

The association of the rs670 variant of APOA1 gene with insulin resistance and lipid profile in morbid obese patients after a biliopancreatic diversion surgery

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Abstract. – **OBJECTIVE:** A common G-to-A transition (rs670) of the Apoprotein subtype 1 APOA1 gene has been evaluated. The presence of the A allele has been related with increased activity. We investigated the role of this genetic variant (rs670) on lipoprotein levels and anthropometric parameters after biliopancreatic diversion (BPD) surgery in morbid obese patients.

PATIENTS AND METHODS: Sixty-three patients with morbid obesity without diabetes mellitus type 2 were enrolled. Biochemical and anthropometric evaluation were registered before and after one, two and three years follow-up.

RESULTS: Genotype distribution was 73% (n=46) GG, 25.6% (n=16) GA and 1.4% (n=1) AA for the rs670 polymorphism. Percent excess weight loss, anthropometric and biochemical parameters improved in both groups (GG vs. GA±AA). The decrease of fasting insulin levels at 1 years (delta: -3.7 ± 1.4 mUI/L vs. -2.9 ± 1.2 mUI/L; $p=0.02$), 2 years (delta: -4.8 ± 0.3 mUI/L vs. -4.0 ± 0.2 mUI/L; $p=0.01$) and 3 years (delta: -6.7 ± 3.1 mUI/L vs. -3.9 ± 2.1 mUI/L; $p=0.03$) was higher in A allele carriers than in non carriers. The improvement of HOMA-IR levels at 1 years (delta: -3.7 ± 1.4 mUI/L vs. -2.9 ± 1.2 mUI/L; $p=0.02$), 2 years (delta: -4.8 ± 0.3 mUI/L vs. -4.0 ± 0.2 mUI/L; $p=0.01$) and 3 years (delta: -6.7 ± 3.1 mUI/L vs. -3.9 ± 2.1 mUI/L; $p=0.03$) was also higher in A allele carriers than non-carriers. Finally, the increase of HDL-cholesterol levels at 1 years (delta: 2.2 ± 0.6 mg/dl vs. -1.2 ± 0.2 mg/dl; $p=0.001$), 2 years (delta: 2.5 ± 0.4 mg/dl vs. 0.3 ± 0.1 mg/dl; $p=0.01$) and 3 years (delta: 2.4 ± 0.6 mg/dl vs. 0.4 ± 2.3 mg/dl; $p=0.02$) was higher in A allele carriers than non-carriers.

CONCLUSIONS: This variant of the APOA1 gene showed important effects on HDL-cholesterol, HOMA-IR and insulin resistance after DBP for 3 years.

Key Words

Biliopancreatic Diversion, Insulin resistance, HDL cholesterol, rs670, Morbid obesity

Introduction

Among the surgical procedures for the treatment of morbid and extreme obesity, biliopancreatic diversion (BPD) is considered to be a good technique due to its low morbidity, mortality rate and efficacy^{1,2}. Biliopancreatic diversion (BPD) is a mixed operation with a gastrectomy with a Roux on Y gastroenterostomy on the distal bowel loop. So, this surgical technique generates changes in the physiology and anatomy of the gastrointestinal tract, producing to changes in the absorption process. Nowadays, obesity is a major health problem worldwide³. The effectiveness of bariatric techniques has been extensively investigated. Other therapeutic approaches to induce weight loss have been widely investigated, such as caloric restriction, drugs (orlistat, sibutramine, rimonabant, and so on) or surgical treatments^{4,5}. In this context, bariatric techniques have been proven to be the most powerful and fast method to reduce weight in morbid obese patients⁶. However, predisposition to resistance to weight loss after surgical treatment can be genetically determined². The role of genetics in the modulation of weight loss is related to genes involved in different pathways such as regulation of thermogenesis, circuits of appetite and satiety adipogenesis, energy expenditure and lipid metabolism. The gene for Apoprotein subtype 1 (ApoA1) is located in the chromosome 11; this gene encoding ApoA1 is highly polymorphic and common single nucleotide polymorphisms (SNPs) have been reported in relation to lipoprotein concentrations^{7,8}. Researchers⁹ have demonstrated that overexpression of the human APOA1 gene increased HDL-C levels and protect mice from the atherosclerosis secondary to a high fat diet. A G-to-A transition located 75

base pairs upstream (rs670) from transcription start site of the APOA1 gene has been described¹⁰. The presence of the A allele has been related with increased promoter activity¹¹, and with higher ApoA1 and HDL-cholesterol levels. Moreover, there are contradictories data, with studies reporting either positive¹²⁻¹⁴ or negative association¹⁵ between this variant in APOA1 gene and lipoprotein levels. Moreover, rs670 variant has a direct effect on plasma LDL-cholesterol responsiveness to change in the amount of total dietary fat in normolipemic subjects¹⁴. Further, in the literature there are no studies evaluating the effect of this SNP of APOA1 gene on lipoprotein levels modifications after a bariatric surgery. Therefore, we decided to investigate during 3 years follow up, the role of this genetic variant (rs670) on lipid levels and anthropometric parameters after biliopancreatic diversion (BPD) surgery in morbidly obese subjects.

Patients and Methods

Patients

We recruited sixty-three Caucasian patients (53 females and 10 males) with grade III obesity without diabetes mellitus type 2 (body mass index ≥ 40). These patients underwent BPD in this prospective non-randomized observational study (Table I). The surgical technique consisted in the set-up of 175-cm alimentary limb and 70-cm common limb with the addition of a partial gastrectomy with a closure of the duodenal stump, transection of the small bowel half way from the Treitz angle to the ileocecal valve followed by a Roux Y gastroenterostomy on the distal bowel loop and an end-to-side enteroileostomy of the proximal bowel loop on the ileum 50-75 cm before the ileocecal valve. All procedures performed in this study were in accordance with the Declaration of Helsinki and were approved by the

Local Ethical Committee (HCUVA-Committee-3/2016). Written informed consent was obtained from all subjects.

Clinical and Biochemical Parameters

In this study, preoperative findings and those evaluated at 1, 2 and 3 years following the operation were recorded. Exclusion criteria were: severe liver or chronic renal diseases, malignancies, coagulopathy, gastrointestinal tract diseases, diabetes mellitus, drug therapy to hyperlipemia and drug addiction. Inclusion criteria were: body mass index (BMI) ≥ 40 kg/m² and a history of failed weight loss on hypocaloric diets prior to the surgery. The following parameters were recorded: age, weight, height, body mass index (BMI), waist circumference, fat mass by impedance, percent excess weight loss (EWL%), systolic and diastolic blood pressure, serum lipid levels (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides), fasting glucose, insulin, (homeostasis model assessment of insulin resistance) HOMA-IR, and associated morbidities (percentage of patients with hypertension or hyperlipidemia). Genotype of ApoA1 gene (rs670) was evaluated. Body weight was measured to an accuracy of 25 g. Body mass index (BMI) was calculated as body weight (in kg) divided by height (in m²). Waist circumferences (WC) were measured with a flexible non-stretchable measuring tape (Type SECA, SECA, Birmingham, UK). Percent excess weight loss (EWL%) was calculated ($\%EWL = \frac{\text{preoperative weight} - \text{current weight}}{\text{preoperative weight} - \text{ideal weight}} \times 100$). Ideal weight was calculated with an ideal BMI 22 kg/m². Electrical bioimpedance was used to determine fat mass with an accuracy of 50 g (Akern, EFG, Milan, Italy)¹⁵. Blood pressure was measured twice after a 10 minutes rest with a sphygmomanometer (Omrom, Los Angeles, CA, USA) and averaged. Blood samples were collected after an overnight fast of 12 hours. After

Table I. Preoperative characteristics of the patients.

	Basal time	1 year n=62	2 years n=59	3 years n=59
Morbid obese	63	40	15	5
Super-obese	6	3	1	0
Gender (women/men)	10/53	10/52	9/50	9/50
Age (years)	47.3±8.1	47.2±7.8	48.1±6.9	48.8±7.0
BMI (kg/m ²)	49.9±5.1	38.2±4.4	34.9±3.1	33.1±5.1

Morbid: BMI > 40 kg/m² and < 50 kg/m². Super obese > 50 kg/m².

centrifugation, serum was stored at -80°C . Serum total cholesterol, HDL-cholesterol and triglyceride concentrations were determined by enzymatic colorimetric assay (Roche Diagnostics, Basel, Switzerland). LDL-cholesterol was determined using Friedewald formula¹⁶. Plasma glucose levels were measured by using an automated glucose oxidase method (Glucose analyzer 2, Beckman Instruments, Brea, CA, USA). Insulin was measured by enzymatic colorimetric (Insulin, WAKO Pure-Chemical Industries, Osaka, Tokyo, Japan)¹⁷ and the homeostasis model assessment for insulin resistance (HOMA-IR) was calculated using insulin and values¹⁸.

Genotyping

Genomic DNA was extracted from 5 ml of peripheral blood at the beginning of the study. DNA was extracted from the buffy coat fraction using a commercial kit (Bio-Rad®, Hercules, CA, USA). Its quantity and quality were measured with a NanoDrop ND-1000 spectrometer (Bio-Rad®, Hercules, CA, USA). Primers were designed with the Sequenom Assay Design v4 (Sequenom, Inc. San Diego, CA, USA). Genotyping for the rs670 polymorphism was performed by polymerase chain reaction Real-time analysis. This polymerase chain reaction (PCR) was carried out with 30 ng of genomic DNA, 0.1–0.15 μl each of oligonucleotide primer for rs670 (primer forward: 5'-ACGTTGGATGAAGTTCCACATTGCCAGGAC-3' and reverse 5'-ACGTTGGATGCAGGGCCTATTTATGTCTGC-3' in a 2.5- μl final volume (Termociclador Life Technologies, San Diego, CA, USA). DNA was denatured at 85°C for 5 min; this was followed by 45 cycles at 65°C for 15 s, and annealing at 58.1°C for 45 s. Hardy Weinberg equilibrium was calculated with a statistical test (χ^2) and the variant of ApoA1 gene was in Hardy Weinberg equilibrium ($p=0.32$).

Statistical Analysis

Sample size estimation was performed based on the effects on weight loss using polymorphism frequency (30%) in morbidly and extreme obese subjects ($n=60$). All analysis was performed under a dominant genetic model with rs670 A- allele as the risk allele (AA+AG vs. GG). Data are reported as mean $\pm$ standard deviation. The normal distribution of variables was studied with the Kolmogorov-Smirnov test. Non-parametric variables were analyzed with the Mann-Whitney test and Wilcoxon test. Parametric test was analyzed with ANOVA test and Bonferroni post-hoc test. Qualitative

variables were analyzed with the χ^2 -test, with Yates correction as necessary, and Fisher's test as necessary. The statistical analysis to evaluate the time $\times$ group interaction was a univariate ANCOVA, adjusting by baseline levels of BMI, age and gender. We used linear regression analysis to evaluate the effects of this SNP on anthropometric composition and biochemical variations, adjusting for age, sex and initial weight. A p -value under 0.05 was considered statistically significant.

Results

Genotype frequencies of the sixty-three subjects (age 47.3 ± 8.1 years, 84.1% females) showed 73% ($n=46$) GG, 25.6% ($n=16$) GA and 1.4% ($n=1$) AA for the rs670 polymorphism. Allelic frequency was G (0.85) and A (0.15). The gender distribution was similar in the different genotypes (GG; 13.0% ($n=6$) males and 87.0% ($n=40$) females), (GA; 18.8% ($n=3$) males and 81.2% ($n=13$) females) and (AA; 0% ($n=0$) males and 100% ($n=1$) females). Average age was also similar in all genotype groups (GG: 47.7 ± 5.2 years vs. GA+AA 47.1 ± 3.2 years: ns). Table I shows the characteristics of the patients included in the study. Table II shows the parameters of subjects before and after DBP. All parameters showed a statistically significant reduction after surgery after 1, 2 and 3 years. No preoperative differences in weight, BMI, fat mass, waist circumference and blood pressure were observed among genotypes. Improvements in these variables were similar in both genotypes and all parameters were significantly different from basal values. In both genotypes, the percentage of excess of weight loss (EWL%) exhibits a significant improvement at all times during follow-up. Table III shows the changes in biochemical parameters. No significant preoperative differences in glucose, HOMA-IR, insulin, total cholesterol, LDL cholesterol and triglyceride were detected between genotypes. Only HDL-cholesterol levels were higher in A allele carriers than non A allele carriers. These elevated levels of HDL remained during the three years follow-up of the study. Fasting glucose, total cholesterol, LDL-cholesterol and triglyceride levels decreased in both genotype groups during follow up. Although the improvement in insulin and HOMA-IR was significant in both genotypes, this change was significantly higher in the A allele carriers. So, the decrease of fasting insulin levels after the first year ($\text{delta: } -3.7 \pm 1.4 \text{ mUI/L}$ vs.

Table II. Changes in anthropometric variables rs670 (mean+S.D).

Characteristics	rs670 GG (n=46)				rs670 GA or AA (n=17)			
	0 time	At 1 year	At 2 years	At 3 years	0 time	At 1 year	At 2 years	At 3 years
BMI	46.4±5.0	36.1±6.1*	33.4±4.2*	32.7±3.2*	47.0±4.1	37.1±3.4*	32.3±4.1*	31.8±4.7*
Weight (kg)	122.8±23.6	93.5±12.1*	86.2±10.1*	80.7±6.1*	127.8±17.2	94.2±9.1*	89.7±6.1*	81.7±9.3*
Fat mass (kg)	47.2±10.4	35.1±9.0*	32.1±7.1*	31.8±7.2*	44.7±8.7	35.1±9.2*	33.4±7.1*	32.0±5.0*
WC (cm)	117.5±9.0	114.2±8.1*	104.9±9.1*	98.7±6.2*	121.3±6.2	112.4±6.1*	103.0±7.0*	99.8±7.2*
EWL%	—	58.3	62.2	66.7	—	59.1	61.3	67.0
SBP (mmHg)	149.0±7.0	132.1±8.1*	130.1±8.0*	129.3±7.0*	150.1±9.0	133.4±5.3*	130.2±7.3	128.9±6.3*
DBP (mmHg)	90.1±4.0	83.7±4.1*	84.0±4.0*	83.7±3.3*	92.3±3.0	84.7±6.1*	84.6±4.0	81.0±4.1*

DBP: Diastolic blood pressure; SBP: Systolic blood pressure; WC: Waist circumference; EWL%: Percent excess weight loss. (*) $p < 0.05$, in each genotype group with basal values. There are no statistical differences in demographic, anthropometric and metabolic characteristics between the two-genotype groups.

Table III. Biochemical parameters (mean+S.D).

Characteristics	rs670 GG (n=46)				rs670 GA or AA (n=17)			
	0 time	At 1 year	At 2 years	At 3 years	0 time	At 1 year	At 2 years	At 3 years
Glucose (mg/dl)	105.1±7.1	96.6±6.1*	89.3±8.2*	87.2±7.1*	108.5±9.1	100.1±6.2*	92.1±8.2 *	89.7±5.1*
Total ch. (mg/dl)	198.8±36.1	138.6±18.1*	127.1±12.1*	126.8±9.1*	201.8±30.1	154.2±22.4 *	134.1±20.0*	126.1±13.4*
LDL-ch. (mg/dl)	124.1±10.1	70.5±9.1*	61.6±8.1*	64.0±9.1*	120.9±22.3	98.0±12.1 *	63.6±8.1*	70.3±10.1*
HDL-ch. (mg/dl)	49.4±8.1	48.2±10.2	49.7±9.0	49.0±8.1	53.7±11.7\$	55.9±7.4*\$	56.2±6.8*\$	56.1±7.2*\$
TG (mg/dl)	148.9±21.1	130.2±11.4*	113.1±9.6*	90.2±12.1*	150.1±29.6	117.2±23.0*	112.8±21.1*	99.8±26.1*
Insulin (mUI/L)	17.1±4.2	14.1±5.0*	13.0±4.1*	13.2±5.1*	16.8±6.0	13.1±4.0*	12.0±3.8*	10.1±6.1*
HOMA-IR	4.2±2.0	3.5±1.5*	3.2±1.2*	3.0±0.9*	4.1 ±2.1	3.0±1.2*	2.9±1.8*	2.7±1.3*

LDL: Low density lipoprotein; HDL: High density lipoprotein; Chol: Cholesterol; TG: Triglycerides; HOMA-IR (homeostasis model assessment). (*) $p < 0.05$, in each group with basal values. \$ $p < 0.05$, between genotypes.

-2.9±1.2 mUI/L; $p=0.02$), the second year (delta: -4.8±0.3 mUI/L vs. -4.0±0.2 mUI/L; $p=0.01$) and the third year (delta: -6.7±3.1 mUI/L vs. -3.9±2.1 mUI/L; $p=0.03$) was higher in A allele carriers than in non-A allele carriers. On the other hand, the improvement of HOMA-IR levels at year one (delta: -3.7±1.4 mUI/L vs. -2.9±1.2 mUI/L; $p=0.02$), year two (delta: -4.8±0.3 mUI/L vs. -4.0±0.2 mUI/L; $p=0.01$) and at year three (delta: -6.7±3.1 mUI/L vs. -3.9±2.1 mUI/L; $p=0.03$) was also higher in A allele carriers than non-A allele carriers. Finally, the increase of HDL-cholesterol levels at year 1 (delta: 2.2±0.6 mg/dl vs. -1.2±0.2 mg/dl; $p=0.001$), year two (delta: 2.5±0.4 mg/dl vs. 0.3±0.1 mg/dl; $p=0.01$) and year three (delta: 2.4±0.6 mg/dl vs. 0.4±2.3 mg/dl; $p=0.02$) were higher in A allele carriers than non-A allele carriers. The multiple linear regression analysis showed that the rs 670 variant was not associated with weight loss during the follow-up (data not shown). However, the model adjusted for sex, age and basal weight reported that A allele of rs670 polymorphism was associated with HDL concentrations improvement at 3 years (Beta 0.21 95% CI 0.46-4.63; $p=0.02$), insulin levels decrease (Beta 0.48 95% CI 0.13-8.99; $p=0.01$) and HOMA IR decrease (Beta 0.11 95% CI 0.04-7.63; $p=0.03$) after BPD.

Discussion

In the present study, we evaluated the contribution of variant rs 670 of APOA1 gene to anthropometric markers and biochemical changes in a sample of non-diabetic morbid obese subjects undergoing a BPD. We observed an effect of A allele of rs670 variant, located in *APOA1* gene, in modulating changes of HDL-cholesterol, insulin levels and HOMA-IR after a huge weight loss during 3 years follow-up. This is the first time that an analysis of this polymorphism in morbid obese patients is carried out. A allele frequency of the ApoA1 polymorphism in our study (0.15) was similar to previous literature data in Caucasian (0.11-0.15)^{19,20} and Non-Caucasian population (0.13-0.15)^{21,22}. The concordance of our allelic frequency with the data reported in other studies of non-morbid obese patients and the absence of differences in the baseline data of the anthropometry in the two analyzed genotypes suggest that this polymorphism does not have a direct influence on adiposity parameters. The second finding of our study was the association

between HDL-cholesterol levels and A allele of rs670 variant. This relationship of A allele with HDL-cholesterol concentrations has been observed in a lot of investigations with different populations^{10-12, 23,24}, as also showed in our design with morbid obese subjects. Nevertheless, there is a lack of information in the literature about the influence of massive weight loss after a bariatric surgery on this association between A allele and HDL-cholesterol levels or adiposity parameters. Only one previous study²⁵ reported a relationship between A allele of this SNP and weight changes after a dietary intervention. However, this design cannot be compared to our work, because it was performed in adolescents for less than 3 months of intervention with a standard hypocaloric diet. To date, we have found no data in the literature that evaluates the effect of this polymorphism on the metabolic effect of biliopancreatic diversion technique. Our present results suggest that rs670 variant of *APOA1* gene is related with differential regulation of HDL-cholesterol synthesis and it may contribute to the improvement in insulin resistance and HDL-levels secondary to weight loss during 3 years follow-up. To explain these metabolic findings, in addition to the direct effect of the polymorphism itself on the metabolic pathways, nutrient composition of dietary intake could also be involved. For example, Phillips et al²⁶ showed that metabolic deleterious effects secondary to rs670 (G allele) were worsened among individuals consuming high-fat diet. A cross-sectional study²⁷ reported an interaction between rs670 variant of APOA1 gene and saturated fat dietary intake on LDL-cholesterol levels without a dietary intervention or weight loss. A diet rich in polyunsaturated fatty acids has demonstrated to induce greater LDL-cholesterol decrease in A allele carriers than non A allele carriers compared with a high saturated fatty acid enriched diet²⁸. Finally, these data have been confirmed again in another study with a similar design²⁹. Moreover, in a two months lifestyle intervention (EVASYON STUDY)²⁵, A allele carriers showed a higher decrease of adiposity parameters than in non A allele carriers, without an interaction with HDL-levels. Another area with few data is the association between rs670 and the metabolism of glucose. Phillips et al (26) have reported that non A allele carriers showed an increased abdominal obesity and impaired insulin resistance. This metabolic association has not been detected in our sample of patients with morbid obesity. Also, AA homozygotes have been associated with increased risk

of hyperglycemia (30). Our data have shown that patients with both genotypes improved insulin levels and HOMA-IR; however, the improvement in the levels of both parameters were higher in the carriers of the A allele. This relationship between the A allele and the glucose metabolism can be explained biologically. APOA1 gene is stimulated by insulin through SP-1 binding elements³¹ and ApoA1 rs670 as lying in a sequence homologous to the binding site for this nuclear factor SP-1. The better effect of weight loss on insulin and HOMA-IR changes in patients carrying the allele A than in non A allele carriers may be due to an unknown abnormality in the promotor region of ApoA1 or other regions of this gene. Other potential factors involved in this relationship may be dietary parameters. In a recent study³², A allele of rs670 variant appear to be protective for metabolic syndrome risk in participants with high intake of sugar-rich foods. Phillips et al²⁶ showed in high fat consumers and non-A allele carriers further impairments to insulin concentration and insulin resistance and weight. Finally, it is assumed that A allele has an effect on Apo A-I expression, because LDL predominantly originates from VLDL, so, it is reasonable to speculate that differences in the postprandial metabolism of triglyceride-rich lipoproteins may explain the effects on insulin levels and insulin resistance observed. The effect of this SNP on the response of the modification of HDL levels after bariatric surgery is important since several findings³³ suggest that improvements in lipid metabolism after bariatric surgery may be weight independent and can be due to the effects of surgery, specifically its malabsorption component. Evidence to support this data includes the fact that changes detected in lipid levels occur early after surgery even before weight loss occurs³³. The genetic effect of rs670 and other SNPs could explain these early changes in lipid levels after bariatric surgery. Hsu et al³⁴ have reported that subjects in homozygous (AA) ApoA1 rs670 A/A showed poor post-surgery prognosis in breast cancer survival. This group hypothesized that ApoA1 rs670 indicate a post-surgery risk of breast cancer disease progression. This new association opens new ways of study on the effect of this polymorphism in different types of surgeries. Limitations of our study are: first, lack of measurement of subclasses of HDL-C; second, many uncontrolled non-genetic factors could influence the relationships in our design (exercise, hormone status, and so on); third, the lack of a dietary assessment throughout the study in order to calcu-

late saturated and unsaturated fat intakes. Finally, our population is a morbid obese adult sample without diabetes mellitus; this factor could modulate the response to massive weight loss to another direction.

Conclusions

In this study we observed that the variant rs670 of the APOA1 gene showed important effects on HDL-cholesterol, HOMA-IR and insulin resistance after derivation biliopancreatic during 3 years. A allele carriers showed high levels of HDL cholesterol. Our data may explain the variability of lipid profiles after bariatric surgery in an interesting population (obese patients) with a lot of different clinical implications³⁵.

Statement of Informed Consent

"Informed consent was obtained from all individual participants included in the study." All procedures performed in studies involving human participants were in accordance with the Ethical Standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable Ethical standards.

Conflict of Interests

The Authors declare that they have no conflict of interests.

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