ABCA1 Gene Variants Regulate Postprandial Lipid Metabolism in Healthy Men

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Objective—Genetic variants of ABCA1, an ATP-binding cassette (ABC) transporter, have been linked to altered atherosclerosis progression and fasting lipid concentration, mainly high-density lipoproteins and apolipoprotein A1; however, results from different studies have been inconsistent.

Methods and Results—To further characterize the effects of ABCA1 variants in human postprandial lipid metabolism, we studied the influence of 3 single nucleotide polymorphisms (i27943 [rs2575875]; i48168 [rs4149272]; R219K [rs2230806]) in the postprandial lipemia of 88 normolipidemic young men who were given a fatty meal. For i27943 and i48168 single nucleotide polymorphisms, fasting and postprandial values of apolipoprotein A1 were higher and postprandial lipemia was much lower in homozygotes for the major alleles, total triglycerides in plasma, and large triglyceride-rich lipoprotein triglycerides. These persons also showed a higher apolipoprotein A1/apolipoprotein B ratio. Major allele homozygotes for i48168 and i27943 showed additionally higher high-density lipoproteins and lower postprandial apolipoprotein B.

Conclusion—Our work shows that major allele homozygotes for ABCA1 single nucleotide polymorphisms i27943 and i48168 have a lower postprandial response as compared to minor allele carriers. This finding may further characterize the role of ABCA1 in lipid metabolism. (Arterioscler Thromb Vasc Biol. 2010;30:00-00.)

Key Words: atherosclerosis ■ ATP-binding cassette transporters ■ lipids ■ postprandial state ■ triglycerides

A TP-binding cassette (ABC) transporters are a family of proteins that act as transmembrane carriers of molecules using ATP hydrolysis as energy source.1 ABCA1, a member of the ABC family, has been implicated in monocyte differentiation and phagocyte/dendritic cell commitment,2 but the most studied aspect regarding ABCA1 is its regulation of lipid metabolism. ABCA1 is a major regulator of high-density lipoprotein (HDL) metabolism.3 Moreover, mutations in the ABCA1 gene are the underlying mechanism of Tangier disease, an affliction defined by a stark HDL deficiency, mildly to moderately increased triglyceride levels, and decreased low-density lipoprotein cholesterol.3–5 Based on in vitro and in vivo studies, a broader importance in lipid metabolism has been attributed to ABCA1, which now is known to regulate the migration of lipid molecules through the cell membrane.6–8 Its expression is highly influenced by intracellular cholesterol changes,9 pro-oxidant substances,10 and lipid loading (via LXR receptors).10,11 The human ABCA1 gene maps to chromosome 9q31, and its 50 exons span over 150 kbp.12,13 Although the exact physiological effects of ABCA1 are not fully understood, a role in atherosclerosis progression via reverse cholesterol pathway has been proposed.

A common strategy to indirectly define ABCA1 function has relied on assessing the clinical phenotype associated with variations in its gene. One of the most studied ABCA1 variants is R219K (rs2230806). The status of minor allele carriers has been linked to reduced atherosclerosis, with a decrease in the intima media thickness of the carotid artery,14,15 less severe coronary artery disease, and slower coronary artery disease progression.14,16 Other gene variations also have been studied, with variable effects on lipid concentrations or atherosclerosis.14,17,18 We recently reported the interaction of ABCA1 with ABCG5/ABCG8 gene variants on HDL concentration.19 However, and paradoxically, with increasing evidence for an effect of these variants on atherosclerosis and coronary artery disease comes contradiction regarding their effects on fasting lipid concentrations.14 Al-
though a typically plausible underlying mechanism of this altered atherosclerosis was the change in HDL concentration, this has not been found in the majority of studies.\textsuperscript{14,15} Looking for additional physiological pathways underlying ABCA1 effects on lipid metabolism and atherosclerosis, we investigated and report here the effects of ABCA1 variants i27943, i48168, and R219K on postprandial lipid metabolism of healthy males.

Subjects and Methods

Eighty-eight healthy men aged 18 to 33 years were selected among students from the University of Cordoba. We included only young normolipemic apolipoprotein E E3/E3 males to avoid possible effects of different apolipoprotein E isoforms or gender. Other results of this cohort have been published elsewhere.\textsuperscript{20–22} No participants had diabetes or liver, renal, or thyroid disease, nor were they using any medication. Anthropometric measures (weight, height, and body mass index) and blood pressure were assessed, and all subjects were encouraged to maintain regular lifestyle and levels of physical activity. All volunteers had plasma cholesterol and triacylglycerol concentrations <200 mg/dL. Baseline characteristics of the participants are summarized in Table 1. The study in which these participants were enrolled was approved by the Ethics Committee for Clinical Investigations of the Reina Sofía University Hospital in Cordoba, and participants previously signed an informed consent to join the study.

Study Design

After an overnight 12-hour fast, subjects were given a fatty meal enriched with 60 000 U of vitamin A per m\textsuperscript{2} body surface area. The amount of fat given was 1 gram of fat and 7 mg of cholesterol per kg body weight. This meal contained 60% of its energy in the form of fat (35% saturated, 19% monounsaturated fat, 6.3% polyunsaturated fat), 15% as protein, and 25% as carbohydrate, and it was consumed within 20 minutes. After the meal, subjects were not allowed another energy intake for 11 hours but were permitted to drink water. Blood samples were taken just before the meal and postprandially every hour until 6 hours, and then every 2 hours and 30 minutes until 11 hours. Taking samples at such late time points allowed many lipid measures to return to near-fasting levels.

Biochemical Determinations

Single Nucleotide Polymorphisms Selection, DNA Amplification, and Genotyping

R219K G>A is a well-characterized single nucleotide polymorphism (SNP) that has been extensively studied and is associated with cardiovascular disease; however, its influence on postprandial lipemia has not been tested.\textsuperscript{14} We have reported previously on other effects of SNP i27943G>A and i48168G>A.\textsuperscript{19} Computational analysis ascribed potential functional characteristics to each variant allele of these SNP.\textsuperscript{19} Additionally, for the i48168 G>A polymorphism, analysis by MAPPER indicated a potential allele-specific binding site for the cartilage paired-class homeoprotein 1 (CART1 or ALX1) transcription factor, with a motif that appears enriched in certain genes involved in cholesterol metabolism (Parnell and Or dovas, unpublished data). Finally, both SNP showed informative allele frequencies in reference populations. Based on these premises, we selected these 3 SNP as good potential candidates. SNP were genotyped using the Applied Biosystems TaqMan assay.\textsuperscript{23–25} Allele discrimination was performed on polymerase chain reaction products. Fluorescence data were collected by a 7900 Sequence Detection System (Applied Biosystems).\textsuperscript{23}

Lipoprotein Separation and Lipid Analysis

Large and small triglyceride-rich lipoproteins (TRL) were manually extracted after centrifugation in subdued light as previously described and samples were stored at −70°C until analyzed.\textsuperscript{25} Total cholesterol and triglycerides (TG) in plasma and lipoprotein fractions were assayed by enzymatic procedures.\textsuperscript{26,27} Apolipoprotein (apo) A1 and apoB were determined by turbidimetry.\textsuperscript{28} HDL cholesterol was measured by analyzing the supernatant obtained after precipitation of a plasma aliquot with dextran sulfate–Mg\textsuperscript{2+}, as described.\textsuperscript{29} Low-density lipoprotein cholesterol levels were estimated using the Friedewald formula, based on the cholesterol, TG, and HDL cholesterol values.\textsuperscript{30}

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics of the Study Participants</th>
<th>CHOL, mg/dL</th>
<th>TG, mg/dL</th>
<th>HDL, mg/dL</th>
<th>LDL, mg/dL</th>
<th>apoA1, mg/dL</th>
<th>apoB, mg/dL</th>
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<tr>
<td><strong>ABCA1 R219K (rs2230806)</strong></td>
<td></td>
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<tr>
<td>GG n=50</td>
<td>153.61±3.39</td>
<td>86.7±4.6</td>
<td>45.64±1.38</td>
<td>90.68±3.1</td>
<td>103.64±2.55</td>
<td>67.88±2.48</td>
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<td>GA/AA n=34/4</td>
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<td>72.90±5.5</td>
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<td>88.84±3.46</td>
<td>109.36±3.58</td>
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<td>0.545</td>
<td>0.695</td>
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<td>0.965</td>
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<td><strong>ABCA1 i48168 (rs4149272)</strong></td>
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<tr>
<td>CC n=23</td>
<td>152.54±4.78</td>
<td>73.64±7.29</td>
<td>50.06±2.07*</td>
<td>88.05±4.07</td>
<td>116.43±4.04*</td>
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<td>85.36±5.74</td>
<td>115.78±4.28†</td>
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<td>GA n=52</td>
<td>153.34±2.99</td>
<td>79.88±4.59</td>
<td>45.89±1.32</td>
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<td>AA n=15</td>
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<td>46.12±2.57</td>
<td>87.46±4.44</td>
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<td>0.395</td>
<td>0.574</td>
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<td>0.385</td>
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</table>

CHOL indicates cholesterol; LDL, low-density lipoprotein. P in each cell corresponds to univariate ANOVA, with each genotype as an independent factor and each phenotype variable as a dependent factor (with age and body mass index as covariates). Within each cell, the upper genotype corresponds to homozygotes for the major allele, the intermediate to heterozygotes, and the lower to homozygotes for the minor allele. All values are mean±SE.

*P<0.05 ABCA1 i48168 CC vs CT.
†P<0.05 ABCA1 i27943 GG vs GA.
determine the influence of the covariates on the dependent variables. A linear regression model was constructed to identify factors and body mass index and age as covariates. For any lipid fraction studied, a linear regression model was analyzed by 1-way ANOVA for area under the curve (AUC), defined as the area between the plasma concentration vs time curve.

### Table 2. AUC of Lipid Fractions in the Postprandial Study

<table>
<thead>
<tr>
<th>Lipid Fraction</th>
<th>ABCA1 R219K</th>
<th>ABCA1 i48168</th>
<th>ABCA1 i27943</th>
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<tr>
<td>Total TG</td>
<td>GG 79.5±5.0</td>
<td>CC 56.6±7.3*</td>
<td>GG 56.8±7.8‡</td>
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<tr>
<td></td>
<td>GA/AA 70.9±5.9</td>
<td>CT 76.5±4.7</td>
<td>GA 76.4±4.7</td>
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<td></td>
<td>TT 89.6±9.0</td>
<td>AA 87.1±9.1</td>
<td></td>
</tr>
<tr>
<td>CHOL</td>
<td>GG 80.9±1.7</td>
<td>CC 79.9±2.7</td>
<td>GG 78.5±2.8</td>
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<tr>
<td></td>
<td>GA/AA 80.8±2.1</td>
<td>CT 81.1±1.7</td>
<td>GA 81.9±1.7</td>
</tr>
<tr>
<td></td>
<td>TT 79.9±2.7</td>
<td>AA 79.0±3.3</td>
<td></td>
</tr>
<tr>
<td>Large TRL TG</td>
<td>GG 33.4±2.5</td>
<td>CC 20.9±3.5*</td>
<td>GG 21.6±3.7‡</td>
</tr>
<tr>
<td></td>
<td>GA/AA 28.7±3.0</td>
<td>CT 31.8±2.3</td>
<td>GA 31.3±2.3</td>
</tr>
<tr>
<td></td>
<td>TT 38.2±4.4</td>
<td>AA 37.3±4.5</td>
<td></td>
</tr>
<tr>
<td>Small TRL TG</td>
<td>GG 23.7±2.0</td>
<td>CC 20.3±3.1</td>
<td>GG 20.1±3.2</td>
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<td>CT 23.9±2.0</td>
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<td>TT 24.9±3.9</td>
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<tr>
<td>Large TRL CHOL</td>
<td>GG 4.7±0.3</td>
<td>CC 4.7±0.4</td>
<td>GG 4.8±0.4</td>
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<td>GA/AA 4.8±0.3</td>
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<td>GA 4.7±0.3</td>
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<td>TT 4.6±0.5</td>
<td>AA 4.7±0.5</td>
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<tr>
<td>Small TRL CHOL</td>
<td>GG 6.3±0.4</td>
<td>CC 5.5±0.7</td>
<td>GG 5.7±0.7</td>
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<td></td>
<td>GA/AA 6.0±0.5</td>
<td>CT 6.1±0.5</td>
<td>GA 5.9±0.4</td>
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<td>TT 6.5±0.9</td>
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<tr>
<td>apoA1</td>
<td>GG 54.0±1.3</td>
<td>CC 60.1±1.9†</td>
<td>GG 59.1±2.1§</td>
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<td>GA/AA 56.6±1.5</td>
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<td>GA 54.2±1.2</td>
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<td></td>
<td>TT 55.9±2.4</td>
<td>AA 55.9±2.4</td>
<td></td>
</tr>
<tr>
<td>apoB</td>
<td>GG 35.1±1.1</td>
<td>CC 32.6±1.7</td>
<td>GG 31.8±1.7§</td>
</tr>
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<td></td>
<td>GA/AA 35.5±1.3</td>
<td>CT 36.2±1.1</td>
<td>GA 36.5±1.0</td>
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<td></td>
<td>TT 34.8±2.0</td>
<td>AA 34.2±2.0</td>
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<tr>
<td>HDL</td>
<td>GG 23.7±0.8</td>
<td>CC 26.0±1.2</td>
<td>GG 25.3±1.3</td>
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<tr>
<td></td>
<td>GA/AA 24.2±0.9</td>
<td>CT 23.5±0.7</td>
<td>GA 23.9±0.8</td>
</tr>
<tr>
<td></td>
<td>TT 23.8±1.4</td>
<td>AA 23.8±1.5</td>
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</tbody>
</table>

Univariate ANOVA using body mass index and age as covariates. All values are expressed as (min*mg/dL)/103. Mean ± SE.

**P<0.05 ABCA1 i48168 CC vs CT and CC vs TT. †P<0.05 ABCA1 i48168 CC vs CT. ‡P<0.05 ABCA1 i27943 GG vs AA. §P<0.05 ABCA1 i27943 GG vs GA.**

### Statistical Analysis

Statistical analysis methods used here are similar to those that we have published previously with respect to the gene–postprandial state interaction.20,25

### Genotype Analysis

Linkage disequilibrium was tested using Helix-Tree software (Helix-Tree, version 4.3.2; Golden Helix). Likelihood ratio test was used to determine the existence of linkage disequilibrium. When linkage disequilibrium was observed, $r^2$ was used to measure its strength. Using $r^2$ values, we classified linkage disequilibrium as weak ($<0.30$), moderate ($0.30–0.80$), or strong ($>0.80$). Hardy-Weinberg equilibrium was tested by Fisher exact test.

### Analysis of Lipid Parameters

The influence of the SNP on the size of the postprandial lipid fractions was analyzed by 1-way ANOVA for area under the curve (AUC), defined as the area between the plasma concentration vs time curve, using the trapezoidal rule, with the SNP included as independent factors and body mass index and age as covariates. For any lipid fraction studied, a linear regression model was constructed to determine the influence of the covariates on the dependent variables.

### Results

Characteristics of participants at fasting state and genotype frequencies are shown in Table 1. The apoA1 was higher in homozygotes for the common allele of i27943 and i48168 vs heterozygotes for both SNP. HDL was higher in homozygotes for the common allele of i48168 vs heterozygotes. For the 3 SNP analyzed, there was no departure from Hardy-Weinberg ($P>0.05$). Pair-wise linkage disequilibrium in correlation coefficients of the 3 SNP were as follows. SNP i27943 and i48168 were in strong linkage disequilibrium ($P<0.05$; $r^2=0.827$). R219K was not in linkage disequilibrium with either of the other 2 SNP ($r^2<0.012$; $P>0.05$). The influence of the SNP on postprandial lipid levels is described and is summarized in Table 2 and Figures 1 through 3.

### R219K

A statistical study is presented for a genotype-dominant effect based on previously published data.14 In parallel, an additive model was also performed but we did not observe any differences compared with the dominant model. A trend for

![Figure 1. Evolution of TG and large TRL TG concentrations depending on ABCA1 i48168 (A, B) and i27943 (C, D) genotype.](Image)
lower fasting TG and large TRL TG was found in minor allele carriers compared to major allele homozygotes ($P=0.056$ and $P=0.070$, respectively; Table 2). We did not find other significant differences in the postprandial lipid metabolism.

### i48168

CC individuals of i48168 (homozygotes for the common allele) showed a lower AUC for total TG compared to the other 2 genotypes ($P=0.006$ vs TT and $P=0.025$ vs CT; Table 2). In the repeated-measures ANOVA, we found lower TG for CC vs TT from hours 1 to 8.5, and vs CT from time points 2 to 5 (Figure 1A). CC participants had lower AUC of large TRL TG than the other 2 groups (Table 2). The differences were noted at time points 3 to 8.5 vs TT, and 2 to 6 vs CT (Figure 1B).

Subjects homozygous for the major allele displayed lower amounts of accumulated TG from the third hour to the end of the study compared to CT and TT (all $P<0.05$; Figure 2A). We found no differences in the postprandial state for total cholesterol, large TRL cholesterol, small TRL cholesterol, or small TRL TG, depending on this SNP. A trend for higher AUC of HDL was noted for CC homozygotes vs heterozygotes ($P=0.074$). In the repeated-measures ANOVA, the differences were significant at fasting in CC vs CT ($P=0.034$). AUC of apoA1 was higher in CC subjects than in CT subjects ($P=0.006$). Differences between CC and CT were significant at all time points, from fasting to hour 11 (Figure 3A). Although the trend was similar for CC vs TT, significance was not achieved at any time point ($P=0.07–0.45$). The apoA1/apoB ratio was higher in CC vs TC individuals ($P=0.008$).

### i27943

Major allele homozygotes for i27943 (GG) had a lower AUC of TG than GA and AA subjects (Table 2). In the repeated-measures ANOVA, differences were significant at time points 2 to 8.5 vs AA, and 2 to 6 vs GA (Figure 1C). AUC of large TRL TG was lower for GG participants than for GA and AA participants (Table 2). Differences were noted at time points 3 to 8.5 hours in GG and AA subjects, but only at hour 3 between GG and GA (although $P<0.10$ at time points 2, 5, and 6; Figure 1D). We did not find any effects of this SNP on small TRL TG, total cholesterol, large TRL cholesterol, small TRL cholesterol, or HDL. AUC of apoA1 was higher for GG vs GA (Table 2). In the post hoc analysis we found differences between GG and GA at fasting and hours 1, 4, 6, and 11 after the meal (with additional $P<0.10$ at time points 2, 3, 5, and 8.5); we found differences between GG and AA at time point 8.5 (Figure 3B). A lower AUC of apoB was observed for GG vs GA subjects (Table 2). In the repeated-measures ANOVA, there was lower apoB in GG vs GA at all time points (all $P<0.05$) except at fasting and hour 11. The ratio of apoA1 to apoB was higher in GG vs GA.

### Discussion

Persons homozygous for the major alleles of ABCA1 SNP i27943 and i48168 have lower postprandial lipemia than carriers of minor alleles (in healthy young men). These results derive from a highly controlled, standardized trial of apoE E3/E3 participants who were subjected to a lipemia test meal. The interaction between genes and postprandial lipemia is well-reported.31 The complexity of conducting a study with hourly blood draws and a total duration of 11 hours is high; therefore, this type of study is rarely conducted and cannot be performed in larger and broader epidemiological studies because of methodological issues. Although other simpler designs for postprandial lipemia assessment have been reported, our method allows deep evaluation into the postprandial state.32

The relationship between ABCA1 polymorphisms and altered atherosclerosis is well-stated.14,17,33 To date, the strongest associations have linked ABCA1 variants with altered HDL concentrations,14,18,34 which are probably mediated by apoA1 metabolism.15 However, these variations in HDL have not been stated universally. Furthermore, in a recent report of type 2 diabetic patients, the ABCA1 SNP associated with coronary heart disease (including R219K) were not associated with HDL, and those associated with HDL were not associated with coronary heart disease.35 The explanation for these contradictory findings has been set on the limited effects that gene variation can have on final HDL levels, gene–environment interactions, or the influence of ABCA1 gene variants on other lipid molecules and enzymes that secondarily can mildly influence HDL concentrations.15

The minor allele of R219K has been associated with limited atherosclerosis,15 reduced risk for myocardial infarction, or progression of coronary disease in various studies.16,36–42 Here, we noticed only a trend toward lower fasting TG ($P=0.059$), according to previous studies.14 Currently, this variant is thought to affect lipids mildly, but gene–environment interactions are strong, with greater effects on
lipid concentration when oxidative stress or inflammation is elevated in subjects.\textsuperscript{14,15,39,40} Such is not the case in our study. However, marginal effects not reaching significance were found in our study for practically all lipid parameters toward a protective effect for the minor allele of R219K, which could become significant when the subject is exposed to the aforementioned stressors or even simply with increasing age.

Because SNP i27943 and i48168 are in strong linkage disequilibrium in our population, it is possible that part of the results obtained for 1 SNP may be attributable to linkage disequilibrium and not to real functional effects. If this were the case, then we hypothesize that i48168 has a greater likelihood to be the functional SNP based on 3 points. First, i48168 has been shown to influence lipids in which i27943 showed no effects.\textsuperscript{19} Second, computational analysis indicated a potential allele-specific binding site for the cartilage paired-class homeoprotein 1 (CART1) transcription factor, whose motif appears enriched in certain genes involved in cholesterol metabolism.\textsuperscript{39} Third, the significance coefficient whose motif appears enriched in certain genes involved in paired-class homeoprotein 1 (CART1) transcription factor, cated a potential allele-specific binding site for the cartilage variants, as in the study in Puerto Rico.

To the best of our knowledge, this is the first report of postprandial data on these 2 \textit{ABCA1} SNP, probably because HDL metabolism has been the primary focus of research in humans. Nevertheless, animal models have repeatedly shown effects on the postprandial state, although the influence of loss of \textit{ABCA1} function has been linked to increased and decreased postprandial triglycerides.\textsuperscript{44,45} Furthermore, and supporting postprandial effects of these proteins in humans, patients with Tangier disease follow a pattern similar to the one that we observed, with delayed TG clearance.\textsuperscript{46} In a recent review of metabolic regulation of intestinally derived lipids, these apparent contradictory findings were noted, with the authors stating, “clearly, either positively or negatively, \textit{ABCA1} appears to influence postprandial lipid metabolism.”\textsuperscript{46}

Further study is clearly required to unify the classic model in which effects of \textit{ABCA1} polymorphisms were found mainly in apoA1 and HDL concentrations with our results, in which most of the effects appear to be produced in the postprandial state. This is probably best accomplished by in vitro/in vivo studies, which will require a focus on the postprandial clearance of particles in models with these SNP. In our opinion, apoA1 may be the cornerstone of the effects found with SNP i48168 and i27943. As is broadly known, apoA1 protein is mainly present in HDL cholesterol. However, it is also present on the surface of nascent chylomicrons. We have reported recently that an \textit{apoA1} SNP (\textit{apoA1} \textsuperscript{–}2803; \textit{rs2777841}) clearly influences postprandial lipemia in healthy males.\textsuperscript{20} Furthermore, effects of this variant on postprandial lipemia were quite similar to those we report here that show a clear influence on the molecules that initiate postprandial metabolism, such as total and large TRL TG (which express apoA1 on their surface), and that show no effect on molecules implicated in the final phase of postprandial metabolism (mainly small TRL), which do not express apoA1 in their surface. Our explanation for the effects of \textit{apoA1} \textsuperscript{–}2803 variant, which also can be applied to the \textit{ABCA1} SNP reported here, stated that effects of the variant on postprandial metabolism may be mediated by altered levels of apoA1 present on the surface of large TRL. Supporting this theory, we have found alterations in total apoA1 concentrations depending on the \textit{ABCA1} variants i48168 and i27943.

In conclusion, in our study, healthy young men carrying the minor alleles for i48168 and i27943 of \textit{ABCA1} show much higher postprandial lipemia. This feature has been associated with a higher risk for accelerated progression of atherosclerosis and eventually cardiovascular disease, but identification of phenotype association in a clinical trial to increase cardiovascular risk can be overlapping and requires further investigation. Extrapolation to other age groups or to people with associated conditions, however, may not be correct, because it has been reported that the effects of other variants of \textit{ABCA1} on lipid metabolism are highly dependent on those factors.

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Disclosures

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