Comparison between the effects of mixed dyslipidaemia and hypercholesterolaemia on endothelial function, atherosclerotic lesions and fibrinolysis in rabbits

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ABSTRACT

We compared the impact of hypercholesterolaemia and mixed dyslipidaemia on vascular function, vascular structure and fibrinolytic balance in rabbits. To this end, vascular reactivity was studied in aortic rings from rabbits fed a control diet, a diet containing 0.5% cholesterol + 14% coconut oil (mixed dyslipidaemia) or a diet containing 1% cholesterol (hypercholesterolaemia) for 12–14 weeks. Morphometric analysis of aorta was also performed and plasminogen activator inhibitor-1 (PAI-1) as well as tissue-type plasminogen activator (t-PA) plasma activities were measured. Both diets induced a similar increase in cholesterol plasma levels, although triacylglycerols (triglycerides) were increased in animals with mixed dyslipidaemia. Hypercholesterolaemia was associated with intimal thickening, reduction in acetylcholine-induced relaxation (P < 0.05) and increased vasoconstriction induced by acetylcholine + Nω-nitro-L-arginine methyl ester (L-NAME) when compared with controls (P < 0.05). These effects were more marked (P < 0.05) in animals with mixed dyslipidaemia. Incubation with ifetroban, a thromboxane A2/prostaglandin H2 receptor antagonist, increased acetylcholine-induced relaxation (P < 0.05) and reduced acetylcholine + L-NAME contraction (P < 0.05) in both diet groups. In contrast, the presence of PD 145, an endothelin (ET)A/ETB receptor antagonist, exerted these effects only in rabbits with mixed dyslipidaemia. Both hypercholesterolaemia and mixed dyslipidaemia induced a similar increase in PAI-1 and a similar decrease in t-PA plasma activities. These data suggest that hypertriglyceridaemia can increase the deleterious effects of hypercholesterolaemia on endothelial function and vascular structure. This additional harmful effect exerted by triacylglycerols on endothelial function could, in part, be mediated by ET.

INTRODUCTION

Alterations in plasma lipid levels exert an important impact on vascular function, because they can affect several endothelial cell processes. In this regard, numerous studies [1–5] have shown that hypercholesterolaemia is associated with functional endothelial alterations. This endothelial dysfunction not only involves changes in vascular tone regulation, but also alterations in vascular smooth muscle cell growth and migration, leucocyte adhesion and platelet function, which can play an important role in the development and progression of atherosclerotic lesions.

Key words: endothelial function, fibrinolytic balance, hypercholesterolaemia, intimal thickening, mixed dyslipidaemia.
Abbreviations: AUC, area under respective dose–responses curves; ET, endothelin; LDL, low-density lipoprotein; l-NAME, Nω-nitro-L-arginine methyl ester; PAI-1, plasminogen activator inhibitor-1; PGH2, prostaglandin H2; t-PA, tissue-type plasminogen activator; TXA2, thromboxane A2.
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atherosclerosis [6,7]. In addition, endothelium is the source of a number of components for the fibrinolytic system that can also be affected by plasma lipids. In fact, hypercholesterolaemia has been associated with an impaired fibrinolysis due to either reduced tissue-type plasminogen activator (t-PA) or enhanced plasminogen activator inhibitor-1 (PAI-1), which can participate in the complication of atherosclerosis [8,9]. Although hypercholesterolaemia is the most common alteration observed in plasma lipids in patients, other alterations, such as hypertriglyceridaemia, are also frequently observed in the clinic. Indeed, hypertriglyceridaemia is also associated with endothelial dysfunction and changes in fibrinolysis [5,9–13]. Moreover, in some different pathological situations both alterations can be associated. However, whether or not the association between hypercholesterolaemia and hypertriglyceridaemia can further impair vascular function and atherosclerotic lesion progression is not well established. Therefore the aim of the present study was to evaluate whether or not hypertriglyceridaemia can potentiate the effects of diet-induced hypercholesterolaemia on both intimal thickening and endothelial function as well as on fibrinolytic balance in rabbits. In addition, since high triacylglycerol (triglyceride) and cholesterol plasma levels have been associated with enhanced levels of endothelin (ET) and thromboxane A2 (TXA2) [14,15], we investigated whether these vasoconstrictor factors participated in the endothelial dysfunction associated with changes in plasma lipids. To this end, we compared the effect of mixed dyslipidaemia and hypercholesterolaemia on endothelial function, vascular structure and fibrinolytic balance in rabbits.

**METHODS**

**General procedures**

Twenty-four male New Zealand rabbits (Granja Cunicular San Bernardo, Navarra, Spain) initially weighing 2040 ± 37 g were used for the study. Animals were maintained under controlled light and temperature conditions and fed with three different diets: normal rabbit chow (control), a diet containing 0.5% cholesterol (0.1 μmol/l) or 3.8% trisodium citrate through a catheter inserted in the car artery of awake rabbits to measure cholesterol and triacylglycerol or fibrinolytic balance respectively. Plasma triacylglycerol and cholesterol levels were measured using colorimetric reactions employing commercial kits (Roche Diagnostics, Zurich, Switzerland). Plasma t-PA and PAI-1 activities were evaluated using an immunoactivity assay using commercial kits (Biopool International, Ventura, CA, U.S.A.).

**Vascular reactivity**

After taking blood samples, the animals were anaesthetized with sodium pentobarbital (25 mg/kg, intravenously), and the descending thoracic aorta was exposed through a midline incision, excised and processed as described previously [4,16]. Rings were allowed to equilibrate for 60–90 min with changes of Kreb’s buffer (119 mmol/l NaCl, 5 mmol/l NaHCO3, 11.1 mmol/l glucose, 1.6 mmol/l CaCl2, 4.7 mmol/l KCl, 1.2 mmol/l KH2PO4 and 1.2 mmol/l MgSO4, pH 7.4) every 15 min, and several adjustments of length were made until baseline tension stabilized at 2 g. In preliminary experiments, we found that 2 g of resting tension was optimal for expression of KCl-induced contraction of aortic rings obtained from normal rabbits. When isometric tension was stable, the experiments were initiated by obtaining a reference contractile response to KCl (80 mmol/l).

The vasorelaxing response to the endothelium-dependent vasodilator acetylcholine (10−8–10−5 mol/l) was studied in aortic rings from control, dyslipidaemic and hypercholesterolaemic rabbits precontracted with a submaximal dose of phenylephrine (10−6 mol/l). Endothelium-dependent contractions induced by acetylcholine (10−8–10−4 mol/l) were evaluated in aortic rings preincubated for 15–20 min with the NO synthase inhibitor Nω-nitro-l-arginine methyl ester (l-NAME; 10−4 mol/l). In order to evaluate the possible role of endogenous endothelium-dependent contracting factors in these responses, the vasorelaxing and vasoconstrictor responses to acetylcholine were also studied in the presence of the TXA2/prostaglandin H2 (PGH2) receptor antagonist ifetroban (10−5 mol/l) and/or ETα/ETβ receptor antagonist PD 145 (10−5 mol/l). Ifetroban and PD 145 were added to the bath 20 min prior to assessing the responses to acetylcholine. In preliminary experiments, we evaluated the effectiveness of ifetroban (10−5 mol/l) in blocking TXA2/PGH2 receptors by ascertaining that the constrictor response to a high dose (10−4 mol/l) of the TXA2 analogue, U46619 [52,9x,11x,13E,15(S)-155-hydroxy-9(11)-methanoepoxyprosta-5,13-dien-1-0ic acid], was reduced by more than 75% in the presence of ifetroban. Likewise, the effectiveness of PD 145 (10−5 mol/l) in blocking ETα/ETβ receptors was evaluated by ascertaining that the constrictor respon-
siveness to a high dose of ET-1 (10^{-7} \text{mol/l}) was reduced by 80\% after the addition of PD 145.

In additional experiments, endothelium-independent relaxation and contraction to sodium nitroprusside (10^{-10}–10^{-6} \text{mol/l}) or phenylephrine (10^{-9}–10^{-5} \text{mol/l}) respectively, was studied in aortic rings from control, dyslipidaemic and hypercholesterolaemic rabbits.

**Morphological analysis**

Aortic segments were fixed in 15\% formaldehyde/PBS, processed, impregnated, embedded in paraffin and cut into 3–4 \mu m sections by using a microtome. The sections were stained with Masson trichrome and haematoxylin/eosin, and the lesion area was determined as described previously [4,16] using a QWIN Leica image analyser (Leica Imaging Systems Ltd, Cambridge, U.K.). To determine the luminal area, the cross-sectional area enclosed by the internal elastic lamina was corrected to a circle applying the form factor $F/4\pi$ to the measurement of the internal elastic lamina, where $l$ is the length of the lamina. Vessel area was determined by the cross-sectional area enclosed by the external elastic lamina corrected to a circle applying the same form factor $(F/4\pi)$ to the measurement of the external elastic lamina.

**Drugs**

Ifetroban and PD 145 were kindly supplied by Bristol Myers Squibb (Madrid, Spain) and Pfizer (Madrid, Spain) respectively. The TXA_2 receptor agonist U46619 was obtained from Cascade Biochem Ltd (Reading, Berks., U.K.). Products for morphological analysis were purchased from Merck (Darmstadt, Germany). All other drugs were obtained from Sigma (St. Louis, MO, U.S.A.). Ifetroban was initially dissolved in DMSO and redissolved in Kreb’s solution at a final concentration of 10^{-8} \text{mol/l}. This DMSO concentration did not have any effect on vascular reactivity. U46619 was dissolved in methyl acetate (10 mg/ml) and diluted further in Kreb’s solution. Concentrations are expressed as final molar concentration in the organ chamber.

**Calculations and statistical analysis**

Contractile responses were expressed as a percentage of the reference constrictor response to 80 mmol/l KCl. Relaxation responses were expressed as percentage reductions of tension in phenylephrine-preconstricted state. Results are expressed as means ± S.E.M. from eight rabbits unless otherwise specified. Vascular reactivity dose–response curves were compared by multivariate analysis of variance for repeated measures (‘MANOVA’) using the Complete Statistical System (CSS) program (Statoft Inc, Tulsa, OK, U.S.A.). All other data were analysed using a one-way ANOVA, followed by a Newman–Keuls test if differences were noted. The null hypothesis was rejected when the $P$ value was less than 0.05. Area under respective dose–responses curves (AUC) was used to calculate approximate endothelium-dependent constriction induced by acetylcholine+1-NAME.

**RESULTS**

Both non-control diets produced a similar increase in cholesterol plasma levels as compared with animals fed a control diet. However, only the diet enriched with coconut oil increased triacylglycerol plasma levels ($P < 0.05$; Table 1). At the end of the experiment, no differences were observed in body weight within any group (Table 1).

As shown in Figure 1 and Table 2, both lesion area and the degree of stenosis were bigger ($P < 0.05$) in dyslipidaemic rabbits than in animals with hypercholesterolaemia. No changes in either media or vessel area were found. Aortic media/lumen ratio was higher in hypercholesterolaemic rabbits ($P < 0.05$) and further enhanced in animals with mixed dyslipidaemia as compared with control animals ($P < 0.05$; Table 2).

When compared with control animals, the vasorelaxing response to acetylcholine was either reduced or abolished in aortic rings from rabbits with hypercholesterolaemia or mixed dyslipidaemia respectively (Figure 2). In these animals, a negative correlation was found between the maximal relaxation elicited by acetylcholine and lesion area ($r = -0.63; P < 0.05$). Preincubation of aortic rings with ifetroban (10^{-5} \text{mol/l}) enhanced ($P < 0.05$) the vasorelaxation induced by acetylcholine in both diet groups, but did not modify this response in control animals (Figure 2). In contrast, the presence of PD 145 (10^{-4} \text{mol/l}) in the incubation media increased ($P < 0.05$) the relaxing responses to acetylcholine in aortic rings only from rabbits with mixed dyslipidaemia (Figure 2).

Acetylcholine constrictor responses in the presence of 1-NAME were higher ($P < 0.05$) in aortic rings from dyslipidaemic rabbits than from hypercholesterolaemic rabbits, in which this response was higher than those

<table>
<thead>
<tr>
<th>Group</th>
<th>Cholesterol (mmol/l)</th>
<th>Triacylglycerols (mmol/l)</th>
<th>Body weight (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.92 ± 0.05</td>
<td>1.04 ± 0.22</td>
<td>3186 ± 59</td>
</tr>
<tr>
<td>Mixed dyslipidaemia</td>
<td>55.20 ± 4.10</td>
<td>6.90 ± 0.81*</td>
<td>3217 ± 54</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>49.80 ± 3.20</td>
<td>1.90 ± 0.35</td>
<td>3095 ± 28</td>
</tr>
</tbody>
</table>
Figure 1 Representative microphotographs of sections of aorta from control (A), mixed dyslipidaemic (B) and hypercholesterolaemic (C) rabbits

Sections of aorta were stained with haematoxylin/eosin after isolation from rabbits fed control, mixed dyslipidaemic or hypercholesterolaemic diets for 12–14 weeks, as described in the Methods section. Magnification × 7.5.

Table 2 Effect of hypercholesterolaemia and mixed dyslipidaemia on aortic structure in rabbits

<table>
<thead>
<tr>
<th>Group</th>
<th>M/L ratio</th>
<th>Lesion area (mm²)</th>
<th>Stenosis (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>0.31 ± 0.01</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Mixed dyslipidaemia</td>
<td>0.69 ± 0.12*#</td>
<td>0.52 ± 0.14*#</td>
<td>26.7 ± 4.6*#</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>0.53 ± 0.09*</td>
<td>0.17 ± 0.03*</td>
<td>12.1 ± 3.4*</td>
</tr>
</tbody>
</table>

observed in control rabbits (Figure 3). As shown by AUC, these differences were always observed even in the presence of either ifetroban or PD 145 (Figure 3, insets). The presence of ifetroban in the incubation media significantly reduced ($P < 0.05$) the constrictor response induced by acetylcholine + L-NAME in aortic rings from dyslipidaemic and hypercholesterolaemic rabbits (Figure 3). However, incubation of the rings with PD 145 reduced ($P < 0.05$) this constrictor response only in aortic rings from rabbits with mixed dyslipidaemia (Figure 3). None of the drugs were able to significantly modify this constrictor response in rings from control rabbits. No differences were observed in the dose–response curves to phenylephrine, ET or U46619 in any group. Neither were differences observed in the vasorelaxation to sodium nitroprusside (results not shown).

As shown in Figure 4, hypercholesterolaemic and dyslipidaemic rabbits had higher ($P < 0.05$) PAI-1 plasma activity when compared with control animals, this increase being similar in both non-control diet groups. In addition, t-PA plasma activity was comparably reduced ($P < 0.05$) in animals with hypercholesterolaemia and mixed dyslipidaemia when compared with controls.

DISCUSSION

The present study shows that mixed dyslipidaemia produces a more harmful effect on endothelial function than hypercholesterolaemia alone. This deleterious effect seems to involve ET-1 in addition to TXA$_2$, which appear to participate in the endothelial dysfunction associated with hypercholesterolaemia. Moreover, aortas from dyslipidaemic animals had a larger intimal thickening than those from hypercholesterolaemic animals. This suggests that hypertriglyceridaemia can worsen the effect of hypercholesterolaemia on both endothelial function and vascular lesion but not on fibrinolytic balance.

Hypercholesterolaemia, a major risk factor for atherosclerosis, induces a deleterious effect on vascular structure, since it participates in the development of atherosclerotic lesion through different mechanisms, including membrane fluidity alterations and changes in endothelial cell function [6,7]. In this regard, and in agreement with previous studies [17,18], the present results show an aortic vessel wall enlargement in hypercholesterolaemic rabbits, a consequence of intimal thickening and hence luminal narrowing. Moreover, hypertriglyceridaemia further potentiates the deleterious effect induced by high cholesterol levels on vascular structure, since the lesion area and degree of stenosis was bigger in animals with mixed dyslipidaemia than in hypercholesterolaemic rabbits. Similarly, combined hyperlipidaemia enhanced intimal thickening and cellularity in aortic allografts in rats when compared with either hypercholesterolaemia

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Figure 2 Vasorelaxation induced by acetylcholine in aortic rings from control, mixed dyslipidaemic and hypercholesterolaemic rabbits precontracted with a submaximal dose of phenylephrine

Aortic rings, isolated from rabbits fed control (CT), mixed dyslipidaemic (MD) or hypercholesterolaemic (HC) diets for 12–14 weeks, were precontracted with a submaximal dose ($10^{-6}$ mol/l) of phenylephrine (PE) and then preincubated in the absence (vehicle) or presence of either an ETA/ETB receptor antagonist (PD 145; $10^{-5}$ mol/l) or a TXA2/PGH2 receptor antagonist (Ifetroban; $10^{-5}$ mol/l). Aortic rings were then treated with acetylcholine ($10^{-9}$–$10^{-5}$ mol/l) and vasorelaxation determined as described in the Methods section. Values are expressed as a percentage of the phenylephrine contraction and are means ± S.E.M. from eight rabbits. *P < 0.05 compared with control rabbits; #'P < 0.05 compared with hypercholesterolaemic rabbits.

or hypertriglyceridaemia in isolation [19]. The putative mechanisms underlying this harmful effect of triacylglycerol could involve several mechanisms, including alterations in vascular permeability, since it has been reported [20] that lipolytic remnants of triacylglycerol-rich lipoproteins alter endothelial barrier function. Likewise, an increase in monocyte adhesion cells could also participate, because triacylglycerols can induce an increase in monocyte–endothelial cell adhesion in patients with combined dyslipidaemia [21].

The data in the present study also suggest that hypertriglyceridaemia reinforces the deleterious effect on endothelial function exerted by high cholesterol levels, because it further potentiates the reduction or increase
Figure 3  Isometric tension induced by acetylcholine + L-NAME in aortic rings from control, mixed dyslipidaemic and hypercholesterolaemic rabbits

Aortic rings, isolated from rabbits fed control (CT), mixed dyslipidaemic (MD) or hypercholesterolaemic (HC) diets for 12–14 weeks, were preincubated in the absence (vehicle) or presence of either an ETA/ETB receptor antagonist (PD 145; 10^{-5} mol/l) or a TXA2/PGH2 receptor antagonist (Ifetroban; 10^{-5} mol/l) and then treated with acetylcholine (10^{-9}–10^{-5} mol/l) in the presence of L-NAME (10^{-4} mol/l). Contractile responses were determined as described in the Methods section. Values are expressed as a percentage of the contractile response to KCl. Insets, the AUC, expressed in arbitrary units (au), of the endothelium-dependent contraction induced by acetylcholine (10^{-8}–10^{-4} M) in the presence of L-NAME (10^{-4} M) for each diet. Values are means ± S.E.M. for eight rabbits. *P < 0.05 compared with control rabbits; #P < 0.05 compared with hypercholesterolaemic rabbits

induced by hypercholesterolaemia in endothelium-dependent relaxation or contraction respectively. In contrast, hypercholesterolaemia alone or combined with hypertriglyceridaemia was not able to alter smooth muscle function, since endothelium-independent relaxation and contraction were not modified by changes in plasma lipids. Although there is scant information about the effect of the combination of high cholesterol-
Dyslipidaemia and vascular function and structure

Figure 4 Plasma levels of PAI-1 and t-PA from control, mixed dyslipidaemic and hypercholesterolaemic rabbits

Plasma levels of PAI-1 (upper panel) and t-PA (lower panel) were determined from rabbits fed control (CT), mixed dyslipidaemic (MD) or hypercholesterolaemic (HC) diets for 12–14 weeks, as described in the Methods section. Values are means ± S.E.M. for eight rabbits. *P < 0.05 compared with control rabbits. UI, international units.

Several mechanisms could explain the reduced relaxation in response to acetylcholine observed in hypercholesterolaemic rabbits, one of them being a diminished NO availability, a consequence of both a reduced synthesis and/or major degradation [26,27]. This effect could rely on an increased production of oxidized-LDL, which has been demonstrated to not only reduce the expression of NO synthase in endothelial cells, but also enhance oxidative stress [28,29]. In addition, an increase in the vasoconstrictor factor TXA₂, which can counteract the effect of NO, could also account for this endothelial dysfunction. This assertion is based on the observation that incubation with ifetroban, the TXA₂/PGH₂ antagonist, improved the endothelium-dependent relaxation in both non-control diet groups. Likewise, ifetroban diminished the vasoconstrictor effect induced by acetylcholine in the presence of l-NAME in rabbits with both hypercholesterolaemia and mixed dyslipidaemia. This suggests a role of this vasoconstrictor prostanooid in endothelium-dependent contraction. In agreement with this, it has been shown that the administration of aspirin or a TXA₂/PGH₂ antagonist improved acetylcholine-relaxation in atherosclerotic patients and in cholesterol-fed rats respectively [30,31]. The deleterious effect of triacylglycerol on endothelial function seems to also involve, in addition to other mechanisms [22,32], the vasoconstrictor factor ET-1. This assertion is based on the fact that the presence of the ET₄/ET₃ receptor antagonist PD 145 in the incubation media increases the relaxing response to acetylcholine and reduces the endothelium-dependent contraction in dyslipidaemic rabbits. Therefore, in animals with mixed dyslipidaemia, ET-1 can potentiate the harmful mechanisms produced by hypercholesterolaemia on endothelial function. The participation of TXA₂ and ET-1 could involve an enhancement of their availability and not a hyperreactivity response to these agents, because, in additional studies, we found a similar contraction in response to both U46619, the TXA₂ analogue, and ET-1 in rings from control, dyslipidaemic and hypercholesterolaemic rabbits. Indeed, a correlation between both plasma triacylglycerols and ET levels in patients with Type II diabetes and dyslipidaemia [14] and cholesterol and urinary excretion of TXA₂ in hypercholesterolaemic patients [15] has been reported. In addition to the above mechanisms, the minor response to acetylcholine observed in dyslipidaemic rabbits can also be attributed to intimal thickening, which produces a structural barrier preventing NO from reaching smooth muscle cells. In this regard, the biggest lesion area accompanied the minor response to acetylcholine observed in rabbits with mixed dyslipidaemia. In fact, the maximal relaxing response to acetylcholine negatively correlated with the extent of the lesion.

Numerous studies have shown that lipids can modulate fibrinolysis, since both hypercholesterolaemia and hypertriglyceridaemia are associated with alterations in fibrinolytic balance [8,9,13]. In the present study, hypertriglyceridaemia was not able to alter further either the increase in PAI-1 or the decrease in t-PA activities induced by hypercholesterolaemia, since animals from both non-control diet groups presented similar PAI-1/t-PA ratios. This lack of additional effect of triacylglycerols on fibrinolytic balance in hypercholesterolaemic rabbits may suggest a common harmful mechanism of lipid plasma on fibrinolysis and could involve, among
other mechanisms, the effect exerted by oxidized-LDL and very-LDL (‘VLDL’) on t-PA and PAI-1 synthesis, as it has been shown [33,34] that they can reduce t-PA and increase PAI-1 release in endothelial cells.

In summary, the present study shows that hypertriglyceridaemia potentiates further the deleterious effect of hypercholesterolaemia on endothelial function and atherosclerotic lesion. This effect seems to be, in part, mediated by ET in addition to the role played by TXA2 in the functional alterations induced by hypercholesterolaemia. Furthermore, the results support that, in mixed dyslipidaemia, the fibrinolytic balance is altered mainly by hypercholesterolaemia and not by hypertriglyceridaemia.

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