International Journal of Cardiology 167 (2013) 1159–1163

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Increased serum angiopoietin-2 is associated with abdominal aortic aneurysm prevalence and cardiovascular mortality in older men ☆

Jonathan Golledge [a,*], Paula Clancy [a], Bu B. Yeap [b,c], Graeme J. Hankey [b], Paul E. Norman [d]

[a] Vascular Biology Unit, School of Medicine and Dentistry, James Cook University, Townsville, Australia
[b] School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia, Australia
[c] Department of Endocrinology and Diabetes, Fremantle Hospital, Fremantle, Western Australia, Australia
[d] School of Surgery, University of Western Australia, Perth, Australia

ARTICLE INFO

Article history:
Received 13 December 2011
Received in revised form 8 February 2012
Accepted 10 March 2012
Available online 6 April 2012

Keywords:
Abdominal aortic aneurysm
Angiopoietin-2
Cardiovascular deaths

ABSTRACT

Background: Angiopoietin-2 (Angpt2) has been implicated in the mediation and regulation of angiogenesis and inflammation which are believed to be critical mechanisms in the pathogenesis of both abdominal aortic aneurysm (AAA) and cardiovascular events. The aim of this study was to assess whether serum Angpt2 was associated with the prevalence of AAA and the occurrence of cardiovascular mortality in older men.
Methods: A cohort of 997 elderly men was recruited in 1996–99. Aortic ultrasound identified an AAA in 308 (31%). In 2001–04, blood was collected and serum Angpt2 later measured by immunoassay. The association of Angpt2 with AAA was assessed using multiple regression analysis. All men were followed by means of the Western Australia Data Linkage System until July 31st 2009. The association of Angpt2 with cardiovascular mortality was assessed using Cox proportional hazard analysis.
Results: Median serum Angpt2 was significantly higher (3.16 ng/ml, inter-quartile range 2.51–4.54) in men with AAA compared with men without AAA (2.70 ng/ml, inter-quartile range 2.03–3.72; $p<0.001$). After adjusting for cardiovascular risk factors, men with serum Angpt2 in the highest quartile (>3.95 ng/ml) had a 2.57-fold (95% CI 1.66–3.97, $p<0.001$) increased odds of AAA and a 4.12-fold (95% CI 1.90–8.94, $p<0.001$) increased relative risk of cardiovascular mortality compared to men with serum Angpt2 in the lowest quartile (<2.13 ng/ml).
Conclusions: Serum Angpt2 is elevated in men with AAA and associated with an increased risk of cardiovascular mortality in older men.

© 2012 Elsevier Ireland Ltd. All rights reserved.

1. Introduction

Angiopoietin-2 (Angpt2) is a member of a family of proteins implicated in the control of blood vessel formation during early and adult life [1]. Angpt2 is produced by a range of cell types present in both healthy and diseased blood vessels, including endothelial cells, vascular smooth muscle cells and monocyte/ macrophages [2–4]. Angpt2 has been implicated as a mediator of angiogenesis, arteriogenesis and inflammation [4–7], and reported to be highly expressed in samples removed from human atherosclerotic arteries [8].

Although increased circulating concentrations of Angpt2 have been associated with various types of cancers and their prognosis, the association of Angpt2 with vascular diseases has received relatively little attention [9–19]. Increased Angpt2 concentrations have been reported in patients with pulmonary hypertension [15], critical limb ischemia [16], acute coronary syndrome [17] and cardiac failure [18], but results have been conflicting [18,19]. Increased serum Angpt2 has also been associated with an increased risk of myocardial infarction in one study of patients with hypertension [14].

Abdominal aortic aneurysm (AAA) is an important cause of mortality in older adults [20], either directly because of aortic rupture or indirectly due to associated coronary or cerebrovascular athero-thrombosis causing myocardial infarction and stroke [21,22]. Animal and human studies have implicated angiogenesis in the pathogenesis of AAA [23–25] but the epidemiological relationship between Angpt2 and AAA is unknown. The aims of the current study were to determine whether increased serum concentrations of Angpt2 was independently and significantly associated with the prevalence of AAA and the occurrence of cardiovascular mortality in a group of older men.

2. Methods

2.1. Patients

Subjects were recruited from the Health in Men Study (HIMS) which has been described in detail previously [26]. This cohort comprises men who took part in a trial of ultrasound screening for AAA in 1996–99, of whom a sub-set returned in 2001–4 for

☆ Funding from the Queensland Government and National Health and Medical Research Council (540405) supported this work. JG and PEN hold Practitioner Fellowships from the National Health and Medical Research Council, Australia (431503 and 435805). JG holds a Senior Clinical Research Fellowship from the Queensland Government.

* Corresponding author at: The Vascular Biology Unit, Department of Surgery, School of Medicine and Dentistry, James Cook University Townsville, QLD, Australia 4811. Tel.: +61 7 4796 1417; fax +61 7 4796 1401.
E-mail address: jonathan.golledge@jcu.edu.au (J. Golledge).

0167-5273/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijcard.2012.03.120

blood sampling. In the current study we included 308 men with AAA (aortic diameter ≥30 mm), and 689 randomly selected men without AAA (diameter <30 mm), for whom serum samples were available. This sample size provided an 80% power (alpha 0.05) to detect approximately 25% higher concentrations of Angpt2 in subjects with AAA and those dying of cardiovascular causes, based on previously reported serum Angpt2 concentrations in a similar cohorts [14,15,17]. Ethics approval was granted from the Human Research Ethics Committee at the University of Western Australia and all study participants gave their written informed consent.

2.2. Risk factors

Men completed questionnaires, designed to assess past medical history and treatment, at the time of blood sampling; and a nurse measured blood pressure as well as weight, height, and waist and hip circumference in accordance with guidelines of the International Society for the Advancement of Kinanthropometry [27]. Diabetes and hypertension were defined by a history of diagnosis or treatment of diabetes or hypertension. Coronary heart disease (CHD) was defined by a history of myocardial infarction, angina or treatment for coronary artery disease. Previous stroke was defined by a previous history of any stroke. Smoking was defined by history as ever having smoked regularly or never having smoked regularly. Current prescription of aspirin and statin medication was noted.

2.3. Aortic imaging

Aortic ultrasound was performed during the recruitment of the men in the period 1996–99, as previously described [26]. The greatest diameter of the infrarenal aorta was measured using a Toshiba Capasee ultrasound machine with a 3.75 MHz probe (Toshiba Australia, North Ryde, NSW). The reproducibility of the ultrasound measurements has been previously reported with 95% of differences in each of the anteroposterior and transverse diameters being <3 mm [28].

2.4. Blood assays

Blood was collected between 2001 and 2004 and serum isolated and stored at −80 °C. Serum Angpt2 was measured with a commercial assay (R&D Systems, Minneapolis, USA) by an experienced scientist unaware of the AAA status or outcomes of the subjects. The inter-assay coefficient of variation was <5%. Serum creatinine was measured by an automated assay as previously described [26]. Serum C-reactive protein (CRP) was measured by a high-sensitivity assay, with the use of the particle-enhanced immunonephelometry system on the BNII analyser as previously described [28]. The inter-assay coefficient of variation was 4–7%. Serum low density lipoprotein (LDL) and high density lipoprotein (HDL) concentrations were analyzed using automated assays, as previously described (Hitachi 917, Roche Diagnostics GmBH, Mannheim, Germany) [29]. The interassay coefficient of variation for these assays was between 2.1% and 4.8%.

2.5. Follow-up

All men were followed from the time of recruitment until 31st July 2009 by means of the Western Australian Data Linkage System. The Western Australian Data Linkage System provides electronic linkage to the state's death, hospital, and cancer registries, including data for admissions to all hospitals in the state since 1970 [30]. For hospital morbidity the Western Australian Data Linkage System linkage based on ICD-10 or equivalent coding has comparable accuracy to adjudication of medical records [31].

2.6. Outcome assessment

Primary cause of death was ascertained via the Western Australian Data Linkage System, which contains both the original death certificate, and an ICD-10 coded record generated from this data and other sources by the Australian Bureau of Statistics. This dataset has been found to be robust and informative [32,33]. Deaths due to cardiovascular diseases were identified using ICD-10 codes in the ranges I00-I99. Deaths secondary to cardiac causes were identified using ICD-10 codes in the ranges I20-I25 and I30-I52.

2.7. Statistical analyses

Quantitative data were not normally distributed (as assessed by Kolmogorov-Smirnov and Shapiro-Wilk tests) and therefore were presented as median and inter-quartile range and compared by Mann Whitney *U* test. Nominal data were presented as number and percentages and compared by chi-squared test. The association of serum Angpt2 with AAA prevalence was assessed using multiple regression analysis adjusting for age, CHD, hypertension, diabetes, smoking, stroke, waist-to-hip ratio (WHR), serum creatinine, serum low and high density lipoprotein, serum CRP, statin and aspirin prescription. The association of serum Angpt2 with mortality was assessed using Kaplan Meier estimates and Cox proportional hazard analysis. Cox proportional hazard analysis was adjusted for age, CHD, hypertension, diabetes, smoking, stroke, AAA, waist-to-hip ratio (WHR), serum creatinine, serum LDL, serum HDL, serum CRP, statin and aspirin prescription. For these analyses, men were grouped on the basis of serum Angpt2 quartiles defined as <2.13, 2.131–2.83, 2.831–3.95 and >3.95 ng/ml. Cumulative mortality was compared between Angpt2 quartile using log rank test.

3. Results

3.1. Association of serum Angpt2 with AAA

Risk factors for AAA are shown in Table 1. Men with AAA (n = 308) were older, and more likely to have a history of CHD, smoking, hypertension, diabetes and stroke. Men with AAA were more commonly prescribed statins and had a greater WHR, higher serum creatinine, higher serum CRP, lower serum LDL and lower serum HDL as previously reported [27,29,34]. Median (inter-quartile range) serum Angpt2 was 3.16 (2.51–4.54) and 2.70 ng/ml (2.03–3.72) in men with and without AAA, respectively, $p<0.001$. Serum Angpt2 was associated with AAA in a positive and graded fashion after adjusting for other risk factors (Table 2). Men with serum Angpt2 in the highest quartile had a 2.57-fold increased risk of AAA (95% confidence intervals, CI, 1.66–3.97) compared to subjects with serum Angpt2 in the lowest quartile.

3.2. Association of serum Angpt2 with mortality

Median follow-up for survivors was 5.9 years (range 5–8 years). A total of 204 deaths occurred during follow-up, of which 84 were due to cardiovascular causes. Most of the cardiovascular deaths were cardiac related (n = 71, 85%) and only 2 (2%) related to AAA rupture or surgery. Fig. 1 illustrates the relationship between serum Angpt2 quartiles and subsequent all cause, cardiovascular and non-cardiovascular mortality. Serum Angpt2 quartile was strongly positively associated with all cause (Fig. 1a) and cardiovascular mortality (Fig. 1b), both $p<0.001$. Serum Angpt2 was not significantly associated with non-cardiovascular mortality, $p=0.172$ (Fig. 1c). Over the subsequent 5 years men with serum Angpt2 in the first, second, third and fourth quartiles had a cumulative incidence of cardiovascular mortality of 3.3, 5.9, 8.5 and 15.5%, respectively, $p<0.001$. Men with serum Angpt2 in the highest quartile had a 4.12-fold (95% CI 1.90–8.94, $p<0.001$) increased risk of cardiovascular mortality after adjusting for other cardiovascular risk factors including AAA (Table 3).

4. Discussion

There were two novel findings from this study. Firstly, serum concentration of Angpt2 was found to be positively associated with AAA. Secondly serum Angpt2 was shown to predict the incidence of cardiovascular mortality in older men.

Table 1
Comparison of subjects with and without AAA undergoing serum Angpt2 measurement.

Characteristic	AAA	No AAA	P value
Number	308	689	
Aortic diameter (mm)	33.4 (31.3–38.0)	21.9 (20.2–23.1)	<0.001
Age (years)	77 (74–80)	76 (74–79)	<0.001
Hypertension	112 (36.4%)	198 (28.7%)	0.016
Diabetes mellitus	53 (17.2%)	71 (10.3%)	0.002
Ever smoker	266 (86.4%)	448 (65.0%)	<0.001
CHD	84 (27.3%)	96 (13.9%)	<0.001
Previous stroke	29 (9.4%)	39 (5.7%)	0.030
WHR	0.97 (0.93–1.01)	0.95 (0.91–0.99)	<0.001
Serum creatinine (μM)	95 (82–115)	89 (78–100)	<0.001
Serum LDL (mM)	2.60 (2.10–3.30)	2.90 (2.30–3.50)	<0.001
Serum HDL (mM)	1.25 (1.10–1.48)	1.40 (1.10–1.60)	<0.001
Serum CRP (mg/L)	2.55 (1.37–5.13)	1.79 (0.96–3.57)	<0.001
Serum Angpt2 (ng/ml)	3.16 (2.51–4.54)	2.70 (2.03–3.72)	<0.001
Aspirin prescription	150 (48.7%)	285 (41.4%)	0.031
Statin prescription	157 (51.0%)	231 (33.5%)	<0.001

Nominal variables are presented as numbers (%) and compared by chi-squared. Continuous variables are presented as median (inter-quartile range) and compared by Mann Whitney *U* test. AAA = Abdominal aortic aneurysm; CHD = Coronary heart disease; WHR = Waist to hip ratio; Angpt2 = Angiopoietin-2; HDL = High density lipoprotein; LDL = Low density lipoprotein; CRP = C-reactive protein.

Download English Version:

https://daneshyari.com/en/article/5975451

Download Persian Version:

https://daneshyari.com/article/5975451

Daneshyari.com