APOA1 (-75 G>A and 83 C>T) and APOB (2488 C>T) polymorphisms and its association with Myocardial Infarction, lipids and apolipoproteins in patients with Type 2 Diabetes Mellitus

Type
Research paper

Keywords
lipids, Myocardial infarction, type 2 diabetes mellitus, apolipoproteins

Abstract
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We studied 135 patients with DMT2 and MI (DI); another 85 non-infarcted diabetic individuals with DMT2 but without previous ischemic events (NID) and 242 Healthy subjects (HS), all three groups were selected with the aim to investigate the association between the polymorphisms and infarction when T2DM is present or absent.

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-75 G>A polymorphism: differences were found in genotype distribution between DI and NID individuals (OR: 2.01, CI:1.117-3.623, p= 0.019) with an increased risk for A in the dominant model (OR: 1.77, CI: 1.020-3.084, p= 0.042); also concentrations of ApoA-I for A/A were lower in comparison with G/A (p = 0.038) and LDL-C and HDL-C levels were lower in G/A respecting to G/G carriers. 83 C>T polymorphism of APOA1: for DI individuals: HDL-C was lower in T/T respecting to C/C and triglyceride levels were lower in C/T respect to C/C carriers.

Conclusions
The -75 G>A APOA1 polymorphism could be considered as a susceptibility factor for Myocardial Infarction in individuals with T2DM and 2488 C>T APOB polymorphism is associated with changes in HDL-C and LDL-C and triglycerides in the same group.
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ABSTRACT:
The increased risk of myocardial infarction (MI) in T2DM is well documented. Polymorphisms in APOA1 and APOB genes allow us to identify new genetic markers in Mexican population with T2DM and MI. Material and Methods: We studied 135 patients with DMT2 and MI (DI); another 85 non-infarcted diabetic individuals with DMT2 but without previous ischemic events (NID) and 242 Healthy subjects (HS), all three groups were selected with the aim to investigate the association between the polymorphisms and infarction when T2DM is present or absent. Results: -75 G>A polymorphism: differences were found in genotype distribution between DI and NID individuals (OR: 2.01, CI:1.117-3.623, p= 0.019) with an increased risk for A in the dominant model (OR: 1.77, CI: 1.020-3.084, p=0.042); also concentrations of ApoA-I for A/A were lower in comparison with G/A (p = 0.038) and LDL-C and HDL-C levels were lower in G/A respecting to G/G carriers. 83 C> T polymorphism of APOA1: for DI individuals: HDL-C was lower in T/T respecting to C/C and triglyceride levels were lower in C/T respect to C/C carriers. Conclusions: The -75 G>A APOA1 polymorphism could be considered as a susceptibility factor for Myocardial Infarction in individuals with T2DM and 2488 C>T APOB polymorphism is associated with changes in HDL-C and LDL-C and triglycerides in the same group.
Introduction:

In the world, more than 415 million people live with type 2 diabetes mellitus (T2DM), it is estimated that by 2040 there will be about 642 million \(^1\). In Mexico, in 2015, it was reported nearly 100 thousand deaths due to T2DM accounting the 15.0% of all deaths \(^2\). Some researchers have predicted a prevalence of T2DM of 22.52% by 2050 \(^3\). However, the reported number is underestimated as there is a percentage of people with diabetes who do not know their condition.

T2DM is caused by a compound of genetic susceptibility, environmental and other related behavioural effects. There are more than 80 common genetic variants for T2DM, with increased risk ranging from 5-40% \(^4\); however, the vast majority of these studies of susceptibility have been conducted in populations with European ancestry, so the identified variants have been insufficient to characterize the risk of T2DM \(^5\).

To date, it is known that common variants represent only about 10% of the heritability of T2DM and it has been proposed that interactions between gene-environment and gene-gene and epigenetic events (which are strongly influenced by environment) are the other percentage of heritability \(^4\). Hence it is imperative to study common variants in populations with a high prevalence of predisposing risk factors such as obesity, hypertension, dyslipidemia and with a questionable ancestry linked to the susceptibility of diabetes, such as haplotypes commonly found in Mexicans \(^6\), or thrifty alleles common found in Mexican Amerindians and mestizo populations \(^7\).

The increased risk of arteriosclerosis in T2DM has partially been attributed by low levels of ApoA-I \(^8\) and increased concentrations of ApoB which might be favoring the formation of chylomicrons and low-density lipoproteins \(^9\).
Since there are unique factors of T2DM that may modify the transcriptional activity of \textit{APOA1} and \textit{APOB} genes and due to the elevated risk of myocardial infarction (MI) in T2DM, it is necessary to study the susceptibility to MI due to genotypes on these genes that allow us to identify new genetic markers in the scenario of an exposed population. These genotypes could propitiate changes in levels of apolipoproteins and other lipids.

Thus, we evaluated some of the most relevant polymorphisms related to changes in the concentration of apolipoproteins and other lipids levels that could be used as genetic markers of susceptibility for MI: in \textit{APOA1}: a substitution of G to A in the region 75 of the promoter (-75 G>A, rs670) and a change of C to T in codon 83 (83C>T, rs5070); in \textit{APOB}: the polymorphism XbaI CT 2488 (rs693) located in exon 26 involving a silent mutation at the third nucleotide of codon threonine at amino acid 2488.

\textbf{Materials and Methods}

\textbf{Study Design and Participants}

Subjects.
We studied 462 genetically unrelated individuals from Western Mexico. Ethnic origin was defined as those having at least two generations of ascendants born in Mexico. These subjects had the following characteristics.

(1) One hundred thirty-five patients older than 45 years with DMT2 and infarction (DI), with a history of T2DM diagnosed previously by their physician and confirmed by us as fasting glucose bigger than 126 mg/dl according to the American Diabetes Association (ADA)\textsuperscript{10}. Some of the most relevant biochemical tests indicative of
cardiovascular risk were measured. Classical risk factors, as defined by ADA, were categorized as present or absent.

(2) Eighty-five non-infarcted diabetic individuals (NID) older than 45 years with a previous diagnosis of DMT2 but without records of ischemic events.

(3) Two hundred forty-two individual older than 45 years with no history of ischemic events and without DMT2 (Healthy subjects, HS) as the main exclusion criteria. They denied active infections or receiving any treatment.

The 462 individuals responded to a questionnaire about their medical history and lifestyle characteristics.

All subjects were recruited at "Hospital de Especialidades del Centro Médico Nacional de Occidente del Instituto Mexicano del Seguro Social (CMNO-IMSS)." Subjects with overlapping heart disorders or other diseases such as familial hypercholesterolemia, as well as genetically related individuals were not included.

The study was conducted following the Declaration of Helsinki (2013). An informed written consent was obtained. Ethical approval was granted by the Ethics and Biosafety Committee of the Centro Universitario de Ciencias de la Salud, CUCS, UdeG.
Genetic Analysis of polymorphisms

Genotyping was performed according to the technique described in our previous study. Twenty-five per cent of samples were double-genotyped with a concordance rate of 100%.

Statistical Analysis

The statistical analysis was carried out using SPSS statistical package version 22.0 and Excel 2010. The χ² test was used to compare discrete variables and to test the Hardy-Weinberg equilibrium. The data for continuous variables were expressed as means ± standard deviation (SD) and median comparison were evaluated by Mann-Whitney U test. The odds ratio (OR) was the measure of association for genotype, allele frequencies and for risk factors, the cutoff of significance was p < 0.05.

RESULTS

Clinical Variables

We aim to investigate the association between the polymorphisms with MI when T2DM is present or absent. Therefore, we selected three groups for comparisons.

Risk Factors in HS, NID and DI are shown in table 1, the most common risk factor in the three groups was High Blood Pressure with a percentage of 25.0 60.0 and 79.3% respectively. The average age was 60, 65 and 56 years accordingly.

We compared some of the classical biochemical parameters indicative of cardiovascular risk and statistically significant differences were observed in all of
them (p <0.001), the most notable settings were: in DI patients, an increase in fasting glucose [Media (M) = 165.0 mg/dl]; decreased levels of HDL-C, (M = 20.0 mg/dl) and increased levels of C-reactive protein (C-RP) (M = 24.0). All classical biochemical parameters related to cardiovascular risk were statistically different among groups (p<0.001) (Table 2).

**Susceptibility conferred by polymorphisms in DI and NID.**

**-75 G>A polymorphism of APOA1**

Statistically significant differences were found in genotype distribution between DI and NID groups (OR: 2.01, CI:1.117-3.623, p= 0.019, table 3). There is an increased risk for A allele carriers as seeing in the dominant model (OR: 1.77, CI: 1.020-3.084, p= 0.042, table 3). It is worth noting that this association is only obtained in the scenario of DMT2 as we did not find such risk when we compared the DI group against HS individuals in which we know there is no any suspicion of DMT2.

Given this finding, we determined how this polymorphism affected ApoA-I concentrations and other biochemical parameters in this DI group (Table 4, it is only shown those parameters with statistical significance). Concentrations of ApoA-I on A/A carriers were significantly decreased in comparison with heterozygous (p = 0.038) and LDL-C and HDL-C levels were lower in heterozygous respecting to G/G carriers (table 4).

**83 C>T polymorphism of APOA1**

Neither genotype nor allelic distributions of 83 C>T polymorphism were different between DI and NID (table 3). There were no associations between biochemical parameters and genotypes.
2488 C> T polymorphism of APOB

According to clinical characteristics, some differences were observed between genotypes in the DI group: HDL-C was lower in T/T carriers relative to C/C carriers (17.0 mg/dl vs 18.5 mg/dl, respectively, p = 0.009), also, triglyceride levels were statistically lower in heterozygous respect to C/C carriers (90 mg/dl vs 96 mg/dl respectively; p = 0.029) (table 5).

DISCUSSION:

Clinical and Biochemical Characteristics of the groups.

It is estimated that the rate of death from coronary heart disease in diabetic patients is almost three times higher than that of subjects without this condition. Factors such as high blood pressure, smoking, insulin resistance, hyperglycemia, inflammation and dyslipidemia are also known to increase this risk, and Mexicans have a high burden of all these factors, being one of the most afflicted by cardiovascular disease in the world.

As an example of the high influence of risk factors, in our study, the percentage of individuals with High Blood Pressure (HBP) in NID and DI (diabetic scenario) is 2.4 and 3.2 times higher respectively than the proportion observed in HS (non-diabetic scenario). The same trend is observed with sedentary lifestyle as 1.6 and 4.3 times higher; dyslipidemia as 1.9 and 3.7 times higher and obesity as 1.5 and 2.5 times higher. The percentage of overweight and smoking were similar between HS and NID (15.1 and 15.3 respectively) but was three times higher for DI (48.9%), which means that at least these two risk factors are involved in the susceptibility to MI independently if an individual has T2DM or not (table 1). To the best of our knowledge there is not another study in which this comparison had been done in
three groups of individuals, remarking the importance in the difference of susceptibility between them.

In this study, 58% of all diabetic individuals (mean age: 62.5) had Body Mass Index (BMI) ≥ 25 kg/m²; 70% had HBP and 32% were frequent smokers; this percentage was reported as 75%, 50% and 34% respectively in the diabetic population (mean age: 54.5) surveyed by ENSA (Encuesta Nacional de Salud) 15 and most recently, (but only data for HBP and dyslipidemia is reported), in an analysis of diabetic population (mean age: 56.9) by ENSANUT as 47% and 32% respectively 16.

The prevalence of T2DM was 8.18% according to ENSA in 2000 and according to the National Health and Nutrition Survey (ENSANUT) 17; it increased to 9.14 in 2016. This change in prevalence and other changes in behavior during the last 15 years reflects the importance of monitoring risk factors in the population.

Biochemical parameters indicative of cardiovascular risk are also altered in our population. Although the comparison of medias between the 3 groups is statistically significant, the unique median values out of normal range were: in the HS group: HDL-C: 36.0 mg/dl, ApoA-I: 198.3 mg/dl and ApoB: 164.7 mg/dl; in the NID group: glucose: 134.0 mg/dl, HDL-C: 34 mg/dl, ApoA-I: 189.7 mg/dl and ApoB: 163.6 mg/dl; and in the DI group: glucose: 165.0 mg/dl, HDL-C: 20.0 mg/dl and C-RP: 24.0 mg/dl (table 2).

Levels of LDL-C and triglycerides are lower than expected in the three groups, it is known that about the 55% of the population with T2DM older than 40 years, receive treatment for high cholesterol due to presence of cardiovascular disease risk (HBP, overweight, obesity, etc.) or because they have history of ischemic events 16; therefore such parameters could not be used as a measure of prognosis after MI in this aged population, as these values are generally altered due to
medication and diet, but we could use others parameters such as ApoB and ApoA-I as it is well known, its ratio indirectly reflects the disequilibrium between pro-atherogenic and atherogenic particles and their levels are not affected by fasting state\textsuperscript{18}.

**Genetic analysis:**

Studies of genome-wide association have identified Loci associated with susceptibility to T2DM; for example, the 2488C>T polymorphism in \textit{APOB}, is a variant associated with T2DM primarily with changes in levels of TG, LDL-C and HDL-C\textsuperscript{19}. The other two variants analyzed in this study, have not been associated with T2DM, but they have been associated primarily with changes in levels of ApoA-I and HDL-C, which we known are deregulated in T2DM and have a significant impact in the formation of atherosclerotic plaque.

Polymorphic variants can exert their biological effects depending on what type of comorbidity is present; for example, in obesity it is known that TNF alpha is closely related to insulin resistance and hyperinsulinemia and has demonstrated deregulate the expression \textit{APOA1} by lowering 50% the levels of some transcription factors that can act as second messengers and increase the expression of such gene\textsuperscript{20}.

Diabetic dyslipidemia also contributes to changes in the expression of \textit{APOA1}, which intervenes on the function and survival of pancreatic beta cells, obesity and insulin resistance in muscle and liver\textsuperscript{21}; These are just some examples that can help us to explain the increased risk of MI in the scenario of T2DM.

\textit{APOA1} gene polymorphisms and its relation to cardiovascular disease in T2DM
The risk of ischemic heart disease in patients with T2DM is up to three times higher than in those without the disease, and not all patients with T2DM develop some coronary event associated \(^{22}\). This makes it clear that the genetic component occurring in patients with T2DM is probably involved in these cardiovascular events. Other factors such as habits of the individual and the presence of other comorbidities are also contributing to the development of ischemic events.
-75 G> A polymorphism in APOA1 gene

We have found that the -75 G> A polymorphism is associated with the DI. G/A carriers have 2.01 times more susceptibility to DI compared with G/G genotype (OR: 2.01 C.I.: 1.117-3.623), only one copy of A allele contributes to the risk as can be seen in the dominant model (Table 3; OR: 1.77 CI: 1.020-3.084).

We also found associations of this polymorphism with levels of ApoA-I, HDL-C and LDL-C: levels of ApoA-I significantly decreased in the presence in homozygous polymorphic genotype AA respect to reference genotype G/G (170.9 mg/dl vs 185.0 mg/dl, p = 0.038). Another effect of risk is reflected in levels of HDL-C in G/A respect to G/G carriers (24.0 vs 37.0 mg/dl, p = 0.044) (Table 4). Once again it looks likes that the A allele is contributing to the risk.

To the best of our knowledge, this variant has not been studied to determinate the susceptibility to MI in diabetic patients, but in the same way as us, it has been reported as a variant responsible of changes in lipids by altering the function of the promoter of APOA1 gene. The A allele of this polymorphism has been associated with hypertension 23; with higher systolic blood pressure and blood glucose levels in adolescents with higher BMI; the genotype G/A has been shown to confer an increased risk of atherogenic dyslipidemia in Turkish adults 24; and Chinese obese children carriers of G/A genotype have shown to have higher levels of VLDL, LDL-C and TG 25. Other authors have found G allele as the responsible for the risk in Coronary Artery Disease, is primarily associated with low HDL-C levels 26.

It is possible that lower plasma concentrations of HDL-C are due to a decreased response of APOA1 gene to insulin; which could be explained by the marked increase of free fatty acids in T2DM preventing APOA1 promoter activation by the transcription factor Sp1, a specific second messenger of insulin 27. It is likely,
therefore, that the affinity of some transcription factors could be altered in the presence of the variant.

Although the biological mechanism of -75G>A variant is not fully established, its role in lipid metabolism and other risk factors related to cardiovascular disease in different populations are evident and consistent with our findings. Although those authors did not find those associations under T2DM, we can assert that the presence of A allele in DI, is associated with decreased levels of ApoA-I and HDL-C in T2DM which could contribute to explain the increased cardiovascular risk of these individuals.

The sometimes-inconclusive effect of an allele or genotype (as protective or non-protective) is most of the time due to ethnicity differences but lately some authors have found novelty systematical reviews to determine the most likely statistical association of a genetic variant with a cardiovascular disease, such as it is the case of the study of Xu and Zhou who determined that -75 G>A polymorphism is a protective factor for Cardiovascular disease.28

83 C> T polymorphism of APOA1 gene

The biological mechanism of 83C> T variant has not been established but there is evidence of their involvement in lipid metabolism, and other risk factors related to cardiovascular disease and T2DM: the -75A and 83T alleles have shown an association with hypertension and 83C allele with obesity and hypertension.23 Although we have not found an association of this genetic variant with MI in DMT2, There is evidence in which 83C> T variant significantly decrease the levels of ApoA-I and HDL-C in patients with heart disease and diabetics unlike non-diabetics.29
2488C>T polymorphism of *APOB* gene

Although we did not find an association of this polymorphism with DI, the C/T carriers have lower levels of TG compared to the reference genotype C/C (90.0 vs 96.0 mg/dl, \(p = 0.029\)) and lower levels of HDL-C on T/T carriers against C/C. (17.0 vs 18.5 mg/dl, \(p = 0.009\)) (table 5). This result is concordant with a meta-analysis of 61 studies (50,018 subjects) in which it was found that T carriers have higher levels of ApoB, TG, TC and LDL-C and lower levels of HDL-C than non-carriers \(^{30}\).

There is a study of genome-wide association conducted in a Finnish and Swiss population where about 1500 patients with T2DM and controls were studied. This study identified Loci associated with susceptibility to T2DM which in turn are associated with changes in levels triglycerides, HDL-C and LDL-C; being the 2488C>T variant (between about 400,000 variants studied) as one of the main variants highly associated with levels of these parameters \(^{19}\).

In an analysis of 16 European cohorts, which included an average of about 20,000 individuals, the number of T2DM patients was not as large as in the earlier report, and yet this variant was found with the fourth highest impact on triglycerides, HDL-C and LDL-C levels; therefore the authors suggest this variant could have an independent effect and not being associated with T2DM \(^{31}\).

In another study of association, three different cohorts were evaluated, and also there was an association with LDL-C (\(p = 1\times10^{-21}\)) and triglycerides (\(p = 2\times10^{-7}\)) \(^{32}\).

The polymorphic site located at position 2488 in exon 26 of the *APOB* gene involves a silent variant in the third nucleotide of threonine codon at amino acid 2488 \(^{33}\). This silent variant is only of 600 to 900 residues near to two binding domains of the protein to its receptor (LDL Receptor), so it has been proposed that
this SNP is in linkage disequilibrium with polymorphisms affecting these binding regions, variants in this site may lead to a different affinity to the LDL receptor, leading to a distinct catabolism for LDL-C \(^{34}\) and this dysregulation in the production of LDL-C is well known to alter the levels of ApoB, TG and HDL-C as they are involved in the same metabolic pathways contributing to the dyslipidemia observed in people with diabetes \(^{35}\).

Our results have shown that it is important to select individuals sharing a particular comorbidity, because as we know, changes in the DNA sequence (whether a SNP, an insertion, deletion or duplication), can lead to differences in gene-protein affinity and/or activation or inactivation of signaling pathways which may be exacerbated by specific elements of the comorbidity (in our case T2DM). This dysregulated gene-protein interaction in T2DM will trigger complications at the level of different metabolic vias and eventually contribute, or at least partially (we do not have to forget that we are managing a complex disease) to the risk of cardiovascular diseases.

Diabetic dyslipidemia additionally adds changes in the outflow of APOA1, which mediates on the capacity and survival of pancreatic beta cells, weight and insulin obstruction in muscle and liver. Many patients still cannot reach the recommended target levels of Lipids after treatment; therefore, the study of some variants (such as has been the study of PCSK9) have given place to the identification of novel mechanisms of actions resulting in novel therapies in just a short period of time. \(^{36}\)

Classical risk scores are the common measures to assessed clinical outcomes after a coronary event\(^{37}\) but polygenetic risk scores are also an important element to include in the near future.

**Conclusions:**
The -75 G>A APOA1 polymorphism could be considered as a susceptibility factor for Myocardial Infarction in individuals with T2DM. Also, the 83 C>T APOA1 and 2488 C>T APOB polymorphisms are associated to changes in levels of triglycerides, HDL-C and LDL-C in the same group. However, additional genetics studies should be performed in the future to determine a more comprehensive genetic risk score in our population.
1. IDF diabetes atlas - Home.


Table I. Risk factors of the study groups

<table>
<thead>
<tr>
<th>Risk factors</th>
<th>HS (n = 252)</th>
<th>NID (n = 85)</th>
<th>DI (n = 135)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>HBP</td>
<td>63</td>
<td>25.0</td>
<td>51</td>
</tr>
<tr>
<td>Sedentary lifestyle</td>
<td>38</td>
<td>15.1</td>
<td>20</td>
</tr>
<tr>
<td>smoking</td>
<td>38</td>
<td>15.1</td>
<td>13</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>34</td>
<td>13.5</td>
<td>22</td>
</tr>
<tr>
<td>Overweight</td>
<td>40</td>
<td>15.9</td>
<td>17</td>
</tr>
<tr>
<td>Obesity</td>
<td>28</td>
<td>11.1</td>
<td>14</td>
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</table>


Table II. Biochemical characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>HS (N = 252)</th>
<th>NID (N = 85)</th>
<th>DI (N = 135)</th>
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<tr>
<td></td>
<td>percentiles</td>
<td>percentiles</td>
<td>percentiles</td>
</tr>
<tr>
<td>Age</td>
<td>50 75 95</td>
<td>50 75 95</td>
<td>50 75 95</td>
</tr>
<tr>
<td>Total cholesterol (mg / dl)</td>
<td>159.0 192.3 241.6 156.0 189.5 262.5</td>
<td>116.0 142.0 180.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fasting glucose (mg / dL)</td>
<td>90.0 104.0 162.3 134.0 209.5 339.4</td>
<td>165.0 208.0 270.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mg / dl)</td>
<td>96.5 127.8 199.0 114.0 152.3 265.2</td>
<td>93.0 121.5 168.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-C (mg / dl)</td>
<td>63.5 89.0 133.6 69.0 103.0 157.4</td>
<td>41.5 56.0 84.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL-C (mg / dl)</td>
<td>36.0 53.5 75.0 34.0 57.0 73.0</td>
<td>20.0 30.0 49.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CRP (mg / L)</td>
<td>2.0 3.8 23.0 3.0 4.0 17.6</td>
<td>2.0 36.0 39.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ApoA-I (mg / dl)</td>
<td>198.3 213.3 236.1 189.7 215.3 262.2</td>
<td>165.6 184.9 231.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ApoB (mg / dl)</td>
<td>164.7 184.6 225.5 163.6 185.4 277.0</td>
<td>128.3 153.4 195.5</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* p = Mann-Whitney, DI: Infarcted Diabetics; NID: Non-infarcted Diabetics, HS: Non-Diabetic, Non-infarcted.
Table III. Genotype and allele distribution of the *APOA1* and *APOB* polymorphisms NID and DI groups

<table>
<thead>
<tr>
<th>75 G&gt; A Genotype <em>APOA1</em></th>
<th>NID n = 85 (%)</th>
<th>DI n = 130 (%)</th>
<th>OR (CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>G / G</td>
<td>50 (58.8)</td>
<td>58 (44.6)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>G / A</td>
<td>27 (31.8)</td>
<td>63 (48.5)</td>
<td>2.01 (1.117-3.623)</td>
<td>0.019</td>
</tr>
<tr>
<td>A / A</td>
<td>8 (9.4)</td>
<td>9 (6.9)</td>
<td>0.970 (0.348-2.702)</td>
<td>0.42</td>
</tr>
<tr>
<td>alleles</td>
<td>2n = 170 (%)</td>
<td>2n = 260 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>G</td>
<td>127 (74.7)</td>
<td>179 (68.8)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>A</td>
<td>43 (25.3)</td>
<td>81 (31.2)</td>
<td>1.33 (0.866-2063)</td>
<td>0.19</td>
</tr>
</tbody>
</table>

**MODELS**

- **Dominant**
  - G / G
  - G / A + A / A
- **Recessive**
  - G / G + G / A
  - A / A

<table>
<thead>
<tr>
<th>83 C&gt;T Genotype <em>APOA1</em></th>
<th>NID n=80 (%)</th>
<th>DI n=135 (%)</th>
<th>OR (CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>C/C</td>
<td>67 (83.8)</td>
<td>123 (91.1)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C/T</td>
<td>13 (16.2)</td>
<td>12 (8.9)</td>
<td>0.503 (0.217-1.164)</td>
<td>0.10</td>
</tr>
<tr>
<td>T/T</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>0.547 (0.011-27.85)</td>
<td>1.00</td>
</tr>
<tr>
<td>Alleles</td>
<td>2n=160 (%)</td>
<td>2n=270 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>147 (87.5)</td>
<td>258 (95.6)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>T</td>
<td>13 (12.5)</td>
<td>12 (4.4)</td>
<td>0.526 (0.234-1.183)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2488 C&gt;T Genotype <em>APOB</em></th>
<th>NID n=82 (%)</th>
<th>DI n=135 (%)</th>
<th>OR (CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>C/C</td>
<td>32 (39.0)</td>
<td>56 (41.5)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>C/T</td>
<td>36 (43.9)</td>
<td>60 (44.4)</td>
<td>0.909 (0.642-1.287)</td>
<td>0.59</td>
</tr>
<tr>
<td>T/T</td>
<td>14 (17.1)</td>
<td>19 (14.1)</td>
<td>0.701 (0.425-1.156)</td>
<td>0.16</td>
</tr>
<tr>
<td>Alleles</td>
<td>2n=164 (%)</td>
<td>2n=270 (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>100 (61.0)</td>
<td>172 (63.7)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>T</td>
<td>238 (39.0)</td>
<td>98 (36.3)</td>
<td>0.89 (0.597-1.734)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

DI: Infarcted Diabetics (cases); NID: Non infarcted Diabetics (controls); CI: Confidence interval; OR: Odds Ratio. * Models are shown only for 75 G> A polymorphism due to the association found between genotypes.
Table IV. Lipid levels in the DI group related to the genotypes of the −75 G>A APOA1 polymorphism.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>G / G * n = 44</th>
<th>G / A n = 23</th>
<th>p ** G / G vs G / A</th>
<th>A / A n = 7</th>
<th>p ** G / G vs A / A</th>
</tr>
</thead>
<tbody>
<tr>
<td>percentiles</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>25</td>
<td>51.25</td>
<td>25.0</td>
<td>0.029</td>
<td>31.0</td>
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<tr>
<td>50</td>
<td>74.0</td>
<td>53.0</td>
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<td>27.0</td>
<td>32.0</td>
</tr>
<tr>
<td>75</td>
<td>106.5</td>
<td>40.0</td>
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<td>53.0</td>
<td>53.0</td>
</tr>
</tbody>
</table>

* Genotype reference. ** p = U of Mann-Whitney (<0.05)

Table 5. Lipid levels in the DI group related to the genotypes of the 2488 C>T APOB polymorphism.

<table>
<thead>
<tr>
<th>PARAMETER</th>
<th>C / C* n = 56</th>
<th>C / T n = 60</th>
<th>p ** C / C vs C / T</th>
<th>T / T n = 19</th>
<th>p ** C / C vs T / T</th>
</tr>
</thead>
<tbody>
<tr>
<td>percentile</td>
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</tr>
<tr>
<td>25</td>
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<td>16.0</td>
<td>0.237</td>
<td>9.0</td>
<td>17.0</td>
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<tr>
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<td>18.5</td>
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<tr>
<td>75</td>
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<td>53.0</td>
<td>0.512</td>
</tr>
</tbody>
</table>

* Genotype reference. ** p = U of Mann-Whitney (<0.05)