Demographics

Variables	Control group (N=93)	Ov/ob group (N=99)	p-value
Sex N (Male % / Female %)	42.5 / 50.9	54.8 / 49.1	0.469 <sup>a</sup>
Age (years) (mean ± SD) (Median)	10±2.1 (10)	9.9±2.8 (10.1)	0.717 <sup>e</sup>
Wt (Kg) (mean ± SD) (Median)	32.9±7.7 (32.7)	58.1±21 (54.4)	<b>0.001<sup>e</sup></b>
Ht (cm) (mean ± SD) (Median)	138.6±12 (138)	144.6±16 (145.5)	<b>0.003<sup>b</sup></b>
BMI (kg/m <sup>2</sup> ) (mean ± SD) (Median)	16.9±1.9 (16.9)	26.8±5.2 (26)	<b>0.001<sup>e</sup></b>
TC (mg/dl) (mean ± SD) (Median)	172.8±32.9 (169)	161.3±32.1 (162)	<b>0.007<sup>e</sup></b>
Tg (mg/dl) (mean ± SD) (Median)	69.5±32.1 (64)	96.6±52.6 (84)	<b>0.001<sup>e</sup></b>
HDL-C (mg/dl) (mean ± SD) (Median)	60.9±14.8 (61)	45.9±11.5 (46)	<b>0.001<sup>b</sup></b>
LDL-C (mg/dl) (mean ± SD) (Median)	97.9±30.4 (95)	95.8±28 (95)	0.470 <sup>e</sup>
Apo(A) (mg/dl) (mean ± SD) (Median)	154.9±26.5 (156)	136±24.7 (135)	<b>0.001<sup>b</sup></b>
Apo(B) (mg/dl) (mean ± SD) (Median)	71.1±17.6 (69)	67.3±18.7 (64)	<b>0.026<sup>e</sup></b>
Lp(a) (mg/dl) (mean ± SD) (Median)	28.9±37.7 (10.8)	25±32.4 (14.9)	0.901 <sup>e</sup>
PAI-1 (ng/ml) (mean ± SD) (Median)	9.6±2.4 (9.5)	7.8±3.9 (6.9)	<b>0.001<sup>e</sup></b>
Genotype <sup>§</sup>	(N=88)	(N=89)	<b>0.040<sup>c</sup></b>
4G/4G N (%), % <sup>§</sup>	22(25, 37.9)	36(40.4, 62.1)	<b>&lt;0.05<sup>d</sup></b>
4G/5G N(%), % <sup>§</sup>	32(36.4, 50)	32(36, 50)	ns <sup>d</sup>
5G/5G N(%), % <sup>§</sup>	34(38.6, 61.8)	21(23.6, 38.2)	<b>&lt;0.05<sup>d</sup></b>

p-values came out from, a: Fisher's Exact Test, b: Independent Samples T-Test, c: Chi-square test, d: z-test with Bonferroni adjustment (as it is given by the SPSS Output) and e: Mann-Whitney U test. Bold numbers indicate statistically significant results.

Table 2. PAI-1 levels and genotype

Genotype	PAI-1 (Mean±SD (Median))	
	Controls	Ov/ob
4G/4G	10.5±2.4 (10.6)	8.3±4.2 (8.2)
4G/5G	9.2±2.3 (9.3)	8±4.2 (7.1)
5G/5G	9.6±2.4 (9.9)	7.3±3.3 (6.4)

Table 3. Mean, standard deviation and median of the study variables for each combination between group and genotype

	Controls - 4G/4G	Controls - 4G/5G	Controls - 5G/5G	Ov/ob - 4G/4G	Ov/ob - 4G/5G	Ov/ob - 5G/5G
BMI	17.1±2.3 (17.7)	16.8±1.8 (16.9)	17.0±1.8 (17.0)	26.4±5.0 (25.7)	27.1±5.9 (25.6)	27.0±4.8 (27.1)
TC	166.4±25.8 (166.5)	175.1±42.9 (168.0)	174.3±28.1 (172.5)	165.0±39.0 (164.5)	157.1±27.0 (155.5)	162.1±29.7 (163.0)
Tg	75.5±42.0 (68.0)	60.1±19.3 (57.5)	74.4±33.9 (66.0)	99.6±53.7 (88.5)	96.4±59.6 (82.5)	86.1±35.1 (82.0)
HDL	56.4±13.0 (54.0)	61.7±14.4 (64.0)	63.4±15.9 (63.5)	46.0±11.4 (46.5)	46.1±12.5 (46.5)	47.6±10.2 (48.0)
LDL	94.9±22.2 (89.5)	100.8±43.2 (104.5)	96.2±21.1 (94.0)	99.2±34.0 (98.5)	91.3±25.6 (94.5)	97.5±25.8 (96.0)
Apo(A)	147.2±23.9 (142.0)	152.4±28.0 (157.0)	163.1±26.3 (164.0)	136.2±26.8 (137.0)	137.0±24.0 (134.5)	139.5±24.9 (140.0)
Apo(B)	69.2±17.2 (67.0)	69.8±20.9 (70.5)	72.9±15.8 (69.5)	71.5±23.9 (64.0)	64.8±15.7 (63.0)	65.1±15.3 (64.0)
Lp(a)	30.6±42.9 (9.5)	25.2±30.4 (10.7)	27.5±31.0 (11.1)	25.8±25.4 (17.4)	22.7±34.7 (10.6)	28.6±43.4 (16.5)

Table 4. Spearman's rho correlation between plasma PAI-1 levels and each one of the other variables for each combination of group and genotype

	PAI-1															
	Controls		Ov/ob		Controls -4G/4G		Controls 4G/5G		Controls -5G/5G		Ob/ob - 4G/4G		Ov/ob - 4G/5G		Ov/ob - 5G/5G	
	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value	Spearman's rho	p-value
BMI	-0.104	0.32	0.057	0.574	-0.538**	0.01	-0.095	0.605	0.151	0.394	0.162	0.344	-0.011	0.951	0.03	0.898
TC	-0.186	0.075	0.064	0.532	-0.577**	0.005	0.293	0.103	-0.251	0.153	-0.148	0.390	0.036	0.843	0.233	0.309
Tg	-0.015	0.887	0.115	0.257	-0.081	0.721	0.067	0.714	-0.041	0.819	0.103	0.549	0.01	0.956	0.05	0.829
HDL	-0.013	0.901	-0.009	0.931	-0.034	0.882	0.222	0.221	-0.167	0.345	-0.332*	0.048	0.009	0.963	0.318	0.160
LDL	-0.162	0.121	0.056	0.583	-0.553**	0.008	0.195	0.284	-0.138	0.438	-0.022	0.900	0.071	0.699	0.073	0.754
Apo(A)	-0.035	0.74	-0.003	0.975	-0.216	0.334	0.273	0.131	-0.189	0.285	-0.384*	0.021	0.071	0.698	0.355	0.115
Apo(B)	0.046	0.66	-0.027	0.789	-0.382	0.079	0.401*	0.023	0.056	0.754	-0.061	0.726	-0.057	0.755	0.099	0.670
Lp(a)	-0.175	0.093	-0.136	0.18	-0.440*	0.041	-0.289	0.109	-0.005	0.977	-0.289	0.088	0.067	0.717	-0.021	0.927

## Results:

Mean age for ov/ob was 10.2 years (9.9±2.8), for controls 10(10±2.1). TCh, ApoA, PAI-1 levels were statistically significantly higher in controls (p<0.007 and p<0.001 respectively), as LDL-C and Lp(a) (non significant statistically). Tg were higher in ov/ob (p<0.001), HDL-C and ApoB were lower (p<0.001 and p<0.026 respectively), (table 1). Higher mean values PAI-1 were observed in relation to genotypes 4G/4G, 5G/5G and 4G/5G in controls (p=0.011, 0.008 and >0.05 respectively), (table 2). For controls-4G/4G PAI-1 correlated negatively with BMI, TC, LDL-C, Lp(a), for controls-4G/5G correlated positively with Apo(B), where as for ov/ob- 4G/4G correlated negatively with HDL-C, Apo(A). For ov/ob-4G/5G and 5G/5G there was no significant correlation (tables 3 & 4).

## Conclusions:

The ov/ob had lower mean TCh, PAI-1, HDL-C and Apo(A) values and higher Tg values compared to the controls. Genotype 4G was more prevalent in the ov/ob group. It has been reported positive correlation between genotype 4G and CVD, TC and Tg, but further studying is needed in children.

## References:

- Al-Hamodi et al. PAI-1 4G/5G polymorphism is associated with metabolic syndrome parameters in Malaysian subjects. *J Clin Biochem Nutr.* 2012 May;50(3):184-9. doi: 10.3164/jcbn.11-48
- Margaglione M et al. PAI-1 plasma levels in a general population without evidence of atherosclerosis relation to environmental and genetic determinants. *Arterioscler Thromb Vasc Biol.* 1998 Apr;18(4):562-7
- Dellas C, Loskutoff DJ. Historical analysis of PAI-1 from its discovery to its potential role in cell motility and disease. *Thromb Haemost.* 2005 Apr;93(4):631-40. Review
- Yildiz Y S et al. Functional stability of plasminogen activator-1. *Sci World J.* 2014;4:858293. doi: 10.1155/2014/858293. Epub 2014 Oct 15
- Kinik ST et al. PAI-1 gene 4G/5G polymorphism, cytokine levels and their relations with metabolic parameters in obese children. *Thromb Haemost.* 2008 Feb;99(2):352-6. doi: 10.1160/TH07-06-0395

