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Association of PPARγ Allelic Variation, osteoprotegerin and abdominal aortic aneurysm

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Abstract

Objective—We have previously demonstrated high concentrations of the glycoprotein osteoprotegerin (OPG) in biopsies of abdominal aortic aneurysm (AAA) and demonstrated that ligation of the nuclear receptor peroxisome proliferator-activated receptor gamma (PPARγ) downregulates OPG *in vitro* and within a mouse model. The aims of this study were to assess the associations between circulating concentrations of OPG, polymorphisms of the gene encoding PPARγ (PPARG), AAA presence and growth.

Design, patients and measurements—Two genetic polymorphisms in PPARG were assessed in 4227 men, 699 of whom had an AAA. For 631 men, who had AAAs, maximum aortic diameter was monitored by yearly ultrasound for a median of 5 years. Plasma OPG was measured in 838 men, 318 of whom had an AAA.

Results—Plasma concentrations of OPG were independently associated with AAA (adjusted odds ratio 1.38, 95% CI 1.10–1.72). The PPARG c.1347C>T polymorphism was associated with plasma concentrations of OPG (beta 0.12, p<0.01). The PPARG c.34G>C polymorphism was weakly associated with AAA (adjusted odds ratio 1.28, 95% CI 1.01–1.61). PPARG c.1347C>T was associated with increased AAA growth (recessive model, p=0.03).

Conclusions—Circulating concentrations of OPG are associated with AAA and with one PPARG polymorphism. PPARG polymorphisms are weakly associated with AAA presence and growth. Confirmation of these findings is required in other cohorts.

Keywords

Abdominal aortic aneurysm; peroxisome proliferator-activated receptor-gamma; genetic polymorphism; osteoprotegerin

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Introduction

Abdominal aortic aneurysm (AAA) is an important cause of mortality and a better understanding of the pathogenesis of this condition is required in order to improve management [1]. We have previously reported high concentrations of the glycoprotein osteoprotegerin (OPG) in human AAA biopsies and an association between serum concentrations of OPG and AAA progression in a series of 146 men [2]. In addition, *in vitro* OPG induces development of an aneurysm phenotype in normal aortic vascular smooth muscle cells by inhibiting proliferation, promoting apoptosis and stimulating metalloproteinase production, which are all features of human AAA pathology [2]. In a recent report, we demonstrated that thiazolidinedione medication reduced OPG expression in both the aorta of a mouse model of AAA and human AAA biopsies in explant culture [3]. The target receptor for thiazolidinediones family is peroxisome proliferator-activated receptor gamma (PPARγ) [4]. Ligation of PPARγ leads to a number of effects of potential value in antagonising AAA development and progression, such as inhibiting expression of adhesion molecules, cytokine release and proteolysis [4–7].

In humans four isoforms of PPARγ have been identified. PPARγ1 and 2 are produced from a single gene by alternative splicing, PPARγ2 has 30 additional amino acids at its N terminus encoded by exon B [8]. The function of the two isoforms varies e.g. the ligand independent activation domain of PPARγ2 is 6-fold more responsive than that of PPARγ1 [9]. A number of groups have recently identified a mutation in the PPARγ gene (PPARG) that specifically affects the form and expression of PPARγ2 [10–12]. The single nucleotide polymorphism (SNP) G to C variation at position +34 (relative to translation initiation site) occurs in the PPARγ2 specific exon B (PPARG c.34G>C, reference sequence NM_015869, refSNP ID: rs1801282) [13]. When translated the resultant PPARγ2 protein is modified at position 12 with an alanine substituting a proline residue (The SNP is also known as Pro12Ala) [10]. This is a common mutation in PPARG, with the less common Ala12 allele present in 23% of Hispanics and 12% of Caucasians [11]. The Ala12 allele has been associated with increased expression of PPARγ2 in adipose tissue in men, in addition to altered incidence of diabetes [10,12]. Another frequently occurring PPARG polymorphism has been identified in exon 6 at nucleotide 1431 of PPARγ2 resulting in a silent substitution from C to T (PPARG c.1347C>T, reference sequence NM_138712, refSNP ID: rs3856806) [14].

Based on our previously demonstrated association between aortic concentrations of OPG and AAA, along with the known influence of PPARγ on OPG we postulated a relationship between PPARγ SNPs, OPG and human AAA [2,3]. We examined the association of 2 PPARG SNPs, plasma OPG concentrations and AAA.

Methods

Study Design

The aims of this study were 1) to determine if plasma OPG concentration was associated with PPARG SNPs; 2) to examine whether plasma OPG concentrations were associated with AAA presence; 3) to assess whether PPARG SNPs were associated with AAA presence and 4) AAA growth. For aim 3, DNA was genotyped from 4227 subjects from the Health in Men Study (HIMS) of whom 689 had an AAA (maximum aortic diameter ≥30 mm) and 3538 did not (maximum aortic diameter <30 mm). Of the men with AAAs, 631 underwent yearly ultrasound monitoring of the maximum aortic diameter for a median of 5 years (inter-quartile range 2.5–6 years) and were utilised for aim 4. For aims one and 2 plasma OPG was measured in 318 men with an AAA for whom stored blood samples were available and 518

randomly selected subjects who did not have an AAA. The study was approved by the relevant ethics committees, and informed consent was obtained from participating patients.

Patients and clinical definitions

HIMS is a study of men aged ≥65 years who originally participated in a population-based randomised controlled trial of screening for AAA. Details of the design of these studies, including definitions of clinical risk factors, have been reported previously [15–17].

Plasma Analysis

Blood was collected from subjects after an overnight fast as previously described [15–17]. Plasma was stored at −80°C until later batch assessment of OPG concentrations using ELISA according to manufacturer's instructions and expressed as μg/L (R&D Systems). This assay was selected as a previous study demonstrated excellent recovery, intra- and inter-assay reproducibility in our laboratory [18].

Genotyping

Genotyping for both PPARG c.34G>C (Pro12Ala, reference sequence NM_015869, refSNP ID: rs1801282) and PPARG c.1347C>T (reference sequence NM_138712, refSNP ID: rs3856806) was performed using real-time quantitative polymerase chain reaction (PCR) utilizing custom TaqMan probes as described previously [17]. No errors were found in duplicate analysis of 5% of the samples.

Statistical Analysis

Univariate comparisons between men who did and did not have an AAA were performed using Mann Whitney U tests and chi-squared test. Allelic variations were tested for deviations from Hardy-Weinberg equilibrium using an exact Markov-Chain Monte Carlo (MCMC) test [19]. Using the software package SimHap vBeta2.1, the associations between genotypes and PPARγ haplotypes with AAA presence were examined using a Generalized Linear Model framework accounting for co-variates [20]. Linkage disequilibrium (LD) between allelic variants as measured by the D' and r^2 metric were assessed using the Bayesian-MCMC framework implemented in Phase v2.1.1 [21]. The associations between genotype with plasma concentrations of OPG were assessed using Kruskal Wallis test and linear regression analysis to adjust for other potential determinants. The association between plasma OPG and AAA presence was examined using logistic regression adjusting for other risk factors. Increase in aortic diameter per year was calculated taking into account all readings carried out. The association of PPARG genotypes with AAA growth was assessed using linear regression fitted by ordinary least squares, adjusted for initial aortic size, diabetes, peripheral artery disease, coronary heart disease (CHD), smoking and hypertension. All possible two-way interactions were included in the initial model. The Box-Cox method was used to determine the best transformation for the response, which was found to be the cubic root; and permutation tests were used to determine statistical significance. The final "best fit" model to predict AAA growth was selected using a stepwise algorithm comparing the Akaike Information Criterion values of the candidate models.

Results

Plasma OPG, PPARG genotype and AAA presence

We assessed PPARG c.34G>C and PPARG c.1347C>T polymorphisms in a total of 4204 men for whom DNA was available. Genotyping failed for PPARG c.34G>C and PPARG c. 1347C>T in 37 (1%) and 117 (3%) subjects, respectively. We measured plasma OPG in a

subset of 836 of these men (20%). The characteristics of these subjects are shown in Table 1. Both SNPs were in Hardy-Weinberg equilibrium within control subjects. The overall frequency of rare alleles for PPARG c.34G>C and PPARG c.1347C>T were 12.0 and 13.4%, respectively. On univariate analysis plasma OPG was associated with PPARG c.1347C>T but not PPARG c.34G>C (Table 2). Men homozygous for the minor PPARG c.1347C>T allele had higher plasma OPG concentrations compared to subjects with at least one common allele after adjusting for other risk factors (Table 3). Plasma OPG was higher in men with aortic dilatation (Table 1) and independently associated with AAA, after adjusting for other risk factors (odds ratio 1.38, 95% confidence intervals, CI, 1.10–1.72, per ng/ml, p=0.005).

PPARG allelic variation and AAA presence

The C allele of the PPARG c.34G>C SNP was marginally more common in men with AAA assuming a dominant model (Table 2). The frequency of GC and CC genotypes combined was 26 and 22% for AAA and controls, respectively (Odds ratio, OR 1.22, 95%CI 1.01–1.48). In multivariate analyses adjusting for other AAA risk factors (coronary heart disease, dyslipidaemia, smoking, hypertension, diabetes, waist to hip ratio and age) the C allele of the PPARG c.34G>C SNP remained weakly associated with AAA (OR 1.28, 95%CI 1.01–1.61). The T allele of the PPARG c.1347C>T SNP was also more common in subjects with AAA assuming a dominant model. The frequency of CT and TT genotypes combined was 29 and 25% for AAA and controls, respectively (OR 1.25, 95%CI 1.04–1.50). After adjusting for other AAA risk factors the T allele of the PPARG c.1347C>T SNP was of borderline significance (OR 1.25, 95%CI 0.99–1.56). Neither SNP was associated with AAA when recessive models were used. The D' and r^2 as estimates of linkage disequilibrium between SNPs were 0.70 and 0.43, respectively.

PPARG allelic variation and AAA growth

The mean aortic diameters in men with the GG (n=471), GC (n=146) and CC (n=11) genotypes of PPARG c.34G>C and the CC (n=430), CT (n=161) and TT (n=13) genotypes of PPARG c.1347C>T were 35.0±5.4, 34.5±4.9 and 34.3±4.4; and 35.2±5.4, 34.0±4.6 and 35.1±5.7mm, respectively. The mean annual increase in aortic diameters in men with the GG, GC and CC genotypes of PPARG c.34G>C and the CC, CT and TT genotypes of PPARG c.1347C>T were 1.5±1.8, 1.6±1.5 and 1.8±1.8; and 1.6±1.9, 1.4±1.4 and 2.5±1.7mm, respectively. Using univariate analysis and a recessive model the PPARG c.1347C>T SNP was mildly associated with AAA: Mean AAA growth for the patients' who had the T allele was 2.5±1.7 (n=13) and that for those with the C allele was 1.5±1.7, p=0.05. The best fitting model of AAA growth explained nearly 21% of the variation in aortic diameter (R^2=20.5). Larger initial aortic diameter and absence of diabetes were associated with more rapid aortic expansion, as previously described. After adjusting for other determinants of AAA progression PPARG c.1347C>T was associated with AAA growth using a recessive model (Table 4). Subjects with the TT genotype had significantly faster AAA progression after adjusting for other risk factors (Table 4). PPARG c.34G>C was not selected for the final "best fit" model, and therefore it was not associated with AAA progression (Table 4).

Discussion

A large body of evidence now associates the glycoprotein OPG with cardiovascular disease in humans. Circulating and local OPG concentrations are associated with the presence of coronary and peripheral artery disease and the development of new cardiovascular events independent of traditional risk factors [24,25]. Previous work by our group demonstrated that the expression of OPG was greater in biopsies of human AAA compared to those from

aortic occlusive disease, OPG induced important functional changes in VSMC and monocytes *in vitro*, and that circulating serum OPG were associated with AAA expansion in a small cohort [2]. In the current study we demonstrate for the first time to our knowledge that plasma concentrations of OPG are independently associated with AAA, after adjusting for other risk factors including coronary heart disease. These findings suggest OPG may be a useful biomarker for AAA, comparable to others we have identified, such as osteopontin and resistin [16,26]. A direct causative role of OPG in cardiovascular disease, including AAA, is currently controversial since animal studies carried out to date have not clearly demonstrated a role for OPG in vascular pathology [27,28].

In keeping with a previous study we found that a genetic polymorphism in PPARG was associated with circulating concentrations of OPG [29]. Unlike the previous report however we associated PPARG c.1347C>T rather than c.34G>C with circulating OPG [29]. In the study of Rhee and colleagues the serum concentration of OPG was significantly reduced in subjects with the C allele. A major difference however between the Korean study and the present study is the fact that the former examined a cohort of 125 postmenopausal and 114 premenopausal women. Whether the influence of the PPARG SNPs varies in different sexes and whether this plays a role in the male preponderance for AAA remains to be clearly defined. These findings are suggestive of the ability of the transcription factor PPARγ to control OPG production but confirmation is required in other cohorts since the effect size identified in the current study is small [3].

Based on our initial observation of an interaction between OPG and PPARγ, we examined 2 PPARG SNPs in relation to AAA presence in a large cohort of men aged ≥65 years. We found a weak independent association between PPARG c.34G>C and AAA presence. A borderline association between PPARG c.1347C>T and AAA presence was also found, but this may reflect the linkage disequilibrium between these two SNPs which we have previously reported [17]. We also found a weak association between PPARG c.1347C>T and AAA progression, with patients with the rare TT genotype having faster AAA progression. The latter finding is in keeping with the T allele being slightly more common in patients with AAAs than controls and plasma OPG concentrations being higher in subjects with the TT genotype. Thus it is possible that this association of PPARG with AAA presence and growth reflects the ability of PPARG to modify OPG levels.

The pathogenesis of AAA is multi-factorial and therefore any SNPs associated with disease development would only be expected to play a small role. Thus the size of effect demonstrated for PPARG c.34G>C is in keeping with a possible minor role in AAA development in combination with other environmental risk factors. Our study needs to be considered in light of a number of limitations. We only assessed two SNPs within the PPARG gene. Our choice was determined by the likely functional significance and frequency of these SNPs. It is possible if we had more fully assessed polymorphisms in PPARG we might have identified a stronger association with AAA.

In conclusion this study further supports the association of OPG, PPARγ and AAA. Further studies involving animal models and other human cohorts will be required to further assess this association.

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Table 1

Comparison of patients with and without AAA undergoing plasma OPG measurements.

Characteristic	AAA	No AAA	P value
Number	318	518	
Aortic diameter (mm)	33.2 (31.0–37.5)	20.9 (20.0–21.6)	<0.001
Age (years)	71.9 (68.8–74.9)	70.3 (68.2–73.7)	<0.001
Hypertension	160 (50%)	184 (36%)	<0.001
Diabetes mellitus	32 (10%)	41 (8%)	0.29
Dyslipidaemia	157 (49%)	178 (34%)	<0.001
Ever smoker	267 (84%)	325 (63%)	<0.001
CHD	121 (38%)	82 (16%)	<0.001
WHR	0.97 (0.93–1.01)	0.95 (0.91–0.99)	<0.001
OPG (μg/L)	1.42 (0.97–2.05)	1.13 (0.77–1.67)	<0.001
Creatinine (μM)	94 (81–112)	87 (78–99)	<0.001

Nominal variables are presented as numbers and continuous variables as median (inter-quartile range). Statistical comparisons are by chi-squared test or Mann Whitney U test. CHD= Coronary heart disease; WHR=Waist to hip ratio; OPG= osteoprotegerin.

Table 2

PPARG genotypes in relation to AAA and plasma OPG.

	PPARG c.34G>C			**PPARG c.1347C>T**		
	GG	**GC**	**CC**	**CC**	**CT**	**TT**
AAA	499 (74%)	161 (24%)	12 (2%)	476 (71%)	179 (27%)	13 (2%)
No AAA	2733 (78%)	708 (20%)	54 (2%)	2584 (76%)	782 (23%)	53 (2%)
Total*	3232	869	66	3060	961	66
Plasma OPG (μg/L)	1.21 (0.84–1.80) n=629	1.33 (0.87–1.82) n=184	1.15 (0.87–2.55) n=16	1.21 (0.84–1.75) n=611	1.34 (0.87–1.87) n=207	2.09 (1.02–3.34) n=13†

Shown are numbers (percentages) or median (inter-quartile range).

*Genotyping failed for PPARG c.34G>C and PPARG c.1347C>T in 37 and 117 subjects, respectively.

†Plasma OPG was related to PPARG c.1347C>T genotype, p=0.04 on Kruskal Wallis test.

Table 3

Linear regression model relating plasma OPG to PPARG c. 1347C>T and other risk factors.

Predictors	Standardized Coefficients		
	Beta	**t**	***P***
Age	0.381	11.67	<0.01
Coronary heart disease	−0.008	−0.24	0.81
Ever smoker	0.000	0.01	0.99
Dyslipidaemia	−0.040	−1.13	0.26
Diabetes	−0.017	−0.53	0.60
Hypertension	0.009	0.25	0.80
PPARG c.1347C>T	0.116	3.60	<0.01
Waist to hip ratio	−0.008	−0.25	0.80

Table 4

Association between PPPARG c.1347C>T and AAA growth.

	Estimate	P
Intercept	2.404	<0.001
Initial aortic diameter (IAD)	0.025	0.001
Diabetes (Yes)	−0.120	0.001
*PPARG c.1347C>T (TT)	0.195	0.034
Peripheral artery disease (PAD; Yes)	−0.005	0.888
Smoking (Yes)	0.025	0.456
Hypertension (Yes)	−0.002	0.251

* Calculated using a recessive model. The model also considered interactions between PPARG c.1347 (TT) and PAD; interaction between IAD and hypertension; and interactions between smoking and hypertension.