**APOA5 variants predispose hyperlipidemic patients to atherogenic dyslipidemia and subclinical atherosclerosis**

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**A B S T R A C T**

**Background:** Triglycerides (TG) are the initiators of the metabolic changes leading to the atherogenic dyslipidemia, which is a major inducer of atherosclerosis as a result of quantitative and qualitative changes in lipoprotein subclass distributions. We hypothesized that variation at the APOA5 gene locus, encoding apoAV, a key regulator of TG levels, significantly affect lipoprotein subclass distributions toward a more atherogenic pattern in both hyperTG patients and dyslipemic patients.  

**Methods:** We recruited four hundred and twenty-two subjects attending a Lipid Clinic, prior to lipid-lowering treatment. We genotyped two APOA5 variants, rs662799 (-1131T>C) and rs3135506 (S19W). Circulating lipoproteins were determined by nuclear magnetic resonance (NMR). Intima-media thickness (IMT) was evaluated using B-mode ultrasound.  

**Results:** Carriers of the rare alleles of rs662799 and rs3135506 compared to common allele homozygotes, had a significantly proatherogenic profile of the VLDL and LDL subclasses, resulting in increased concentrations of the proatherogenic subclasses, large VLDLs (+133%, p < 0.001) and small LDLs (+34%, p = 0.014). Significant changes in smaller HDL (+71%, p = 0.032), as well as an 18% decrease in large HDL (p = 0.046), were also observed. This atherogenic NMR subclass distribution was significantly associated with increased carotid IMT. The observed effects were significantly stronger in patients with a BMI ≥ 25 kg/m² and in male and female patients with a waist circumference ≥90 cm or ≥85 cm, respectively.  

**Conclusion:** In a dyslipemic population, genetic variants of APOA5 modulate lipoprotein subclass distributions, inducing an atherogenic profile associated with IMT defined subclinical atherosclerosis. © 2015 Elsevier Ireland Ltd. All rights reserved.

**1. Introduction**

Plasma lipid levels play a pivotal role in the pathogenesis of atherosclerosis and are a major predictor of coronary artery disease (CAD) [1]. Hence, LDL cholesterol is the focus of most strategies directed at reducing cardiovascular risk. Triglycerides (TG) are also important in this regard, not only because they are a risk factor for atherosclerosis [2] but because they are also the initiators of the metabolic changes leading to an atherogenic lipoprotein profile, the so-called atherogenic dyslipidemia. The rationale behind the present investigation is that atherogenic changes induced by TG occur at concentrations as low as 1.7 mmol/L; the level at which small dense LDL become predominant [3]. Thus small dense LDL are clinically relevant not only for hypertriglyceridemic patients but also for those with other dyslipemias.

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The condition that best reflects the pernicious role of TG is atherogenic dyslipidemia, a metabolic disturbance characterized by hypertriglyceridemia and low HDLc that entails an increased cardiovascular disease risk [4–6]. It is a feature of obesity, type 2 diabetes mellitus, and metabolic syndrome, conditions with a high prevalence globally [7,8]. It has been suggested that high plasma TG levels modulate the size and number of certain lipoprotein subclasses, triggering an imbalance that promotes increase in circulating proatherogenic small dense LDL particles and cholesterol-rich remnant particles, as well as a decrease in anti-atherogenic HDL particles.

To gain insight into this scenario two additional issues must be addressed. The first involves the factors that predispose an individual to increased TG; the second is our capacity to detect TG-induced lipoprotein changes via traditional lipid and lipoprotein measurements.

Regarding the first issue, the apolipoprotein A5 (APOA5) gene, encoding apoAV, is one of the major genetic determinants of circulating TG levels. In animal models, an inverse relationship between hepatic APOA5 expression and plasma TG levels has been described [9]. In humans, both single-gene and genome-wide association studies in different populations, have confirmed that APOA5 is one of the strongest genes influencing TG concentrations [10–13]. It has also been reported that APOA5 variants are associated with other lipid parameters, LDL and HDL, suggesting that they are not limited to determining TG levels, but also play an important role in the overall regulation of lipid metabolism.

To date, several mechanisms of apoAV action have been proposed, including plasma TG removal, either by stimulating TG hydrolysis and stabilizing the lipoprotein lipase (LPL) active dimer, or facilitating the attachment between TG-rich lipoproteins and glycosylphosphatidylinositol anchored high density lipoprotein binding protein 1 (GPIHBP1) [14,15], as well as accelerating hepatic uptake of TG-rich lipoproteins and their remnants by heparan sulfate proteoglycan (HSPG) and LDL receptor (LDLR) family members. Intracellular effects of apoAV on VLDL production and secretion by the liver may also explain the effect of apoAV on TG levels, but the evidence supporting this notion is weaker [16].

Regarding lipid measurements, it has been known for some time that lipid constituents of major lipoprotein classes (such as cholesterol and TG), may be further characterized into subclasses using various techniques, among them nuclear magnetic resonance (NMR), a method that helps quantify lipoprotein subclasses [17]. The profile of these subclasses represents an important prognostic factor in both the manifestation and the progression of CAD.

Therefore, the objective of this study was to analyze the effects of APOA5 variants on lipid profiles, lipoprotein subclass sizes and numbers, and carotid atherosclerosis, determined by measures of intima media thickness (IMT) in hyperlipidemic subjects recruited from a lipid clinic.

2. Subjects and methods

2.1. Study subjects

Subjects were recruited at 3 Lipid Clinics (Hospital Universitari Sant Joan de Reus, Hospital Clinic of Barcelona and Hospital Universitario Miguel Servet of Zaragoza) in Spain [18]. The study began in 2005, when clinical, analytical and sonographic methodologies were standardized among centers. All patients ≥17 years of age with a clinical diagnosis of familial hyperlipidemia were included and provided informed consent to participate in a protocol approved by the ethical review boards of each of the participating institutions. Within 2–6 weeks of their first visit, all participants had venipuncture to collect fasting blood samples and underwent a carotid ultrasound according to a predefined protocol. We studied 422 untreated subjects.

Isolated primary hypercholesterolemia was diagnosed in subjects with off-treatment LDLc levels above the age- and sex-specific 95th percentile of a Spanish reference population [19], as well as TG levels below 5.17 mmol/L. The diagnosis of primary hypertriglyceridemia was based on the presence of either combined hyperlipidemia or isolated hypertriglyceridemia in untreated patients whose serum cholesterol and TG concentrations were above the sex- and age-specific 90th percentiles for the Spanish population. The criterion for combined hyperlipidemia was having serum total apolipoprotein B levels ≥120 mg/dL, and for isolated hypertriglyceridemia this was the presence of high TG alone. Secondary causes of hyperlipidemia were excluded in all subjects. A control group consisting of healthy, unrelated male and female volunteers, aged 18–75 years, who underwent a medical examination at the Hospital Miguel Servet of Zaragoza was also studied. Exclusion criteria for control subjects included a personal or parental history of CAD or dyslipidemia, an existing acute illness, or the use of drugs capable of influencing either glucose or lipid metabolism.

Eighteen participants did not report data on BMI and 10 participants did not report data on waist circumference so they were not included into the analysis.

2.2. Laboratory measurements

Fasting blood for biochemical profiles was drawn after patients were off hypolipidemic drug treatment for at least 4 weeks. Cholesterol and TG levels were determined by standard enzymatic methods. HDLc was measured by a precipitation technique. LDLc was estimated with the Friedewald equation, except in samples with triglycerides >3.5 mmol/L, when it was measured in the d = 1.063 g/mL fraction separated by density gradient ultracentrifugation. Apolipoprotein (apo) B and lipoprotein(a) levels were determined by immunoturbidimetry (Unimate 3, Roche, Basel, Switzerland).

2.3. Nuclear magnetic resonance lipoprotein profile measurements

Both lipoprotein subclass particle concentrations and the average sizes of lipoprotein particles were measured by proton NMR spectroscopy (LipoScience, Inc., Raleigh, North Carolina), as previously described [20]. The particle concentrations for lipoprotein subclasses of different size were obtained directly using the measured amplitudes of their spectrosocopically distinct lipid methyl group NMR signals. Weighted-average lipoprotein particle sizes were derived from the sum of the diameter of each subclass multiplied by its relative mass percentage based on the amplitude of its methyl NMR signal. The concentrations of the following subclasses were measured: small LDL (18.0–21.2 nm), large LDL (21.2–23.0 nm), intermediate-density lipoprotein (IDL) (23.0–27.0 nm), large high-density lipoprotein (HDL) (8.8–13.0 nm), medium HDL (8.2–8.8 nm), small HDL (7.3–8.2 nm), large very low-density lipoprotein (VLDL) (>60 nm), medium VLDL (35.0–60.0 nm), and small VLDL (27.0–35.0 nm). VLDL and LDL particle concentrations are expressed in nmol/L, and HDL, in μmol/L.

2.4. Carotid intima media thickness (IMT) measurements

For carotid sonography, we used at each center an Acuson Sequoia instrument (Siemens Medical Solutions, Erlangen, Germany) equipped with a linear array ultrasound transducer (L7, 5–12 MHz). Scanning and image analysis procedures were standardized as previously described [21]. In summary, scans were...
performed from a fixed lateral angle. The far walls of the three bilateral carotid segments were visualized: the right and left common carotid arteries, carotid bifurcations, and internal carotid arteries. Sonographic variables of interest included the maximum IMT in any of the 6 carotid segments (maxIMT), the mean of the maximum IMT at each of the 6 carotid areas (mean-maxIMT), and IMT in any of the 6 carotid segments (maxIMT), the mean of the common carotid arteries, carotid bifurcations, and internal carotid arteries. Sonographic variables of interest included the maximum IMT in any of the 6 carotid segments (maxIMT), the mean of the maximum IMT at each of the 6 carotid areas (mean-maxIMT), and the mean IMT for the 6 carotid segments (mean IMT). All procedures were performed by trained certified sonographers. High resolution images of each of the segments were saved as DICOM stills during the diastole of the vessel. The recordings were subsequently stored on CD for offline analyses. The scans from each center were analyzed by a certified ultrasound reader in Zaragoza. Semi-automated edge-tracking software (eTRACK, AMC Vascular Imaging, Amsterdam, The Netherlands) was used. The ultrasound reader was blinded to the demographic and clinical information of the subjects.

2.5. APOA5 genotyping

DNA was isolated from EDTA blood samples following standard protocols. We genotyped the rs662799 (-1131T>C) and rs3135506 (S19W) APOA5 variants using TaqMan Technology (Applied Biosystems) and the 7900HT Sequence Detection machine (Applied Biosystems) using the 7900HT Sequence Detection machine (Applied Biosystems), as reported previously [22].

2.6. Statistical analyses

Statistical analyses were carried out using SPSS software, version 17.0. The Chi-square ($\chi^2$) test was used to test for Hardy–Weinberg equilibrium. Unpaired t-test was used to compare lipid, apolipoprotein and IMT data amongst genotypes. Not normally distributed variables were log-transformed before analysis. The results are expressed as means (SD). All analyses were adjusted for age, gender and BMI. A Bonferroni correction for multiple comparisons was applied. Statistical significance was accepted at the $p = 0.05$ level.

3. Results

3.1. Subjects’ description

We studied 422 subjects. As we predicted that APOA5 genotypes would modulate lipoprotein profiles in all types of dyslipidemia, we pooled all study subjects. To assess individual dyslipidemias, however, we divided the subjects into different groups (Normolipidemia, Hypercholesterolemia and Hypertriglyceridemia). Table 1 shows the clinical and biochemical parameters of each group. Hypertriglyceridemic and hypercholesterolemic patients were older, and hypercholesterolemic subjects presented with increased total and LDLc levels, whereas hypertriglyceridemic subjects (including those with combined hyperlipidemia) had higher TG and higher total and LDLc levels.

3.2. APOA5 genotypes and conventional lipid parameters

The frequencies of minor alleles -1131C and 19W of were 0.07 and 0.08, respectively which are similar to those observed in Caucasian populations [23]. The genotype distributions were in Hardy–Weinberg equilibrium. We pooled heterozygotes and rare allele homozygotes to increase statistical power. APOA5 genotypes showed no difference in gender distribution, mean age or BMI. Table 2 shows levels of conventional lipids by APOA5 genotypes and conventional lipid parameters.
3.3. APOA5 genotypes and NMR lipoprotein subclasses

To further characterize the effects of APOA5 variants on lipid profiles, we evaluated their association with concentrations of lipoprotein subclasses determined by NMR (Table 3).

The -1131T>C polymorphism was significantly associated with a 25% increase in the number of total VLDL and chylomicron particles (p = 0.032).

C allele carriers also had significantly higher number of total LDL particles (p = 0.014). In further detail this association with LDL was limited to the smaller particles: 35% increase in small LDL (p = 0.014); 40% increase in medium small LDL (p = 0.002) and 34% increase in very small LDL particles (p = 0.001). Patients carrying the minor allele for the -1131T>C variant also presented with an 18% decrease in their levels of large HDL particles (p = 0.046).

Regarding the S19W genotype, carriers of the minor allele presented with a 27% increase in the number of total VLDL and chylomicron particles (p = 0.006). In further detail, this association was limited to the largest VLDL particles: 133% increase in large LDL and chylomicron particles (p < 0.001), as well as 63% increase in median LDL particles (p < 0.001).

Carriers of the rare 19W allele presented with 23% increased median small LDL particles (p = 0.024).

Moreover, patients carrying the minor allele of the S19W variant also presented with a 71% increase in medium HDL particle levels (p = 0.032).

3.4. Influence of adiposity on the association of APOA5 genotypes with NMR lipoprotein subclasses

We performed the following sub-analysis based on BMI and waist circumference stratification: BMI>25 kg/m² (n = 173) and BMI ≤ 25 kg/m² (n = 231). The significant associations described between APOA5 variants and lipid parameters were limited almost entirely to overweight patients (Supplemental data, Table S1 and S2).

We also divided the cohort into two groups of abdominal obesity: waist circumference <90 cm in men (n = 64) and <85 cm in women (n = 109), and waist circumference ≥90 cm in men (n = 153) and ≥85 cm in women (n = 86) (Supplemental data, Table S3 and S4). Again only patients with largest waist circumference showed associations between APOA5 gene markers and lipid parameters.

3.5. NMR subclasses, APOA5 genotypes and carotid IMT

Total VLDL and chylomicron, and small VLDL particle concentrations were increased by 55% (p = 0.028) and 40% (p = 0.012), respectively in the top IMT tertile compared with the bottom tertile (respectively). VLDL remnants (IDL particles) were almost 2 times higher in patients with the highest IMT values (p = 0.006), and significant increases in total LDL particle concentrations between the first and third IMT tertiles were also noted (p = 0.022). Additional lipoprotein particles showed associations with increased IMT tertiles (summarized in Fig. 1). Regarding APOA5 genotypes, the rare 19W allele was associated with higher internal carotid thickness (Fig. 2) (p = 0.028), and this effect was limited to patients with higher waist circumference (Table S5).

4. Discussion

Increased serum TG levels are an independent risk factor for cardiovascular disease because they induce quantitative and qualitative atherogenic changes in TG-rich lipoproteins, as well as in both LDL and HDL particles [24]. The aim was to investigate whether atherogenic changes induced by TG occur at concentrations as low as 1.7 mmol/L (the level at which small dense LDL particles become more numerous) [3], were clinically relevant, not only for hypertriglyceridemic patients, but also for hyperlipidemic patients.

We show that APOA5 variants (-1131C>T and S19W) were associated with increased TG levels and an atherogenic lipoprotein profile characterized by a shift toward smaller LDL and HDL particles.

These changes were present in the entire dyslipidemic population and are not confined only to hyperTG patients. We observed a trend towards an atherogenic lipoprotein profile (in relation to the -1131C allele) among hypercholesterolemic patients with very moderate TG concentrations. However because of the limited sample size these results did not to reach statistical significance.

Table 3

<table>
<thead>
<tr>
<th>APOA5 genotypes vs. NMR lipid parameters.</th>
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<tr>
<td><strong>-1131T&gt;C APOA5</strong></td>
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<tr>
<td>TT (n = 359)</td>
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<tr>
<td>VLDL &amp; Chylo total particles (nmol/L)</td>
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<td>VLDL large &amp; Chylo particles (nmol/L)</td>
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<td>VLDL median particles (nmol/L)</td>
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Data are expressed as a mean (SD). p value is adjusted for age, gender and BMI.

Total LDL particle concentrations are the sum of the intermediate-density lipoprotein, large LDL, and small LDL subclass concentrations which correspond to the sum of median small and very small particles.
The atherogenic lipoprotein subclass changes associated with APOA5 variants showed statistically significantly subclinical atherosclerosis, which was exacerbated by excess body weight and increased waist circumference.

4.1. Triglyceride-driven changes in LDL and HDL by NMR

Atherogenic changes in LDL and HDL particle size are not detectable by routine lipid analyses, but can be uncovered by lipoprotein NMR analysis.

This lipoprotein profile is a common feature of metabolic disturbances associated with an increased cardiovascular risk, such as insulin resistance, diabetes mellitus, lupus erythematosus [25], and other conditions. It is well known that the onset of this atherogenic profile is due to increased fatty acid flux from adipose tissue, which induces increased synthesis and secretion of TG-rich particles (VLDL). These VLDLs are larger, contain more TG, and possess a greater proportion of apoCIII, the inhibitor of LPL, compared with apoCII, which results in impaired LPL activity and deficient TG hydrolysis. In this situation remnant particles are poorly recognized by both the LDL-receptor (LDLR) and LRP receptor (LDLR-related protein), which are responsible for their clearance from the circulation. This increases the time that these lipoproteins remain in circulation and allows for the formation of more remnant-like particles. Due to the actions of CETP (cholesteryl ester transfer protein) and HL (hepatic lipase), these particles become small and dense LDL (sdLDL), which are highly susceptible to oxidation and proatherogenic, as they are associated with at least a 3-fold increase in CHD risk [26]. CETP and HL also promote changes causing large cholesterol-rich HDL particles to become TG-rich and cholesterol poor. The hydrolysis of TG induces rapid changes that yield much smaller alpha HDL particles, which are subject to renal excretion due to their small sizes.

4.2. The APOA5 promotes TG-driven LDL and HDL changes

The data from the lipoprotein subclasses obtained by NMR analysis...
provide a better understanding of the effects of APOA5 variants on lipoprotein profiles. NMR analyses revealed significant associations amongst the APOA5 variants and the number and sizes of chylomicrons and VLDL, LDL and HDL particles. Rare APOA5 alleles were associated with an atherogenic profile characterized by elevations of the levels of large chylomicrons and VLDL particles, and consequently high levels of small dense LDL. This also leads to a reduction in large HDL particles.

Our studies largely concur with those of previous studies. Talmud et al. [27] studied the relationship between APOA5 polymorphisms and lipid profiles obtained via preparative ultracentrifugation in coronary patients and found an association between the -1131T>C polymorphism and increased VLDL levels, but not increased apolipoprotein levels. The S19 allele was associated with an increased size of IDL particle, which are precursors of sDLLD. Lai et al. [28] analyzed the relationship between APOA5 polymorphisms and NMR lipoprotein subclasses in the Framingham Offspring Study and reported that -1131T>C and S19W variants were associated with increased levels of larger VLDL subclasses. In a large meta-analysis of 101 studies with more than twenty thousand coronary heart disease cases and > thirty-five thousand controls, the -1131T>C polymorphism was also associated with an atherogenic profile of lipoproteins as determined by NMR; however, no effects on LDL subclasses were noted [2].

Our results support the importance of a genetic predisposition to hypertriglyceridemia as a risk factor for atherosclerosis. APOA5 variants are associated with increased TG levels and changes in the sizes and concentrations of LDL and HDL subparticles. We have shown how these lipoprotein characteristics are more common among subjects in the highest tertiles of IMT. Moreover, the APOA5 19W allele was significantly associated with increased IMT. These results concur with data from Elosua et al. [29] who showed that -1131T>C and S19W variants were both significantly associated with increased common carotid artery IMT in obese participants, in the Framingham Offspring Study. Our results for 19S allele are in agreement with these.

4.3. Lipoprotein effects of APOA5 variants are not limited to hypertriglyceridemic subjects

With our limited sample size we did not have the statistical power for subgrouping disease types, however our results do show that the atherogenic changes in LDL and HDL are present not only in hypertriglyceridemic subjects, but also in subjects with isolated hypercholesterolemia. In this group, which has a modest mean TG concentration, changes similar to those associated with APOA5 variants are also observed (data not shown).

Abdominal obesity is associated with high plasma TG and with low plasma HDLc levels [30]; therefore, we were interested in a potential link between APOA5 and obesity in our subjects. Interestingly, we found that the relationships between APOA5 gene markers and lipid parameters were more significant if we considered only overweight subjects (defined as a BMI ≥ 25 kg/m²), which may be explained in part by overweight patients having a more dyslipidemic profile than patients with lower BMI (data not shown), a finding that confirms the hypothesis that the effects of APOA5 depend largely on the metabolic background of the subject. This relationship with obesity was previously reported by Evans I [31], who showed that -1131T>C was associated with higher TG levels and lower HDLc levels in a group of dyslipidemic patients attending a lipid clinic but only observed in those with a BMI ≥ 25 kg/m².

In summary, we show that APOA5 variants predispose to higher TG concentrations and also to more atherogenic LDL and HDL particles not detectable by routine analyses. These changes have clinical importance as they are associated with increased subclinical atherosclerosis, and are observed not only in hypertriglyceridemic subjects but also in those with isolated hypercholesterolemia, particularly subjects who are overweight or have large waist circumferences.

Conflict of interest

None.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2015.03.008.

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