EVALUATION OF INDICES OF GLUCOSE AND INSULIN METABOLISM IN A COORT PATIENTS WITH ANGPTL3 DEFICIENCY

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INTRODUCTION

Angiopoietin-like 3 (ANGPTL3) is a regulator of lipoprotein metabolism by inhibiting lipoprotein lipase (LPL) activity. In addition, it has been proposed to be able to influence insulin sensitivity. We have tested this hypothesis in subjects carrying loss-of-function (LOF) mutations in *ANGPTL3*, thus presenting the familial combined hypolipidemia phenotype.

METHODS

72 wild-type and 40 p.S17X LOF carrier subjects (36 heterozygotes and 4 homozygotes) have been studied for insulin sensitivity by glucose tolerance tests (OGTT). Results in carriers and non-carrier controls have been compared.

RESULTS

Table 1 shows baseline clinical features in the whole cohort according with genotypes. Moreover, homozygotes patients were older as compared with other genotypes (*P for trend*=0,045; *P among genotypes*=NS).

Table 1

		%	Mean	SD	95% Confidence Interval		P for trend
					Inferior Limit	Upper Limit	
Age (yrs)	Wild-type	-	56,4	12,4	53,5	59,3	0,045
	Heterozygotes	-	51,1	16,7	45,5	56,8	
	Homozygotes	-	66,5	6,0	57,0	76,0	
Female (%)	Wild-type	50,0	-	-	-	-	NS
	Heterozygotes	52,8	-	-	-	-	
	Homozygotes	25,0	-	-	-	-	
BMI (kg/m)	Wild-type	-	28,7	5,4	27,5	30,0	NS
	Heterozygotes	-	29,4	5,7	27,4	31,3	
	Homozygotes	-	29,8	2,2	26,2	33,4	
WC (cm)	Wild-type	-	97,9	13,5	94,6	101,1	NS
	Heterozygotes	-	98,0	16,1	92,6	103,4	
	Homozygotes	-	104,3	5,1	96,2	112,3	
PAS (mmHg)	Wild-type	-	136,9	24,2	131,2	142,6	NS
	Heterozygotes	-	134,5	16,9	128,7	140,2	
	Homozygotes	-	130,3	8,8	116,3	144,2	
PAD (mmHg)	Wild-type	-	79,5	10,1	77,1	81,8	NS
	Heterozygotes	-	79,3	7,7	76,7	81,9	
	Homozygotes	-	76,3	7,5	64,3	88,2	
TC (mg/dl)	Wild-type	-	187,4	35,1	179,1	195,6	<0,001
	Heterozygotes	-	165,8	33,3	154,4	177,3	
	Homozygotes	-	84,5	9,3	69,7	99,3	
HDL (mg/dl)	Wild-type	-	61,0	15,4	57,4	64,7	<0,001
	Heterozygotes	-	54,5	11,5	50,6	58,5	
	Homozygotes	-	30,0	6,2	20,2	39,8	
Triglycerides (mg/dl)	Wild-type	-	101,6	46,5	90,7	112,5	<0,001
	Heterozygotes	-	80,8	31,8	69,9	91,7	
	Homozygotes	-	33,3	14,0	10,9	55,6	
LDL (mg/dl)	Wild-type	-	105,6	29,9	98,5	112,6	<0,001
	Heterozygotes	-	95,0	28,8	85,1	104,8	
	Homozygotes	-	42,5	17,8	14,2	70,8	
APO B (mg/dl)	Wild-type	-	94,4	26,2	88,3	100,6	0,012
	Heterozygotes	-	87,5	28,5	77,7	97,3	
	Homozygotes	-	53,8	34,3	-0,8	108,3	
Creatinine mg/dl)	Wild-type	-	0,9	0,2	0,8	0,9	NS
	Heterozygotes	-	0,8	0,2	0,8	0,9	
	Homozygotes	-	0,8	0,3	0,4	1,3	
Fasting glucose (mg/dl)	Wild-type	-	98,6	17,4	94,0	103,3	NS
	Heterozygotes	-	95,4	14,0	90,3	100,5	
	Homozygotes	-	96,3	12,6	76,2	116,3	
Fasting insulin (mg/dl)	Wild-type	-	10,1	5,8	8,6	11,7	NS
	Heterozygotes	-	8,4	3,2	7,2	9,6	
	Homozygotes	-	6,9	3,1	2,0	11,8	

As expected, plasma lipids were different between genotypes while no differences were found in fasting glucose and insulin. Despite this, in a multivariate model including BMI, gender and age, we have shown significantly lower homeostatic model assessment of insulin resistance (HOMA-IR) and higher insulin sensitivity index (ISI) in S17X homozygotes as compared with the other genotypes (respectively P=0.011 and P=0.05) (**Figure 2** and **Table 2**).

Figure 2

Table 2

	Wild-Type	Heterozygotes	Homozygotes	P	P _{adj}
N.	57	31	4	-	
HOMA IR	2,5±1,6	2,0±0,8	1,6±0,6	NS	0,011*
ISI-120 INDEX	5,3±3,5	7,2±8,3	8,2±5,2	NS	0,05**

CONCLUSIONS

Our results indicate that the lack of ANGPTL3 is associated with improved measures of insulin sensitivity as demonstrated by lower HOMA-IR and higher ISI values in p.S17X homozygous as compared to heterozygous and wild-type carriers. The mechanism by which reduced ANGPTL3 levels lead to improved insulin sensitivity is not known so that further studies are needed to clarify this point. The beneficial effects of ANGPTL3 deficiency on both glucose and lipoprotein metabolism support the role of AGPTL3 as a potential therapeutic target.