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Original article

Metabolic syndrome in ANCA-associated vasculitis

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Abstract

Objective. The metabolic syndrome (MetS) is a cluster of cardiovascular risk factors and a major cause of morbidity and mortality in the western world. Despite the fact that cardiovascular diseases are a major cause of mortality in patients with ANCA-associated vasculitis (AAV), the relationship between MetS and AAV has not yet been explored. Thus it is the aim of this study to investigate the prevalence of MetS within a cohort of patients with AAV and to assess whether MetS in AAV is associated with a pro-inflammatory state.

Methods. Ninety-one patients with AAV were compared with 89 healthy controls (HCs) in a cross-sectional study. Both groups underwent anthropometric measures and laboratory tests to determine the prevalence of MetS in accordance with the National Cholesterol Education Program Adults Treatment Panel III (NCEP-ATP-III) definitions. Furthermore, the clinical course of AAV was related to the occurrence of MetS.

Results. Within the AAV patient group, 39 (43%) fulfilled the NCEP-ATP-III criteria for MetS compared with 22 (25%) of the controls ($P = 0.012$). This difference in prevalence could not be explained by current or cumulative prednisone use in patients with AAV. Among patients with AAV, the presence of MetS was significantly associated with increased levels of CRP and neopterin. Finally, the relapse rate was higher in patients with MetS as compared with those without MetS.

Conclusion. The prevalence of MetS is significantly increased in AAV. MetS is associated with a more pro-inflammatory state in AAV and might increase the risk of developing a relapse of AAV.

Key words: anti-neutrophil cytoplasmic antibodies, microscopic polyangiitis, vasculitis, granulomatosis with polyangiitis, inflammation, patient attitude to health.

CLINICAL SCIENCE

Introduction

ANCA-associated vasculitis (AAV) is an autoimmune small-vessel vasculitis that is linked to the presence of autoantibodies either directed to PR3 or MPO. It comprises three disease entities: granulomatosis with polyangiitis (GPA), Churg–Strauss syndrome (CSS) and microscopic polyangiitis (MPA) [1]. The clinical presentation is diverse. The upper and lower respiratory airways and the kidneys are commonly involved. Without treatment, the 2-year mortality is 90% [2]. Immunosuppressive therapy reduces mortality significantly. The treatment strategy consists of two phases: during the first phase, remission is induced with cyclophosphamide along with administration of steroids or adjacent therapy; the second phase allows maintenance of remission by other, less toxic immunosuppressive agents like AZA, MTX or MMF [1]. Due to the toxicity of this therapy, patients are exposed to side effects such as infections or increased risk of malignancies. Premature and accelerated atherosclerosis has been demonstrated in patients with AAV and cardiovascular disease is a major cause of mortality in patients with small-vessel vasculitis [3–6]. Next to classical cardiovascular risk factors like diabetes mellitus and hypertension, impaired renal function may cause this increased occurrence of cardiovascular events [5, 6]. Furthermore, activation of the immune system persists in AAV, possibly also increasing the risk of acceleration of the

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atherosclerotic process in these patients [1, 6–9]. Metabolic syndrome (MetS) increases the risk of cardiovascular events in otherwise healthy people [10, 11]. The increased risk of cardiovascular events in MetS is probably due to low-grade inflammation [4–6, 12]. We postulated that the increase in cardiovascular risk in AAV may be at least partly explained by the increased occurrence of MetS. Therefore we examined the prevalence of MetS within our cohort of AAV patients. Secondly, we determined the impact of MetS on the clinical course of AAV and on immune parameters.

Methods

Study participants

The prevalence of MetS within AAV patients and controls was determined in a cross-sectional study design. A total of 93 consecutive AAV patients visiting the outpatient clinic of Maastricht University Medical Center (MUMC) were recruited. Anthropometric measures for weight, height, blood pressure and waist circumference were performed. Furthermore, participants were interviewed regarding medication, medical history and smoking habits. Patient charts were reviewed to obtain information about relapses and prednisone use. After having received induction therapy according to our standard protocol [13], patients received maintenance therapy consisting of AZA, or when intolerant to AZA, MMF or MTX. Maintenance therapy was given for 2 years. Relapses were defined as recurrence of vasculitic disease activity [14] requiring reinstitution or increases of immunosuppressive therapy in combination with prednisone doses of 40–60 mg/day.

Eligible subjects were patients aged >18 years who met the ACR and Chapel Hill classification criteria [15–17]. Patients were classified according to Watt's algorithm for GPA, CSS or MPA [18]. Exclusion criteria were daily use of >10 mg prednisone at the time of inclusion, active disease or malignancy. Two patients of a total of 93 recruited patients were excluded because they did not meet the inclusion criteria. Ninety-one consecutive patients met the inclusion criteria and were examined for the presence or absence of MetS using the National Cholesterol Education Program Adults Treatment Panel III (NCEP-ATP-III) definitions (Table 1) [19, 20]. Partners or relatives of the patients were enrolled as healthy controls. A total of 99 controls also underwent anthropometric measures, blood analysis and the interview. Exclusion criteria were age <18 years, infections, a history of autoimmune disease or malignancy. Also, in control subjects, the prevalence of MetS was determined. The study was approved by the local medical ethical commission (Medisch Ethische Commissie azM/UM) with all participants providing written informed consent prior to enrolment.

Outcome parameters

MetS was determined using the NCEP-ATP-III criteria, which define MetS as fulfilment of three or more of the following conditions: hypertension, central obesity, high glucose levels, low high-density lipoprotein (HDL) cholesterol levels and high triglyceride levels (Table 1). For Asian participants, waist circumference cut-off values were corrected [21].

Blood pressure was measured on the left and on the right arm. Mean values were calculated. In the case of the AAV patients, the mean value was compared with the last measurements during outpatient controls. The average was corrected by calculating the average of the last three outpatient visits. Furthermore, the waist circumference was measured in between the level of the arcus costalis and the level of the spinae iliaca anterior superior [22]. Fasting blood levels for glucose, triglycerides, total cholesterol, low-density lipoprotein (LDL) cholesterol and HDL cholesterol were determined. ANCA, CRP and neopterin levels were also measured [23, 24]. Drug treatment of each participant was defined as the use of drugs needed to control hypertension, high glucose levels and/or elevated cholesterol levels.

Persistency of ANCA positivity was defined as having positive ANCA titres throughout the period of our study, with a maximum of two consecutive intervals of ANCA-negative titres [25]. The period of the study concerned a total period of 21 months, with a range of ANCA titre follow-up of 6–21 months (median 13.8 months).

Disease stages were defined as previously published by Stone [26]. Briefly, limited disease was defined as vasculitis that does not 'pose immediate threats to either a critical individual organ or to the patient's life' [26]. Patients not meeting the criteria of limited disease were defined as having severe disease [26].

Table 1 NCEP-ATP-III 2005 criteria for MetS[a]

Condition	Definition
Hypertension	⩾130/85 mmHg (or drug treatment for hypertension)
Central obesity	Men: waist ⩾102 cm[b] [11]; women: waist ⩾88 cm[b]
Glucose	⩾5.6 mmol/l (or drug treatment for elevated blood glucose)
HDL cholesterol	Men: <1.0 mmol/l; women: <1.3 mmol/l (or drug treatment for low HDL cholesterol)
Triglycerides	⩾1.7 mmol/l (or drug treatment for elevated triglycerides)

[a]Any three or more factors. [b]In Asian patients, waist ⩾90 cm (men) or ⩾80 cm (women). The definitions summarized in this table were taken from [19].

Statistical analysis

The Mann–Whitney U-test or the Fisher's exact test were used to compare two independent groups. The data were non-normally distributed. $P < 0.05$ was considered significant. Data are given as median and interquartile range. SPSS 17 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Basic cohort characteristics and cardiovascular risk factors

A total of 91 AAV patients and 89 HCs were included in this study. Of these 91 AAV patients, 75 were classified as GPA, 9 as CSS and 7 as MPA. Within the HC group, 10 of 99 subjects were excluded due to missing laboratory results (withdrawal due to personal reasons). The cohort characteristics are summarized in Table 2.

The median age was similar between the AAV cohort [58 (45–62) years] and the healthy controls [58 (55–61) years], $P = 0.11$. There was also no significant difference between the groups regarding gender.

Levels of LDL cholesterol, triglycerides and glucose were similar within both groups. HDL cholesterol levels were higher in AAV patients compared with controls (Table 2). Patients with AAV and healthy controls did not differ regarding smoking and/or BMI (Table 2).

MetS is more prevalent in AAV than in controls or in the general population

The NCEP-ATP-III criteria were compared between AAV patients and controls (Table 3). The waist circumference was significantly higher in AAV, with 58 of 91 AAV patients (64%) *vs* 35 of 89 controls (39%) having an increased waist circumference ($P = 0.002$). Moreover, hypertension (60/91) was more prevalent in AAV than in HC (43/89) ($P = 0.02$). There was no significant difference regarding low HDL cholesterol, elevated triglyceride level or elevated glucose levels (Table 3). Treatment for either

Table 3 MetS criteria met by AAV patients and HCs

NCEP-ATP-III criteria	AAV patients ($n = 91$)	Controls ($n = 89$)	*P*-value
Increased waist circumference, %	64	39	0.002
Hypertension, %	66	48	0.02
Low HDL, %	35	42	0.44
Elevated triglycerides, %	36	37	1.00
Elevated glucose, %	31	30	1.00
Drug treatment, %[a]	26	22	0.60
MetS, %	43 ($n = 39$)	25 ($n = 22$)	0.012

[a]Drug treatment for hypertension, diabetes mellitus and/or hypercholesterolaemia.

Table 4 Drug treatment at time of inclusion

Drug treatment	AAV patients ($n = 91$)	Controls ($n = 89$)	*P*-value
Antihypertensive drugs, %	8 ($n = 7$)	16 ($n = 14$)	0.11
Statins, %	16 ($n = 15$)	15 ($n = 13$)	0.84
Glucose lowering drugs, %	9 ($n = 8$)	3 ($n = 3$)	0.21

Table 2 Cohort characteristics

Characteristic	AAV patients ($n = 91$)	Controls ($n = 89$)	*P*-value
Demographics			
Age, median (IQR), years	58 (45–62)	58 (50–68)	0.11
Women, %	51	48	0.77
Men, %	49	52	
Caucasian, %	98	91	0.06
AAV: disease features			
Limited disease, *n* (%) [26]	23 (25)		
Severe disease, *n* (%) [26]	68 (75)		
Renal vasculitis, *n* (%)	40 (44)		
Lipids and glucose			
Cholesterol, median (IQR), mmol/l	5.88 (4.87–6.60)	5.20 (4.70–6.40)	0.07
LDL, median (IQR), mmol/l	3.70 (2.80–4.30)	3.30 (2.80–4.10)	0.10
HDL, median (IQR), mmol/l	1.49 (1.10–1.76)	1.20 (1.00–1.60)	0.02
Triglycerides, median (IQR), mmol/l	1.52 (1.10–2.11)	1.40 (0.90–2.17)	0.29
Glucose, median (IQR), mmol/l	5.10 (4.80–5.70)	5.30 (5.00–5.60)	0.30
Other cardiovascular risk factors			
Smoking, %	8	16	0.11
BMI, median (IQR), kg/m^2	26.57 (23.23–29.41)	25.51 (23.62–28.71)	0.22

hypertension, diabetes mellitus or hypercholesterolaemia at the time of inclusion did not differ between the two groups ($P = 0.60$, Tables 3 and 4).

Applying the NCEP-ATP-III definitions, the prevalence of MetS was significantly increased in AAV patients [39/91 (43%) compared with HC 22/89 (25%), $P = 0.01$; Table 3]. The prevalence of MetS in HC was in line with previous findings reported in three other Dutch cohort studies (Table 5) [10, 11].

As steroids might induce or promote the development of MetS, the actual and cumulative prednisone use of AAV patients with or without MetS was compared (Table 6). No significant difference regarding current prednisone use [24/52 (46%) MetS− AAV *vs* 21/39 (53%) MetS+ AAV patients, $P = 0.53$] or cumulative prednisone use [in years of prednisone use: MetS+ AAV 1.77 years (0.33–3.00 years) *vs* MetS− AAV 1.25 years (1.17–3.50 years), $P = 0.92$] was revealed. Severe disease, however, was more common in the MetS+ AAV group than in the MetS− AAV group ($P = 0.007$).

Table 5 Current prevalence of MetS in the Netherlands

Prevalence of MetS in the Netherlands	MORGEN study ($n = 1125$)	PREVEND study ($n = 5508$)	HOORN study ($n = 1364$)
Male, %	19	16	26
Female, %	12	10	19
Age group, years	28–59[a]	28–59[a]	50–74

[a]Age range differs from HC/AAV MetS study cohort. MORGEN: Monitoring risicofactoren en gezondheid Nederland; PREVEND: Prevention of renal and vascular end stage disease.

MetS in AAV is associated with increased levels of inflammation markers and relapse rate

MetS+ AAV patients had higher levels of CRP compared with MetS− AAV patients, ($P = 0.005$, Table 6). We also found increased levels of neopterin within the MetS+ AAV patients compared with MetS− AAV patients ($P = 0.045$). MetS+ patients did not differ from MetS− patients regarding albuminuria ($P = 0.33$), renal function as measured by MDRD ($P = 0.09$), ANCA positivity at the time of inclusion in the study ($P = 0.40$) or ANCA persistence ($P = 0.20$, Table 6). The presence of MetS, however, was associated with a higher relapse rate in AAV: AAV patients without MetS had a median amount of 0.0 (0.0–0.93) relapses per year compared with 0.10 (0.0–0.29) relapses per year in AAV with MetS ($P = 0.05$).

Discussion

The prevalence of MetS is increased in our cohort of AAV patients. Remarkably, the presence of MetS was not related to current and/or past steroid use. In AAV patients with MetS we found increased levels of inflammation markers such as CRP and neopterin as compared with AAV patients without MetS. Furthermore, the relapse rate was increased in AAV patients with MetS compared with AAV patients without MetS.

Patients with AAV have an increased prevalence of MetS as compared with the general Dutch population and our own control cohort (Table 6) [10, 11]. Increased prevalences of MetS were also observed in other

Table 6 Clinical characteristics of the AAV cohort stratified by MetS status

AAV patients ($n = 91$)	MetS−[a] ($n = 52$) (median)	MetS+[b] ($n = 39$) (median)	*P*-value
Prednisone use, %	46	53	0.53
BMI, median (IQR), kg/m^2	25.5 (21.7–28.0)	28.9 (25.5–33.3)	0.0001
Cumulative prednisone use, median (IQR), years	1.17 (0.33–3.00)	1.25 (1.17–3.50)	0.92
CRP, median (IQR), mg/l	3.0 (1.6–5.1)	5.5 (2.4–10.3)	0.005
Neopterin, median (IQR), ng/ml	1.78 (1.25–2.23)	2.03 (1.70–2.53)	0.045
Albuminuria, g/l, %	11	12	0.33
MDRD, median (IQR), ml/min/1.73m^2	63.0 (52.3–81.3)	56.0 (42.0–74.0)	0.09
Renal involvement, %	39	51	0.29
GFR, median (IQR), by MDRD, of patients with a GFR <60 ml/min/1.73m^2	45.0 (35.0–55.0)	43.5 (34.0–51.0)	0.24
Patients with a GFR <60 ml/min/1.73m^2 (by MDRD), %	49	51	0.20
ANCA-positive titres at inclusion, %	48	59	0.40
ANCA-negative titres at inclusion, %	52	41	
Persistent ANCA-positive titres, %	46	61	0.20
Had relapse, %	38	56	0.82
Relapse/year, median (IQR)	0.0 (0.0–0.193)	0.10 (0.0–0.29)	0.05
Limited AAV, %	37	10	0.007
Severe AAV, %	63	90	

[a]MetS−: AAV patients without MetS; [b]MetS+: AAV patients with MetS.

autoimmune diseases such as SLE, RA, SS and AS [27–30]. Chung *et al*. [28] studied 154 patients with RA and compared them with controls. They found that MetS was associated with the presence of coronary atherosclerosis in RA [28]. Mok *et al*. [29] also found an association between MetS and coronary atherosclerosis within a population of patients with SLE. We postulated that steroid use might be a potential confounding factor as it promotes insulin resistance and central obesity. However, we could not find an association between the current or cumulative use of steroids and presence of MetS. This finding was in line with studies assessing the association between CS use and the presence of MetS in patients with SLE and/or RA [27, 30, 31]. Bultink *et al.* [32] found in a multiple regression analysis that the history of i.v. methylprednisolone use is significantly associated with MetS score in patients with SLE. Interestingly, methylprednisolone is also used in AAV during induction therapy and might also be associated with the increased prevalence of MetS. Methylprednisolone may directly promote the development of MetS by causing metabolic changes. Alternatively, the use of methylprednisolone may simply reflect the need to control severe disease with severe inflammation; the inflammatory processes itself then might contribute to development of MetS [24, 33–35]. Accordingly, there are clear indications that immune processes are involved in the pathophysiology of MetS [12, 35]. Visceral adipose tissue is an active endocrine organ and a source of pro-inflammatory cytokines as well as adipokines [36]. Accordingly, chronic inflammation with elevated TNF-α levels, increased ESR and higher CRP levels is observed in MetS [24]. Additionally, neopterin levels are reported to be elevated in MetS. Neopterin is produced by human macrophages in response to IFN-γ [37]. It is found to be elevated during acute infections, but also in case of immune activation of non-infectious origin [37–39]. Indeed, in our study, AAV patients with MetS had significantly elevated CRP and neopterin levels as compared with AAV patients without MetS. Moreover, AAV patients with MetS had more relapses than AAV patients without MetS, which suggests that the increased inflammatory burden in these patients may play a role in the pathophysiology of AAV [1, 21, 40]. It is likely that there is a bi-directional relationship between MetS and AAV; one has to assume that MetS predisposes to AAV, but also that AAV may predispose to MetS. Chronic, low-grade inflammation, as seen in AAV, may enhance metabolic changes and drive development of MetS [33, 35].

Our study is the first study assessing MetS in AAV using the strict NCEP-ATP-III criteria to define MetS, but is limited by its retrospective nature. In addition, our study does not provide information on the longitudinal course of MetS and its causal relationship to AAV. It remains unclear if MetS evolves before or after onset of AAV. Furthermore, the cohort sizes are small and the recruitment of patients' spouses as HCs may bias the study. The same lifestyle/dietary habits may result in an underestimation of the difference in prevalence between controls and patients. If the importance of MetS can be confirmed in a prospective study, physicians should emphasize even more that their AAV patients should increase a healthy lifestyle.

In conclusion, we demonstrated that the prevalence of MetS in AAV is significantly increased and related to increased inflammatory markers. We suggest that preventing or treating MetS might influence the disease course of AAV.

Rheumatology key messages

- The prevalence of MetS is increased in AAV.
- MetS is associated with a higher propensity to relapse and a higher pro-inflammatory state.
- Treating MetS in addition to standard therapy might improve patient outcome.

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