Paper:
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The -765G>C Cyclooxygenase-2 Promoter Polymorphism is associated with Type 2 Diabetes Mellitus, Low High-density Lipoprotein and Manifest Angina

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Abstract

Background and Aims: Cyclooxygenase-2 (COX-2) catalyses the rate limiting step of prostaglandin biosynthesis. Despite previous studies, it is still unclear whether COX-2 is beneficial or detrimental to cardiovascular risk. The aim of this study was to examine the -765G>C (rs20417) PTGS2 promoter gene variant, which encodes COX-2, in relation to markers of cardiovascular risk in a sample of well-characterised subjects with diabetes mellitus.

Methods and Results: We observed that the CC genotype was more prevalent in Type 2 diabetes mellitus compared to Type 1 (84.2% vs 15.8%; \( p \leq 0.05 \)), and was significantly associated with clinically manifest angina (GG vs GC vs CC: 14.3% vs 15.6% vs 28.0%; \( p=0.009 \)) and lower HDL-cholesterol levels (GG vs GC vs CC: 1.3 mmol/L vs 1.4 mmol/L vs 1.2 mmol/L; \( p=0.032 \)). This is in line with previous studies showing that -765G>C genotype variant alters Sp1 binding, resulting in decreased COX-2 activity which is associated with atherosclerosis.

Conclusion: We conclude that the CC genotype may contribute to a reduction of prostaglandin E2 mediated insulin secretion, predisposing those individuals to Type 2 diabetes mellitus. Further prospective work is warranted in order to examine the association between COX-2 and cardiovascular risk.

Keywords: COX-2; Polymorphism; Type 2 diabetes; HDL; Angina; Cardiovascular

Introduction

Cyclooxygenase exists in three isoforms, COX-1 which is constitutively expressed across all tissues; COX-2 whose expression is induced by a number of physiological stimuli and COX-3 a splice variant of COX-1, commonly called COX-1b. Both COX-1 and COX-2 catalyse the rate limiting reaction in the synthesis of prostaglandins, prostacyclins and thromboxanes, with COX-2, the inducible isoform, favouring the production of lipid mediators in a cell specific manner [1]. Prostaglandins and prostacyclins are mediators of inflammation and also play a regulatory role in cardiovascular homeostasis. COX-2 is of interest from a pharmacological perspective since non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, are routinely used in the prevention of cardiovascular disease and to alleviate pain associated with inflammatory conditions [2].

COX-2 is involved in the pathogenesis of inflammatory conditions including Type 2 diabetes mellitus [3] and atherogenesis [4]. Glucose mediated increases in COX-2 expression result in reduced bioavailability of the vasodilator nitric oxide and subsequent endothelial dysfunction [5,6]. Nitric oxide has an additional cardiac protective role preventing the oxidation of low density lipoproteins (LDL). In the absence of nitric oxide, LDL becomes oxidised, resulting in endothelial dysfunction and subsequent higher atherosclerotic risk [6]. Additionally, the expression of COX-2 is up-regulated in macrophage, endothelial and smooth muscle cells contained in atherosclerotic lesions [7]. Increased production of prostaglandins in these lesions contributes to plaque rupture and subsequent thrombosis which leads to stroke or an acute coronary syndrome [8].

Studies have shown that COX-2 inhibition may improve endothelial function [9] and hence have benefits on cardiovascular function. Conversely, both prostaglandin E2 and prostacyclin synthesis are thought to have an adaptive role in the reduction of high blood pressure in patients with diabetes through increased COX-2 expression resulting in vasodilation [10], as well as playing a cardio protective role [11]. COX-2 also contributes to insulin signalling, as prostaglandin E2 in pancreatic \( \beta \)-cells has a negative effect on insulin secretion [12,13]. It is clear that COX-2 regulates a number of key pathways producing paracrine hormones with a range of physiological functions and has the potential to be a therapeutic to prevent cardiovascular disease [14].

The rs20417 (-765G>C) polymorphism lies in the promoter region of the COX-2 gene and results in a G to C transfer at position -765 \([15]\). The G allele is associated with more efficient binding of Sp1 and NF-\( \kappa \)B transcription factors, increasing transcription of COX-2 \([16]\). The CC genotype has been shown to be associated with increased Type 2 diabetes mellitus prevalence of risk \([17]\).

The aim of the pilot study was to investigate the association between the rs20417 COX-2 polymorphism and coronary heart disease (CHD), and selected relevant cardiovascular risk factors, including HDL-cholesterol and LDL-cholesterol levels and LDL-particle size and oxidised LDL (OxLDL) and total antioxidant status (TAOS) in a cross sectional sample of patients with Type 1 and Type 2 diabetes mellitus.
Methods

Samples

Patients were recruited from the University College London Diabetes and Cardiovascular Study (UDACS), which has been previously described [18]. Briefly, the pilot sample consists of 1011 consecutive subjects (Caucasian v Non-Caucasian v Unknown: 77.1 v 20.6 v 2.3% [Non-Caucasian includes Indian-Asian v Black v Asian ethnicities: 53.8 v 37.5 v 8.7%]) recruited from the diabetes clinic at University College London Hospitals NHS trust between the years 2001-2002. All patients had diabetes diagnosed by the WHO criteria [19]. At the time of study recruitment (2001), the presence of CHD was recorded if any patient had positive coronary angiography/angioplasty, coronary artery bypass, cardiac thallium scan, exercise tolerance test, myocardial infarction or symptomatic/treated angina. Any individual who was asymptomatic or had negative investigations was categorised as 'no CHD'. Microalbuminuria was defined as an albumin:creatinine ratio (ACR) of greater than 2.5 mg/mmol in men and 3.5 mg/mmol in women [20] and ACR>30 mg/mmol. Plasma samples were collected within a twelve month period and stored immediately at -80ºC. None of the samples were fasting at the time of collection. Baseline biochemical measurements (total cholesterol, LDL-cholesterol, HDL-cholesterol and triglycerides) were performed within the local hospital accredited chemical pathology laboratory. All experimental protocols and the process for obtaining informed consent were approved by the appropriate institutional review committee [18].

Genotyping of the rs20417 polymorphism

Genomic DNA was extracted from 5 ml EDTA blood samples. Genotyping was conducted using polymerase chain reaction amplification followed by restriction digest with AcI I. Primer sequences were: forward GGCCTGTATATCTGCTCTATATGC and reverse CCGCTTCCTTTGTCCATCAG [21]. Genotype was confirmed by two independent technicians and any discrepancy resolved by repeat genotyping.

Measurement of plasma total anti-oxidant status

Plasma total anti-oxidant status (TAOS) was measured by Sampson's modification of Leigh's photometric microassay [22], using 2.5 µl citrated plasma samples in 96-well ELISA plates. The TAOS of plasma was determined by its capacity to inhibit the peroxidase-mediated formation of the 2,2-azino-bis-3-ethylbensthiazoline-6-sulfonic acid (ABTS+) radical. Previously, we have shown that basal plasma TAOS is associated with prospective risk and has a good correlation with plasma F2-isoprostanes [23].

Measurement of plasma Ox-LDL

Plasma oxidized LDL (Ox-LDL) was measured using a commercially available Enzyme-Linked Immunosorbent Assay (ELISA) kit supplied by Mercodia (Uppsala, Sweden). In this assay a monoclonal antibody is directed against antigenic determinants in the Ox-LDL molecule (mAB-4E6).

Measurement of low density lipoprotein particle diameter

Low density lipoprotein (LDL) at d 1.019-1.063 g/ml was isolated from EDTA plasma. Electrophoresis was performed as previously described [24]. Polyacrylamide gels were used to determine LDL peak particle diameter (LDL-PPD) and LDL mean particle diameter (LDL-MPD) and the SD-LDL% was determined from the LDL particle size [25].

Statistical analyses

Statistical analyses were performed using SPSS (version 19.0, SPSS Inc., Chicago). Results are presented as mean and standard deviation. Deviations from Hardy-Weinberg equilibrium were considered using chi-squared tests. Allele frequencies are shown with the 95% confidence interval. For data that was normally distributed after log transformation, the geometric mean and approximate standard deviation is shown. Analysis of variance (ANOVA) was used to test the association between genotype and baseline characteristics for data that was normally distributed after log transformation. For data that could not be transformed to a normal distribution the median and interquartile range are shown, data was analysed by the Kruskal-Wallis test and Mann-Whitney tests. Chi-squared tests were used to compare differences in categorical variables by genotype. In all cases a p-value of less than 0.05 was considered statistically significant. Two-sided statistical testing was performed.

Results

Genotype data was available for all subjects. The distribution of genotypes across the sample was not in Hardy-Weinberg equilibrium (GG v GC v CC: 606 v 328 v 77, Χ2= 11.47, p=0.01) with a C allele (rare allele) frequency of 0.24 [0.22-0.26]. There was no difference in ethnic group (Caucasian%) by genotype (GG v GC v CC: 77.7% v 77.7% v 68.8%, p=0.299). A significant proportion of subjects with the CC genotype were seen to have Type 2 diabetes mellitus (GG v GC v CC: 79.5% v 72.2% v 84.2%, p=0.048), with the rare (C) allele frequency of 0.24 for Type 2 diabetes mellitus.

Comparisons between genotypes showed that subjects with the CC genotype had significantly lower levels of HDL-cholesterol (p=0.032), a non-significant borderline association with the presence of CHD (GG v GC v CC: 19.4% v 19.0% v 30.7%, p=0.06) and a significantly higher prevalence of angina (p=0.009) (Table 1), which was still significant after correction for age, sex, diabetes type and HDL-cholesterol (OR 0.43, 95%CI 0.24-0.79). However, genotype was not associated with biochemical markers of oxidative stress including TAOS, OxLDL, OxLDL:LDL or LDL particle size.

Further analysis of combined genotypes showed that the significant prevalence of both CHD and angina was strongest in subjects who were homozygous for the C allele (p=0.024 and p=0.005 respectively) (Table 2), with angina conferring a 2.3 fold increased risk for those carrying two C alleles, and remaining significant after correction for age, sex and CHD (OR 2.26, 95%CI 1.32-3.87).

Discussion

We observed that the CC genotype of the COX-2 -765G>C polymorphism was positively associated with a higher prevalence of Type 2 diabetes mellitus and angina, as well as being associated with lower levels of HDL-cholesterol. HDL-cholesterol has anti-atherogenic, antiinflammatory and antioxidant properties [26] and has been associated with the up-regulation of COX-2 expression and prostacyclin synthesis in endothelial cells [27]. Importantly, HDL-cholesterol plays a role in reverse cholesterol transport from peripheral tissues which are affected by the formation of atherosclerotic plaques.
The efflux of HDL-cholesterol from the macrophage ‘foam’ cells to the liver reduces the amount of cholesterol in the plaque via the cholesterol excretion in bile and faeces [28]. The higher prevalence of CHD and angina seen in the CC genotype may be due to reduced HDL-cholesterol levels, since HDL-cholesterol is effective in countering the formation of these diseases by increasing COX-2 expression within smooth muscle [28,29]. The HDL-cholesterol induced COX-2 expression is directed towards prostacyclin production, a potent vasodilator [29]. Therefore, low HDL-cholesterol levels result in a lower COX-2 expression in the CC genotype which may lead to increased blood pressure and subsequent coronary heart disease manifesting in angina, however this would be more likely be expected of the GG genotype, since endothelial dysfunction is increased with COX-2 activity [5,9].

Prostaglandin E2 is synthesised from prostaglandin H2, the product of the rate limiting reaction catalysed by COX-2 [1], therefore subjects with the CC genotype may not have the capacity to produce prostaglandin E2 at the rate required for the effective negative modulation of insulin secretion in β-cells [12,13].

### Table 1: Baseline characteristics by diabetes type.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Type 1</th>
<th>Type 2</th>
<th>Other1</th>
<th>P-value</th>
</tr>
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<td></td>
<td>(n=176)</td>
<td>(n=783)</td>
<td>(n=52)</td>
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<tr>
<td>Age (yrs)²</td>
<td>48.6 [39-57]</td>
<td>66.1 [58-73]</td>
<td>57.2 [50-62]</td>
<td>&lt;0.001</td>
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<td>Males % (n)</td>
<td>62.4 (108)</td>
<td>62.1 (484)</td>
<td>74.2 (23)</td>
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<tr>
<td>Caucasian % (n)</td>
<td>94.9 (167)</td>
<td>75.0 (587)</td>
<td>48.1 (25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Duration (yrs)²</td>
<td>24.0 [14-33]</td>
<td>9.0 [4-16]</td>
<td>8.0 [3-16]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.9 (5.6)</td>
<td>79.4 (7.1)</td>
<td>75.0 (8.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.1 (1.9)</td>
<td>28.8 (2.3)</td>
<td>25.6 (2.8)</td>
<td>&lt;0.001</td>
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<tr>
<td>SBP (mmHg)²</td>
<td>132 [122-142]</td>
<td>139 [128-152]</td>
<td>135 [127-142]</td>
<td>&lt;0.001</td>
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<td>DBP (mmHg)²</td>
<td>79 [73-85]</td>
<td>80 [73-87]</td>
<td>85 [75-91]</td>
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<td>Cholesterol (mmol/L)³</td>
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<td>4.9 (0.5)</td>
<td>4.9 (0.6)</td>
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<td>LDL-C (mmol/L)³</td>
<td>2.9 [2.3-3.5]</td>
<td>2.7 [2.1-3.3]</td>
<td>2.6 [2.0-3.4]</td>
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<tr>
<td>HDL-C (mmol/L)³</td>
<td>1.7 [1.4-2.1]</td>
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<td>1.2 [1.1-1.4]</td>
<td>&lt;0.001</td>
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<td>Triglyceride (mmol/L)³</td>
<td>1.1 (0.3)</td>
<td>1.9 (0.5)</td>
<td>1.7 (0.4)</td>
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<td>HbA1c (%)</td>
<td>8.1 (0.6)</td>
<td>7.8 (0.7)</td>
<td>8.4 (0.7)</td>
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<td>HbA1c (mmol/mol)³</td>
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<td>61 (7.9)</td>
<td>68 (7.7)</td>
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<td>Glucose (mmol/L)³</td>
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<td>10.6 (2.6)</td>
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<td>ACR²</td>
<td>1.2 [0.0-2.9]</td>
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<td>1.2 [0.0-3.4]</td>
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<td>CHD % (n)</td>
<td>4.0 (7)</td>
<td>24.3 (189)</td>
<td>6.5 (2)</td>
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<td>Angina % (n)</td>
<td>2.9 (5)</td>
<td>19.2 (149)</td>
<td>3.2 (1)</td>
<td>&lt;0.001</td>
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Mean and standard deviation shown for normally distributed data. *Log transformed data shown by geometric mean and approximate standard deviation (analysis performed by Kruskal-Wallis). Categorical data was analyzed using chi-squared. 1Other includes pancreatic diabetes and cases with no recorded diabetes status.

Excessive insulin signalling is thought to contribute to the development of insulin resistance in Type 2 diabetes mellitus [30]. Circulating insulin and prostaglandin E2 were not recorded in this study, however this relationship may explain the association between patients with the CC genotype and Type 2 diabetes mellitus. Prostaglandin E2 prevents pancreatic islet β-cell dysfunction caused by interleukin-1β, therefore in the absence of COX-2 expression, interleukin-1β which is pro-inflammatory can cause β-cell dysfunction leading to the inflammation driven development of Type 2 diabetes mellitus. This model agrees with many pieces of data concerning inflammation as a causative factor in the pathogenesis of diabetes.

In summary, we observed a higher prevalence of Type 2 diabetes mellitus in those with the CC genotype, possibly as a result of a limited production of prostaglandin E2. Additionally, there was a significant association with an increased incidence of angina and a borderline association with coronary heart disease. Higher HDL-cholesterol levels have been reported to be preventative in diseases related to the formation of atherosclerotic plaques [28], this is supported by the significantly lower levels of HDL-cholesterol combined with higher incidences of angina and CHD seen in our CC genotype subjects. However, no COX-2 mediated changes in HDL-cholesterol have been described in the literature. Researching the possibility of COX-2
mediated changes in HDL-cholesterol or other lipoproteins may help elucidate the over physiological role of COX-2 and maybe aid in identifying drug targets to aid in the prevention of atherosclerosis.

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<th>CC</th>
<th>P</th>
<th>GG</th>
<th>GC/CC</th>
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<td>19.4 (114)</td>
<td>19.0 (61)</td>
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</tbody>
</table>

Mean and standard deviation shown for normally distributed data. #Median and interquartile range shown for data that was not normally distributed even after log transformation. Analysis performed by ANOVA for normally distributed data and by Kruskal-Wallis non-normally distributed data. χ²-test was used to compare groups. P-values<0.05 are considered to be statistically significant and are in bold.

Table 2: Baseline differences by combined -765G>C promoter variant.

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