Original article

Coronary Artery Atherosclerosis in Hypertensive Patients: The Role of Fibrinogen Genetic Variability

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A B S T R A C T

Introduction and objectives: We examined whether the rs180070 and rs2070011 polymorphisms of the fibrinogen gene could affect the risk of coronary artery disease in hypertensive patients by modifying the inflammatory process and coagulation.

Methods: A total of 744 participants underwent coronary angiography due to symptoms of stable angina, while hypertension was present in 332 patients.

Results: The presence of the A allele (rs180070) was associated with significantly high levels of fibrinogen in hypertensive patients (P = 0.05). On multivariate analysis, A homozygosity (rs180070) (β = 0.257 ± 18.6; P < 0.001), but not hypertension status (β = 0.05 ± 11.9; P = 0.29) was an independent predictor of fibrinogen levels. In hypertensive patients, higher fibrinogen levels > 441 mg/dl (odds ratio = 3.50; 95% confidence interval, 1.14-10.90; P = 0.029), but not A homozygosity (odds ratio = 3.00; 95% confidence interval, 0.78-11.90; P = 0.110) were independent predictors of the presence of coronary artery disease. Moreover, interleukin-6 levels were higher in A homozygotes for the rs180070 polymorphism compared with all other genotypes (P = 0.046). Indeed, this genotype was the only adjusted independent predictor of interleukin-6 levels (β = 0.151 ± 0.642; P = 0.032). It was also associated with higher D-dimer levels in hypertension compared with G allele carriers (P = 0.048).

Conclusions: The presence of A homozygosity (rs180070) is associated with increased levels of inflammatory mediators and a higher incidence of angiographic coronary artery disease. Importantly, fibrinogen is an independent predictor of the angiographic presence of coronary artery disease in hypertensive patients.

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Ateroesclerosis coronaria en pacientes hipertensos: el papel de la variabilidad genética del fibrinógeno

R E S U M E N

Introducción y objetivos: Se examina si los polimorfismos rs180070 y rs2070011 del gen del fibrinógeno podrían afectar al riesgo de enfermedad coronaria de los pacientes hipertensos al modificar el proceso inflamatorio y la coagulación.

Métodos: Se practicó una angiografía coronaria a causa de síntomas de angina estable a 744 participantes, de los que 332 tenían hipertensión.

Resultados: La presencia del alelo A (rs180070) se asoció a cifras de fibrinógeno significativamente elevadas en los pacientes hipertensos (p = 0.05). En el análisis multivariable, la homocigosis para A (rs180070) (β = 0.257 ± 18.6; p < 0.001), pero no la presencia de hipertensión (β = 0.05 ± 11.9; p = 0.29), fue un factor independiente predictivo de la concentración de fibrinógeno. En los pacientes hipertensos, la concentración de fibrinógeno > 443 mg/dl (odds ratio = 3.50; intervalo de confianza del 95%, 1.14-10.90; p = 0.029), pero no la homocigosis para A (odds ratio = 3.00; intervalo de confianza del 95%, 0.78-11.90; p = 0.110), fueron un factor independiente predictivo de enfermedad coronaria. Además, los valores de interleucina 6 fueron más altos en los individuos homocigotos para el polimorfismo rs180070 que en todos los demás genotipos (p = 0.046). De hecho, este genotipo fue el único factor independiente
INTRODUCCIÓN

El papel de la inflamación y los caminos trombóticos en la progresión de la aterosclerosis es ampliamente reconocido. Además, la hipertensión (HT) es un factor de riesgo mayor para enfermedad cardiovascular, mientras que la inflamación vascular desempeña un papel crucial en todas las fases de la aterosclerosis. Particularmente, en el contexto de los factores de riesgo como el HT, la inflamación vascular se acelera y se asocia con las manifestaciones clínicas de la enfermedad arterial coronaria (CAD).3,4

Entre otros marcadores, el fibrinógeno es un marcador con un perfil de dosificación. Se utiliza tanto en el contexto inflamatorio y, en el contexto de la coagulación, conduce a la disfunción endotelial y la progresión de la aterosclerosis.5,6 En estudio, previa existencia de reportes de un estudio independiente asociación de las niveles de fibrinógeno y el riesgo de CAD.2,5 En particular, los pacientes con síndrome coronario agudo generalmente tienen niveles de fibrinógeno más altos que aquellos con CAD estable o con control de la presión arterial.7 Sin embargo, en algunos casos de fibrinógeno se ha encontrado un efecto mayor en el riesgo de CAD en comparación con los factores de riesgo clásicos, como la HT.8

Recientemente se ha destacado la importancia del papel de fibrinógeno en la variabilidad del riesgo de CAD, pero actualmente hay escasos datos sobre la influencia de la variabilidad de fibrinógeno en el riesgo de CAD.8,10 Además, el intercambio entre factores de riesgo cardiovascular y la función del fibrinógeno no ha sido completamente elucidado.

En el presente estudio, nos propusimos examinar la asociación del fibrinógeno y neucleótidos con la presencia de CAD obstructivo en pacientes hipertensos. En nuestra búsqueda, se buscó investigar si este tipo de interacción podría resultar en un aumento de la incidencia de la angiografía de CAD, en las fases de la inflamación y la coagulación.

MÉTODOS

Población de estudio

Nuestro estudio abarcó a 744 participantes de origen caucásico, admitidos a nuestro hospital para una angiografía coronaria debido a una aspiración de angina de pecho estable de un año de duración. El análisis ajustado (B = 0,151 ± 0,642; p = 0,032). También se asoció a cifras de dímero D superiores en la hipertensión en comparación con los portadores del alelo G (p = 0,048).

Conclusiones: La presencia de homocigosis para A (rs180070) se asocia a un aumento de las concentraciones de mediadores inflamatorios y mayor incidencia de enfermedad coronaria angiógrafica. Tiene importancia que el fibrinógeno es un factor independiente predictivo de la presencia angiográfica de enfermedad coronaria en los pacientes hipertensos.
Biochemical Measurements

All participants were asked to abstain from smoking and from alcohol- and caffeine-containing beverages during the evening before (12 hours) blood sampling. Venous blood samples were centrifuged at 3500 rpm at 4 °C for 15 min, and plasma or serum was collected and stored at −80 °C until assayed. Serum levels of fibrinogen were measured by the Clauss method (Multiﬁbrein U, Siemens; Germany), D-Dimers by an immunonephelometric method (Innovance D-Dimer, Siemens; Germany), while high-sensitivity C-reactive protein (hsCRP) was also measured. In addition, factor V activity in plasma was measured by a 1-stage assay based on prothrombin time (factor V deﬁcient, Dade Behring; Germany) and factor X activity was measured by a standard 1-stage method using single-donor factor X-deﬁcient plasma on a Dade Behring BCS Coagulation Analyzer (Deerﬁeld; Illinois, United States). Interleukin-6 (II-6) and serum levels of soluble CD40 ligand were measured by ELISA (R&D Systems Inc.; United States).

Table 1
Baseline Characteristics According to Tertiles of Fibrinogen Levels

<table>
<thead>
<tr>
<th>Variable</th>
<th>1st tertile (&lt; 347 mg/dL)</th>
<th>2nd tertile (347–443 mg/dL)</th>
<th>3rd tertile (&gt; 443 mg/dL)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients, no.</td>
<td>198</td>
<td>195</td>
<td>196</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>59.0 ± 11.2</td>
<td>61.8 ± 11.0</td>
<td>62.3 ± 10.6</td>
<td>.010</td>
</tr>
<tr>
<td>Gender, male</td>
<td>147 (74.4)</td>
<td>142 (73.7)</td>
<td>151 (77.1)</td>
<td>.700</td>
</tr>
<tr>
<td>Smoking</td>
<td>101 (50.9)</td>
<td>93 (48.1)</td>
<td>94 (48.4)</td>
<td>.860</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>119 (60.3)</td>
<td>111 (57.7)</td>
<td>125 (64.5)</td>
<td>.430</td>
</tr>
<tr>
<td>Hypertension</td>
<td>112 (56.9)</td>
<td>123 (63.8)</td>
<td>133 (68.2)</td>
<td>.090</td>
</tr>
<tr>
<td>DM</td>
<td>32 (16.1)</td>
<td>51 (26.2)</td>
<td>54 (27.5)</td>
<td>.020</td>
</tr>
</tbody>
</table>

Lipid profile

<table>
<thead>
<tr>
<th>Variable</th>
<th>1st tertile (&lt; 347 mg/dL)</th>
<th>2nd tertile (347–443 mg/dL)</th>
<th>3rd tertile (&gt; 443 mg/dL)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>194 ± 43</td>
<td>186 ± 43</td>
<td>187 ± 42</td>
<td>.31</td>
</tr>
<tr>
<td>LDL (mg/dL)</td>
<td>122 ± 74</td>
<td>117 ± 40</td>
<td>119 ± 39</td>
<td>.7</td>
</tr>
<tr>
<td>HDL (mg/dL)</td>
<td>46 ± 12</td>
<td>43 ± 11</td>
<td>42 ± 11</td>
<td>.16</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>123 ± 74</td>
<td>125 ± 61</td>
<td>112 ± 52</td>
<td>.3</td>
</tr>
</tbody>
</table>

Medications

<table>
<thead>
<tr>
<th>Variable</th>
<th>1st tertile (&lt; 347 mg/dL)</th>
<th>2nd tertile (347–443 mg/dL)</th>
<th>3rd tertile (&gt; 443 mg/dL)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statins</td>
<td>100 (50.6)</td>
<td>117 (60.2)</td>
<td>123 (62.7)</td>
<td>.24</td>
</tr>
<tr>
<td>Ezetimibe</td>
<td>12 (6.0)</td>
<td>29 (14.8)</td>
<td>17 (8.7)</td>
<td>.19</td>
</tr>
<tr>
<td>Fibrates</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>7 (3.6)</td>
<td>.06</td>
</tr>
<tr>
<td>ACE inhibitors/ARB</td>
<td>93 (47.0)</td>
<td>96 (49.2)</td>
<td>110 (56.1)</td>
<td>.4</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>108 (54.5)</td>
<td>116 (59.5)</td>
<td>118 (60.2)</td>
<td>.74</td>
</tr>
<tr>
<td>CCB</td>
<td>55 (27.8)</td>
<td>55 (28.2)</td>
<td>55 (28.0)</td>
<td>1</td>
</tr>
<tr>
<td>Diuretics</td>
<td>29 (14.6)</td>
<td>34 (17.4)</td>
<td>55 (28.0)</td>
<td>.07</td>
</tr>
<tr>
<td>Oral hypoglycemic</td>
<td>18 (9.0)</td>
<td>39 (20.0)</td>
<td>25 (12.7)</td>
<td>.14</td>
</tr>
<tr>
<td>Insulin</td>
<td>3 (1.5)</td>
<td>8 (4.1)</td>
<td>4 (2.0)</td>
<td>.5</td>
</tr>
</tbody>
</table>

Genotype distribution

<table>
<thead>
<tr>
<th>Variable</th>
<th>1st tertile (&lt; 347 mg/dL)</th>
<th>2nd tertile (347–443 mg/dL)</th>
<th>3rd tertile (&gt; 443 mg/dL)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs180070 GG</td>
<td>109 (55.4)</td>
<td>104 (53.3)</td>
<td>92 (46.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>rs180070 GA</td>
<td>81 (40.7)</td>
<td>77 (39.7)</td>
<td>70 (35.4)</td>
<td></td>
</tr>
<tr>
<td>rs180070 AA</td>
<td>8 (3.8)</td>
<td>14 (7.1)</td>
<td>34 (17.7)</td>
<td></td>
</tr>
<tr>
<td>rs2070011 GG</td>
<td>71 (36.2)</td>
<td>70 (35.8)</td>
<td>70 (35.7)</td>
<td>.670</td>
</tr>
<tr>
<td>rs2070011 GA</td>
<td>82 (41.4)</td>
<td>90 (46.1)</td>
<td>96 (48.4)</td>
<td></td>
</tr>
<tr>
<td>rs2070011 AA</td>
<td>45 (22.4)</td>
<td>35 (18.2)</td>
<td>30 (15.8)</td>
<td></td>
</tr>
</tbody>
</table>

AR, angiotensin receptor blockers; ACE, angiotensin-converting enzyme; CCB, calcium channel blockers; DM, diabetes mellitus; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Unless otherwise indicated, the data are expressed as mean ± standard error.
P values based on analysis of variance for continuous normally distributed variables and on the chi-square test for categorical variables.

* Pertains to all patients in each group.
was conducted with the measured biochemical parameters as dependent variables and risk factors and polymorphisms as independent variables. Analysis of variance was also used to compare the means of 3 or more variables in the multivariate analysis to determine independent predictors of angiographic CAD and acute myocardial infarction was applied. All significance tests were 2-tailed and conducted at the 5% significance level. All statistical analyses were performed with SPSS (IBM SPSS Statistics, version 22.0).

RESULTS

The demographic characteristics of the 744 consecutive patients examined in our center during a 3-year period, as well as the genotype distribution according to fibrinogen tertiles, are presented in Table 1. Of those patients, 332 had HT, Coronary artery disease was present in 448 patients, whereas no CAD was found in 296 patients. Of note, we observed no differences in lipid profile or medication among the 3 groups (Table 1). In our study cohort, the prevalence of the A alleles of rs180070 and rs2070011, respectively, was similar between patients with and without CAD (\(P = .339\) and \(P = .988\), respectively).

Effects of rs180070 and rs2070011 on Fibrinogen Levels and Coronary Artery Disease Risk

In the overall cohort, there was a significant effect of the presence of the A allele of rs180070 (AA and AG genotypes) on serum fibrinogen levels (AA or AG: 424.26 ± 7.74 vs GG: 401.20 ± 6.64 mg/dL; \(P = .025\)). Importantly, the AA homozygotes had significantly higher fibrinogen levels than the G allele carriers (503.4 ± 18.8 vs 402.6 ± 5.14 mg/dL; \(P < .001\)). In contrast, the presence of the A allele of the rs2070011 allele was not associated with increased fibrinogen levels (AA: 417.1 ± 6.9 vs AG or GG: 404.4 ± 8.8 mg/dL; \(P = .26\)) in HT patients.

Fibrinogen Levels

Patients were also divided in 3 subcategories according to fibrinogen levels (< 347; 347-443; > 443 mg/dL) (Table 1). We further examined the effects of these polymorphisms on serum levels of fibrinogen in HT patients. A graded increase of fibrinogen levels was observed: the presence of the A allele of rs180070 (AA and AG genotypes) was associated with significantly higher fibrinogen levels in HT participants (433.36 ± 10.90 vs 405.70 ± 8.8 mg/dL; \(P = .047\)), while AA homozygosity of rs180070 was also associated with higher fibrinogen levels (541.03 ± 25.20 vs 405.20 ± 6.80 mg/dL; \(P < .001\)) (Figure 1A). The presence of the A allele of rs2070011 had no significant effects on fibrinogen levels in HT patients. On multivariate analysis, AA homozygosity of rs180070 (\(\beta = 0.257 ± 18.6; P < .001\) and CAD (\(\beta = 0.252 ± 12.8; P < .001\)) but not HT (\(\beta = 0.05 ± 11.9; P = .290\)) were independent predictors of fibrinogen levels. In HT patients, the AA genotype of rs180070 (\(\beta = 0.322 ± 23.2; P < .001\)) and CAD (\(\beta = 0.2 ± 16.7; P < .001\)) remained independent predictors of fibrinogen levels (Table 2).

Risk of Coronary Artery Disease

Multivariate logistic regression analysis after adjustment for age, sex, smoking, hypercholesterolemia, HT, diabetes mellitus and log (hsCRP) levels as independent predictors revealed that

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Table 2
Multivariate Analysis for Predictors of Fibrinogen Levels

<table>
<thead>
<tr>
<th></th>
<th>Overall cohort</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\beta ± SE)</td>
<td>(P)</td>
</tr>
<tr>
<td>rs180070 AA genotype</td>
<td>0.257 ± 18.6</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>CAD</td>
<td>0.252 ± 12.8</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>HT</td>
<td>0.05 ± 11.9</td>
<td>.290</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>OR (95CI%)</th>
<th>(P)</th>
<th>OR (95CI%)</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs180070 AA genotype</td>
<td>3.00 (0.78-11.90)</td>
<td>.110</td>
<td>3.20 (1.01-10.10)</td>
<td>.049</td>
</tr>
<tr>
<td>rs2070011 AA genotype</td>
<td>0.79 (0.43-1.46)</td>
<td>.450</td>
<td>1.10 (0.68-1.76)</td>
<td>.700</td>
</tr>
<tr>
<td>Fibrinogen levels (&lt; 443 mg/dL compared with &lt; 347 mg/dL)</td>
<td>3.50 (1.14-10.90)</td>
<td>.029</td>
<td>3.90 (1.70-9.40)</td>
<td>.002</td>
</tr>
<tr>
<td>Fibrinogen levels (347-443 mg/dL compared with &lt; 347 mg/dL)</td>
<td>0.80 (0.39-1.64)</td>
<td>.540</td>
<td>1.02 (0.46-2.24)</td>
<td>.970</td>
</tr>
</tbody>
</table>

95%CI, 95% confidence interval; OR, odds ratio.

* Adjusted for age, sex, smoking, hypercholesterolemia, hypertension, diabetes mellitus and high sensitivity C-reactive protein levels.
Table 4

<table>
<thead>
<tr>
<th>Fibrinogen (mg/dL)</th>
<th>hsCRP (mg/dL)</th>
<th>IL-6 (ng/mL)</th>
<th>D-dimer (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher levels (&gt; 443)</td>
<td>0.23 [0.11-0.39]</td>
<td>4.52 ± 0.26</td>
<td>586.00 ± 40.90</td>
</tr>
<tr>
<td>Intermediate levels (347-443)</td>
<td>0.15 [0.03-0.36]</td>
<td>3.67 ± 0.24</td>
<td>479.40 ± 28.00</td>
</tr>
<tr>
<td>Lower quartile (&lt; 347)</td>
<td>0.13 [0.01-0.35]</td>
<td>3.7 ± 0.3</td>
<td>383.90 ± 34.60</td>
</tr>
</tbody>
</table>

hsCRP, high sensitivity C-reactive protein; IL-6, interleukin-6.

Fibrinogen levels > 443 mg/dL were associated with a higher risk for CAD (OR = 3.90; 95% CI, 1.70-9.40; P = .002) compared with levels < 347 mg/dL in the general population. In contrast, the intermediate fibrinogen level subcategory had no significant effect on the risk of CAD (OR = 1.02; 95% CI, 0.46-2.24; P = .970), while the presence of AA (rs180070) was also significantly associated with an increased risk of CAD (OR = 3.20; 95% CI, 1.01-10.10; P = .049) (Table 3).

In hypertensive patients, higher fibrinogen levels > 443 mg/dL (OR = 3.50; 95% CI, 1.14-10.90; P = .029) (Figure 1B), but not the AA genotype of rs180070 (OR = 3.00; 95% CI, 0.78-11.90; P = .110) were independent predictors of CAD. In our overall cohort, we found that the presence of the A alleles of rs180070 and rs2070011 was not associated with angiographic severity of CAD (OR = 1.36; 95% CI, 0.63-2.95; P = .434 and OR = .99; 95% CI, 0.56-1.78; P = .995 respectively). Finally, neither AA homozygosity of rs180070 nor AA homozygosity of rs2070011 was associated with the occurrence of acute myocardial infarction in the overall cohort (OR = 1.87; 95% CI, 0.37-8.90; P = .46 and OR = 0.75; 95% CI, 0.39-1.43; P = .378 respectively). Similarly, no association between AA homozygotes (rs180070) and acute myocardial infarction was detected in participants with HT. The unadjusted CAD risk for the carriers of the A allele (rs2070011, AA or AG) was not significant (OR = 1.003; 95% CI, 0.72-1.40; P = .988). In the subgroups of patients with HT the unadjusted risk of CAD was significant for carriers of the A allele rs2070011. Homozygotic status (AA, rs2070011) was not associated with an increased risk for CAD in the overall cohort (OR = 1.10; 95% CI, 0.68-1.76; P = .700) (Table 3).

![Figure 2. High sensitivity C-reactive protein (hsCRP) levels according to fibrinogen concentration.](image1)

Effects of rs180070 and rs2070011 Polymorphisms on Inflammatory Mediators

In the general cohort, we found that hsCRP levels were higher in the group of patients with higher fibrinogen levels than in patients with lower intermediate fibrinogen levels (0.23 [0.11-0.39] vs 0.15 [0.03-0.36] vs 0.13 [0.01-0.35] mg/L; P = .013) (Figure 2). However, AA homozygotes for the rs180070 polymorphism did not have higher hsCRP levels (AA: 0.21 [0.12-0.36] vs AG or GG: 0.19 [0.05-0.37] mg/L; P = .6). In addition, in HT patients, hsCRP levels were higher in the group of patients with higher fibrinogen levels than in patients with lower intermediate fibrinogen levels (0.28 [0.12-0.42] vs 0.17 [0.04-0.38] vs 0.18 [0.09-0.39] mg/L; P = .032).

Interleukin-6 levels were higher in the highest subcategory of fibrinogen levels (high fibrinogen levels: 4.52 ± 0.26 vs intermediate fibrinogen levels 3.67 ± 0.24 and vs low fibrinogen levels 3.70 ± 0.30 ng/mL) than in intermediate (P = .027) and low fibrinogen levels (P = .035) (Figure 3). In addition, we found a significant effect of the rs180070 polymorphism on IL-6 levels in HT. Specifically, IL-6 levels were higher in AA homozygotes for the rs180070 polymorphism than in all other genotypes (AG or GG) (4.96 ± 0.69 vs 3.70 ± 0.20 ng/mL; P = .046). In hypertensive patients, multivariate analysis revealed that the AA (rs180070) homozygosity was the only adjusted, independent predictor of IL-6 levels (β = 0.151 ± 0.642; P = .032). On multivariate logistic regression, IL-6 levels were not associated with the risk of CAD, acute myocardial infarction, or multivessel disease in the overall cohort.

The levels of hsCRP were not affected by the presence of homozygotic status for the rs2070011 polymorphism in the overall cohort (P = .486) or in hypertensive patients (P = .677). In the overall cohort, AA homozygosity of rs180070 resulted in significantly higher CD40L levels (2.55 ± 0.35 vs 2.13 ± 0.19 ng/mL; P = .019). However, subgroup analysis of HT patients revealed no differences in CD40L levels in the presence of the AA genotype (rs180070) (P = .144). We observed no significant change in IL-6 or CD40L levels with the presence of the AA genotype of rs2070011 among the studied subgroups.

Effects of rs180070 and rs2070011 Polymorphisms on Coagulation Factors

In the overall cohort, D-dimer levels were higher in the highest subcategory of fibrinogen levels (high fibrinogen levels: 40.90 [0.01-0.35] vs 0.23 [0.03-0.36] vs 0.13 [0.01-0.35] mg/L; P = .032).
586.00 ± 40.90 vs intermediate fibrinogen levels 479.40 ± 28.00 and vs low fibrinogen levels 383.90 ± 34.60 mg/dL compared with intermediate (P = .03) and low fibrinogen levels (P = .001) (Figure 4 and Table 4). The AA homozygosity of rs180070 resulted in significantly higher levels of D-dimer compared with GG + GA (555.3 ± 43.0 vs 469.1 ± 19.6 ng/mL; P = .033). Similar results were observed for AA homozygosity (rs180070) regarding D-dimer levels in HT compared with the G allele carriers (623.3 ± 79.6 vs 388.6 ± 23.5 ng/mL; P = .048). After adjustment for age, sex, smoking, hypercholesterolemia, HT, diabetes mellitus, and the presence of the AA (rs180070) genotype as independent predictors, multivariate logistic regression analysis revealed that D-dimer levels were associated with CAD (OR = 1.001; 95%CI, 1.000–1.002; P = .009). When fibrinogen levels were included in the model, the association between D-dimer and CAD remained significant (OR = 1.001; 95%CI, 1.000–1.001; P = .04). In the subgroups of HT patients, logistic regression showed no association between D-dimer levels and CAD. The presence of the rs180070 or rs2070011 polymorphisms was not related to any changes in the levels of factors V, X, plasminogen, and thrombin in HT patients.

DISCUSSION

To the best of our knowledge, the present study is the first to examine the effects of the rs180070 and the rs2070011 genetic polymorphisms on inflammation, coagulation, and the risk of CAD detected on coronary angiography in HT patients. We observed that AA homozygosity of the rs180070 polymorphism was associated with higher fibrinogen levels and the presence of CAD in the overall cohort, while fibrinogen levels > 443 mg/dL were independently associated with the presence of CAD in HT. The AA genotype (rs180070) was also associated with higher levels of IL-6 and D-dimer in HT. Similarly, the levels of these parameters were higher in patients with fibrinogen levels > 443 mg/dL. In the overall cohort as well as in hypertensive patients, hsCRP was found to be elevated in the high-fibrinogen subgroup. These findings indicate that the presence of the AA genotype (rs180070) is associated with increased levels of inflammatory mediators and a higher risk of CAD. However, the most significant predictor of the presence of CAD was elevated fibrinogen levels > 443 mg/dL. On the other hand, the rs2070011 polymorphism was not associated

with the risk of CAD or levels of inflammatory and coagulation mediators.

Hypertension and Fibrinogen Polymorphisms: Risk of Coronary Artery Disease

The role of HT in atherosclerosis is well known, while studies have shown that these patients have an increased risk of CAD. In addition, research has been conducted on the role of fibrinogen polymorphisms in the risk of CAD, with controversial results. Thus, it was reported that plasma fibrinogen gamma' concentration influences the risk of myocardial infarction, possibly due to the positive effect on fibrinogen levels.10 On the other hand, the b-chain fibrinogen gene –148C/T polymorphism showed no association with the risk of CAD.5 More recent evidence showed that there was a significant association between HT and the rs2070008 polymorphism of fibrinogen in women only, whereas fibrinogen haplotypes were not associated with HT after correction for multiple comparisons in either men or women.17 Finally, the rs4220 polymorphism of the fibrinogen beta chain gene was independently associated with plasma fibrinogen level and HT in Chinese participants, suggesting a possible causal role of fibrinogen in HT development, especially in men.18

However, no clear data exist on the role of the studied polymorphisms on the risk of CAD in patients with HT. Our results indicate that elevated fibrinogen levels are an independent predictor of CAD risk in HT patients. In contrast, the rs2070011 polymorphism did not affect fibrinogen levels or the risk of CAD in our cohort. Although the presence of AA homozygosity (rs180070) resulted in higher fibrinogen levels and risk of CAD in the overall cohort, no significant effect was found (in terms of CAD risk) in the subgroup of HT. This finding may suggest that the AA genotype does not raise CAD risk independently of fibrinogen levels and major risk factors such as HT.

Hypertension and Fibrinogen Polymorphisms: Effects on Inflammation

Several studies have shown that HT is associated with increased circulating inflammatory biomarkers.3,4 Although this risk factor has been widely examined, the role of genetics has not been fully clarified in this population. Previously, the fibrinogen beta chain C148T polymorphism was associated with increased fibrinogen, CRP, and IL-6 in patients undergoing coronary artery bypass grafting.19,20 Wong et al.21 reported that there was a clear genetic influence of the IL6-572C > G polymorphism on plasma levels of fibrinogen and CRP, especially in patients with HT. Moreover, the genetic polymorphism A1675G on the AT2R gene affects cardiovascular risk and the severity of the disease by promoting vascular inflammation, particularly in hypertensive men,22 while the M235T polymorphism of the angiotensinogen gene appears to have no effect.23

In the present study, we confirmed that high-risk patients have higher levels of inflammatory biomarkers. In addition, patients with high fibrinogen levels exhibited higher hsCRP, IL-6, and CD40L levels. This finding suggests that among high-risk individuals, concurrent fibrinogen and hsCRP levels may identify those patients with the highest cardiovascular risk. Importantly, we have shown for the first time a significant effect of the rs180070 polymorphism on IL-6 levels among hypertensive patients. Therefore, IL-6 levels were higher in AA homozygotes for rs180070 compared with all other genotypes (AG or GG) and AA homozygosity was the only adjusted independent predictor of IL-6 levels. The inflammatory process was not affected by the presence of homozygotic status (AA) of the rs2070011 polymorphism both in the overall cohort and in patients with HT.
Hypertension and Fibrinogen Polymorphisms: Effects on Coagulation

Evidence suggests that increased plasma levels of fibrinogen, D-dimer, and prothrombin fragment 1 + 2 are present in hypertensive patients with mildly decreased creatinine clearance, suggesting that the coagulation system is activated in these patients. However, there are scarce data on the effects of fibrinogen genetic variability on the coagulation cascade of patients with HT. The presence of the Ala379Val polymorphism of lipoprotein-associated phospholipase A2 affected fibrinogen levels in a Caucasian hypertensive population, while the fibrinogen alpha Thr312Ala polymorphism was associated with chronic thromboembolic pulmonary HT. Furthermore, it has been reported that the rs2227401 and rs2070016 polymorphisms of fibrinogen genes were associated with significantly higher fibrinogen levels, whereas the rs1049636 polymorphism was associated with lower concentrations of fibrinogen in women, but not in men. Only in a small cohort was it shown that A455 carrier status was associated with increased fibrinogen levels in patients with HT but that study did not examine risk of CAD in this population.

In our cohort, we found that the presence of the A allele of rs180070 was associated with significantly higher levels of fibrinogen in hypertensive participants. However, the presence of the A allele of rs2070011 had no significant effects on the fibrinogen levels in these patients. In the multivariate analysis, the AA genotype of the rs180070 and CAD remained independent predictors of fibrinogen levels. Importantly, we were able to show for the first time that AA homozygosity of the rs180070 polymorphism resulted in significantly higher levels of D-dimer compared with GC + GA and this difference remained significant in patients with HT. Importantly, no differences in lipid profile or medical treatment were observed among the groups, which suggests that initial cardiovascular risk was similar across the fibrinogen tertiles. However, the presence of the rs180070 or rs2070011 polymorphisms was not related to any changes in the levels of factors V, X, plasminogen or thrombin in hypertensive patients.

Limitations

There are some limitations to the interpretation of our data analysis. First, this is a cross-sectional study and we do not report data on clinical follow-up. Additionally, the severity of CAD was not quantified in detail with the use of the SYNTAX score. Finally, potential unmeasured confounders might affect the association between genetic variants and the risk of CAD.

Conclusions

Our study showed that fibrinogen was an independent predictor of the presence of CAD and this strongly related to its levels in HT. Additionally, AA homozygosity of rs180070 was associated with higher fibrinogen, IL-6, and D-dimer levels and risk of CAD in the overall cohort.

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Conflicts of Interest

None declared.

What is known about the topic?

- Fibrinogen is a biomarker that is involved both in inflammatory response and in coagulation pathways, leading to endothelial dysfunction and atherosclerosis.
- An independent association of plasma fibrinogen levels and the risk of CAD have been previously documented.
- Recent evidence suggests the potential role of fibrinogen genetic variability in the risk of CAD but the available data are controversial.
- Previous studies were controversial with regards to potential regulatory effects of genetic polymorphisms, including the rs180070 and rs2070011 polymorphisms, on fibrinogen levels and CAD risk.

What does this study add?

- In this study, we demonstrated that the presence of the A allele of rs180070 was associated with significantly higher levels of fibrinogen while the presence of the A allele of rs2070011 had no significant effects on the fibrinogen levels in hypertensive participants.
- On multivariate analysis, the AA genotype of the rs180070 polymorphism and CAD remained independent predictors of fibrinogen levels.
- AA homozygosity of the rs180070 resulted in significantly higher levels of D-dimer compared with GC + GA and this difference remained significant in patients with HT.

References


