## Title

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Original article

# Hypothyroidism in vasculitis

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## Abstract

**Objective.** To study the prevalence, risk and clinical associations of hypothyroidism among several forms of vasculitis.

**Methods.** Patients with GCA, Takayasu's arteritis (TAK), PAN and the three forms of ANCA-associated vasculitis [AAV; granulomatosis with polyangiitis (GPA), microscopic polyangiitis and eosinophilic granulomatosis with polyangiitis (EGPA)] enrolled in a prospective, multicentre, longitudinal study were included.

**Results.** The study included data on 2085 patients [63% female, 90% White] with a mean age of 54.6 years (S.D. 17.2). Diagnoses were GCA (20%), TAK (11%), PAN (5%), GPA (42%), microscopic polyangiitis (8%) and EGPA (14%). Hypothyroidism was present in 217 patients (10%) (83% female), with a mean age 59.8 years (S.D. 14.5). Age- and sex-adjusted risk of hypothyroidism was GCA, odds ratio (OR) 0.61 (95% CI 0.41, 0.90); TAK, OR 0.57 (95% CI 0.31, 1.03); PAN, OR 0.59 (95% CI 0.25, 1.38); GPA, OR 1.51 (95% CI 1.12, 2.05); microscopic polyangiitis, OR 1.81 (95% CI 1.18, 2.80) and EGPA, OR 0.82 (95% CI 0.52, 1.30). Among patients with AAV, age- and sex-adjusted risk of hypothyroidism was higher with positive MPO-ANCA [OR 1.89 (95% CI 1.39, 2.76)]. The clinical manifestations of vasculitis were similar in patients with and without hypothyroidism, except transient ischaemic attacks, which were more frequently observed in patients with GCA and hypothyroidism (12% *vs* 2%; $P = 0.001$).

**Conclusions.** Differences in the risk of hypothyroidism among vasculitides may be due to genetic susceptibilities or immune responses. This study confirms an association of hypothyroidism with MPO-ANCA.

**Key words:** hypothyroidism, vasculitis, GCA, Takayasu's arteritis, polyarteritis nodosa, granulomatosis with polyangiitis, microscopic polyangiitis, eosinophilic granulomatosis with polyangiitis, antineutrophil cytoplasmic antibody

CLINICAL SCIENCE

**Rheumatology key messages**

- Older age and female sex are risk factors for hypothyroidism in patients with vasculitis.
- Patients with granulomatosis with polyangiitis and microscopic polyangiitis have an increased risk of hypothyroidism.
- Hypothyroidism was strongly associated with myeloperoxidase antibodies in patients with ANCA-associated vasculitis.

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## Introduction

There are shared genetic susceptibilities between multiple autoimmune diseases. For example, polymorphisms in *CTLA4* and *PTNP22* have been reported in patients with AAV and other autoimmune diseases, including autoimmune thyroid disease [1, 2]. Furthermore, patients with one autoimmune condition are at increased risk of other autoimmune diseases [3].

Globally, the prevalence of hypothyroidism ranges from 0.5% and 5.3% [4]. In the USA, the estimated prevalence of hypothyroidism is 3.7% [5]. Furthermore, increasing age and female sex have been associated with hypothyroidism [4–8]. Several studies have found an increased risk of thyroid dysfunction in patients with GCA and ANCA-associated vasculitis (AAV) [9–15]. In patients with AAV, a higher prevalence of thyroid disease has been reported among patients with MPO antibodies, although microscopic polyangiitis (MPA) was overrepresented in two studies [10, 12, 14]. Similarly, studies comparing clinical manifestations of patients with AAV with and without thyroid disease had conflicting results, with one reporting an increase in renal and ENT manifestations, while the other two studies found no differences [10, 12, 14]. The prevalence of thyroid disease in Takayasu's arteritis (TAK) or PAN has not been well studied.

This large, multicentre study compared the risks of hypothyroidism in patients with GCA, TAK, PAN and the three forms of AAV—granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). The study also compared the clinical manifestations of vasculitis in patients with and without hypothyroidism. Finally, a literature review was conducted of studies evaluating thyroid disease in systemic vasculitis.

## Patients and methods

Patients with GCA, TAK, PAN, GPA, MPA and EGPA enrolled in a prospective, multicentre, longitudinal study through the Vasculitis Clinical Research Consortium (VCRC) were included. Patients could be enrolled at any time at or after diagnosis. The study was approved by the institutional review boards at Brigham & Women's Hospital, Boston University, Cleveland Clinic Foundation, Johns Hopkins University, Mayo Clinic, Mount Sinai Hospital, St. Joseph's Healthcare, University of Pennsylvania, University of Pittsburgh and University of Utah. All participants provided written informed consent.

Patients were followed prospectively with standardized clinical assessments, including symptoms attributed to vasculitis, physical examination and laboratory tests. A comorbidity form systematically collected data on the presence and type of thyroid disease at entry into the cohort and every 12 months. This study analysed the presence of hypothyroidism at entry into the cohort. The use of medications, including methimazole and propylthiouracil, was also collected.

Descriptive statistics were used. Age- and sex-adjusted odds ratios (ORs) and 95% CIs for risk of thyroid diseases were calculated using logistic regression. Clinical manifestations at diagnosis were compared among patients with and without hypothyroidism using Fisher's exact test (two tailed). JMP, version 16 (SAS Institute, Cary, NC, USA) was used for statistical analysis.

## Results

The study included 2085 patients (63% female, 90% White), with a mean age of 54.6 years (S.D. 17.2). Diagnoses were GCA [427 (20%)], TAK [225 (11%)], PAN [108 (5%)], GPA [873 (42%)], MPA [170 (8%) and EGPA [282 (14%)] (Table 1). Hypothyroidism was present in 217 patients [10% overall cohort, 83% female, mean age 59.8 years (S.D. 14.5)]. For the entire vasculitis cohort, female sex [OR 3.12 (95% 2.17, 4.48)] and age [OR 1.02 (95% CI 1.01, 1.03) for each additional year] were associated with an increased risk of hypothyroidism. The frequencies of hypothyroidism and age- and sex-adjusted ORs for hypothyroidism for the different vasculitides are presented in Table 1. The highest frequency of hypothyroidism was in patients with MPA (18%). Adjusting for age and sex, patients with GCA had a lower risk of hypothyroidism [OR 0.61 (95% CI 0.41, 0.90)] compared with other patients with vasculitis, while the risk of hypothyroidism was higher in patients with GPA [OR 1.51 (95% CI 1.12, 2.05)] and MPA [OR 1.81 (95% CI 1.18, 2.80)] (Table 1).

The comparisons of demographics and clinical features of vasculitis in patients with TAK and GCA with and without hypothyroidism are outlined in Table 2. In patients with TAK, older age was associated with hypothyroidism. There were no differences in the manifestations of vasculitis between the two groups (Table 2). In patients with GCA, female sex was associated with hypothyroidism (Table 2). A greater proportion of patients with GCA and hypothyroidism had transient ischaemic attacks (TIAs) attributed to vasculitis (12% *vs* 2% for those without; $P = 0.001$, with $P$-values $<0.003$ considered statistically significant, after accounting for multiple comparisons) (Table 2). The use of antiplatelet therapy was similar in patients with GCA with hypothyroidism (57%) or without hypothyroidism (56%) ($P = 1$). Cardiovascular risk factors were similar between the two groups, including hypertension (31 patients, 61% with hypothyroidism *vs* 225 patients, 60% without; $P = 1$), dyslipidaemia (13 patients, 25% with hypothyroidism *vs* 65 patients, 17% without; $P = 0.17$), atrial fibrillation (5 patients, 10% with hypothyroidism *vs* 18 patients, 5% without; $P = 0.14$) or diabetes (1 patient, 2% with hypothyroidism *vs* 11 patients, 3% without; $P = 1$).

The PAN cohort included 108 patients [6 patients (6%) with hypothyroidism, 83% female]. There were no differences between patients with and without hypothyroidism with respect to age, constitutional symptoms or involvement of skin, gastrointestinal,

**Table 1** Rate of hypothyroidism by type of vasculitis

| Variable | GCA ($n = 427$) | TAK ($n = 225$) | PAN ($n = 108$) | GPA ($n = 873$) | MPA ($n = 170$) | EGPA ($n = 282$) |
|---|---|---|---|---|---|---|
| Age, years, mean (S.D.) | 72 (8.5) | 38.4 (12.7) | 48.6 (16.2) | 50.7 (16.3) | 59.7(14.5) | 53.3 (13.8) |
| Female, *n* (%) | 300 (70) | 209 (93) | 60 (55) | 467 (54) | 107 (63) | 159 (56) |
| Ethnicity, *n* (%) | | | | | | |
| White | 413 (97) | 182 (81) | 92 (85) | 800 (92) | 151 (89) | 248 (87) |
| African American | 5 (1) | 10 (4) | 5 (5) | 15 (2) | 4 (2) | 6 (5) |
| Asian | 4 (1) | 28 (12) | 6 (6) | 39 (5) | 5 (3) | 16 (6) |
| Other | 5 (1) | 5 (2) | 5 (5) | 19 (2) | 10 (6) | 13 (5) |
| Hypothyroidism, *n* (%) | 51 (12) | 14 (6) | 6 (6) | 93 (11) | 30 (18) | 23 (8) |
| Hypothyroidism, OR[a] (95% CI) | 0.61 (0.41, 0.90) | 0.57 (0.31, 1.03) | 0.59 (0.25, 1.38) | 1.51 (1.12, 2.05) | 1.81 (1.18, 2.80) | 0.82 (0.52, 1.30) |

[a]Age and sex adjusted.

**Table 2** Demographics and clinical symptoms among patients with TAK or GCA with or without hypothyroidism

| Variable | TAK | | | GCA | | |
|---|---|---|---|---|---|---|
| | Hypothyroidism ($n = 14$) | No hypothyroidism ($n = 211$) | *P*-value | Hypothyroidism ($n = 51$) | No hypothyroidism ($n = 374$) | *P*-value |
| Age, years, mean (S.D.) | 47.4 (13.0) | 37.8 (12.5) | 0.02 | 71.2 (8.9) | 71.6 (8.4) | 0.78 |
| Female | 14 (100) | 195 (92) | 0.61 | 46 (90) | 254 (68) | <0.01 |
| Positive temporal artery biopsy, *n/N* (%) | NA | NA | NA | 34/39 (87) | 244/299 (82) | 0.37 |
| Constitutional | 4 (29) | 70 (33) | 1.00 | 18 (35) | 132 (35) | 1.00 |
| Headache | 3 (21) | 58 (27) | 0.76 | 36 (70) | 270 (72) | 0.82 |
| Jaw/tongue claudication | 1 (7) | 26 (12) | 1.00 | 28 (55) | 194 (52) | 0.68 |
| Carotidynia | 3 (21) | 47 (22) | 1.00 | 2 (4) | 23 (6) | 0.75 |
| Visual manifestations | 2 (14) | 17 (8) | 0.31 | 21 (41) | 134 (36) | 0.44 |
| Partial vision loss | 1 (7) | 1 (0.5) | 0.45 | 10 (20) | 55 (15) | 0.40 |
| Severe vision loss | 0 0 | 1 (0.5) | 1.00 | 5 (10) | 44 (12) | 0.82 |
| Upper extremity claudication | 9 (64) | 117 (55) | 0.59 | 7 (14) | 65 (17) | 0.69 |
| Lower extremity claudication | 4 (29) | 35 (17) | 0.27 | 4 (8) | 28 (8) | 1.00 |
| Musculoskeletal including PMR | 4 (29) | 54 (26) | 0.76 | 27 (53) | 142 (38) | 0.05 |
| Central nervous system | 4 (29) | 69 (32) | 1.00 | 9 (18) | 30 (8) | 0.03 |
| TIA | 1 (7) | 19 (9) | 1.00 | 6 (12) | 6 (2) | <0.01 |
| Stroke | 1 (7) | 12 (6) | 0.56 | 0 0 | 9 (2) | 0.08 |
| Cardiac | 2 (14) | 25 (12) | 0.67 | 1 (2) | 7 (2) | 1.00 |
| Gastrointestinal | 0 0 | 10 (5) | 1.00 | 1 (2) | 2 (1) | 0.32 |
| Renal | 2 (14) | 46 (22) | 0.74 | 1 (2) | 2 (1) | 0.32 |
| Renovascular hypertension | 2 (14) | 41 (19) | 1.00 | 0 0 | 1 (0.3) | 1.00 |

Values presented as *n* (%) unless stated otherwise. NA: not available.

renal, peripheral nerve, central nervous or genitourinary systems ($P > 0.05$) (Supplementary Table S1, available at *Rheumatology* online).

A comparison of demographics and clinical manifestations of vasculitis in patients with AAV with and without thyroid disease is provided in Table 3. Older age and female sex were associated with hypothyroidism (Table 3). A higher proportion of patients with hypothyroidism had positive MPO antibodies (45% *vs* 25% without hypothyroidism; $P < 0.001$) (Table 3). Conversely, a lower frequency of patients with PR3 positivity had hypothyroidism (40% *vs* 53% without hypothyroidism; $P = 0.02$) (Table 3). The association of MPO with hypothyroidism was especially prominent in patients with GPA (34% *vs* 12% without hypothyroidism; $P < 0.001$) (Table 3). Even after adjusting for age and sex, the risk of hypothyroidism was greater in patients with positive MPO [OR 1.92 (95% CI 1.32, 3.14)]. PR3 positivity was not associated with a risk of hypothyroidism after adjusting for age and sex [OR 0.78 (95% CI 0.53, 1.12)]. When evaluating the overall group of patients with AAV, there were no clinical differences in patients with and without hypothyroidism (Table 3).

During follow-up, 40 patients (2% previously without thyroid disease; 75% women) had a new diagnosis of hypothyroidism recorded. The mean duration of follow-up for the cohorts was 3.7 years (S.D. 3.21) for GCA, 4.29 (3.54) for TAK, 4.47 (3.52) for PAN, 4.59 (3.56) for GPA, 2.94 (2.51) for MPA and 3.84 (4.07) for EGPA. The distribution of new cases of hypothyroidism was as follows: 6 patients (2% previously unaffected) with GCA, 5 patients (2% previously unaffected) with TAK, 8 patients (8% previously unaffected) with PAN, 14 patients (2% previously unaffected) with GPA, 2 patients (1% previously unaffected) with MPA and 5 patients (2% previously unaffected) with EGPA.

## Discussion

This study evaluated the presence of hypothyroidism across six different forms of vasculitis. Age and female sex were strongly associated with hypothyroidism in patients with vasculitis, a finding that is in keeping with what is observed in the general population. When comparing across the different forms of vasculitis, the age- and sex-adjusted risk of hypothyroidism was lowest among patients with GCA and highest among patients with GPA and MPA. In patients with AAV, hypothyroidism was associated with MPO antibodies, including the subset of patients with GPA. The manifestations of vasculitis in patients with and without hypothyroidism were similar, with the exception of TIA, which was more frequent in patients with GCA and hypothyroidism.

The literature review identified several studies evaluating the presence of hypothyroidism in patients with GCA (with many studies also including patients with polymyalgia rheumatica) and AAV, but only one study of TAK [9–23] (Table 4). In the current study, the prevalence of hypothyroidism for GCA was 12% while for AAV it was 11%, with the highest prevalence in patients with MPA (18%). These numbers are in keeping with prior studies where estimates of hypothyroidism in GCA ranged from 0 to 30% and for AAV from 4 to 20% (Table 4). While this study did not have a referent population, several of the published studies evaluated the risk of hypothyroidism in GCA and AAV compared with age- and sex-matched controls (Table 4). In GCA, the findings were contradictory, with two studies reporting an increased risk of thyroid disease, while two other studies found no difference (Table 4). In AAV, three of the four studies reported an increased risk of hypothyroidism compared with the general population (Table 4).

In the current study, hypothyroidism was strongly associated with MPO-ANCA in patients with AAV. Three other studies that evaluated thyroid disease (hyperthyroidism or hypothyroidism) in patients with AAV also found that 57–86% of patients with thyroid disease had MPO positivity (Table 4) [10, 12, 14]. In the current study, 45% of patients with AAV and hypothyroidism were MPO positive compared with 25% of patients without hypothyroidism. The current study also included a large number of patients with GPA and EGPA, whereas at least two of the prior studies had >50% of patients with MPA, which may have biased the results with respect to the risk in patients with MPO-ANCA [10, 12, 14]. The results in the current cohort are more likely reflective of the prevalence of MPO with hypothyroidism in AAV. None of the patients in the current study were on methimazole or propylthiouracil, which have been associated with drug-induced AAV, so the findings of ANCA positivity are unlikely explained by medication use. The largest prior study of thyroid disease in AAV included 279 patients, whereas the current study included 1327 patients with AAV. This included 873 patients with GPA, of which 14% were MPO-ANCA positive. Interestingly, the proportion of patients with GPA and hypothyroidism who were MPO positive was 35%; these data from patients with GPA contributed to the observed association of MPO positivity and hypothyroidism. Proposed mechanisms for this association have included homology between thyroid peroxidase antibodies and MPO or a general loss of tolerance to peroxidases [12, 14, 24]. However, this is speculative since none of the studies, including the current one, measured antithyroid peroxidase antibodies in patients with AAV and no studies have evaluated the presence of ANCA in asymptomatic patients with hypothyroidism.

This study also compared the clinical features of vasculitis between patients with and without thyroid disease. In GCA, there was a higher frequency of TIA (attributed to vasculitis) in patients with hypothyroidism, even though the use of antiplatelet therapy or other risk factors like dyslipidaemia, hypertension and diabetes mellitus did not differ between the two groups. While not statistically significant, the proportion of patients in the hypothyroid group with atrial fibrillation was higher than patients without hypothyroidism and may have accounted for this difference. Thyroid disease has been associated with cerebrovascular disease, even in the general population [25, 26]. One

**TABLE 3** Demographics and clinical manifestations of patients with AAV with and without hypothyroidism

| Variable | All AAV | | | GPA | | | MPA | | | EGPA | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Hypothyroidism ($n = 146$) | No hypothyroidism ($n = 1181$) | *P*-value | Hypothyroidism ($n = 93$) | No hypothyroidism ($n = 780$) | *P*-value | Hypothyroidism ($n = 30$) | No hypothyroidism ($n = 140$) | *P*-value | Hypothyroidism ($n = 23$) | No hypothyroidism ($n = 259$) | *P*-value |
| Age, years | 57.4 (14.0) | 51.8 (15.9) | <0.001 | 55.7 (14.3) | 50.2 (16.4) | 0.002 | 62.2 (13.3) | 59.2 (14.7) | 0.23 | 58.1 (12.3) | 52.8 (13.8) | 0.07 |
| Female | 114 (78) | 619 (52) | <0.001 | 67 (72) | 400 (51) | <0.001 | 27 (90) | 80 (57) | <0.001 | 20 (87) | 139 (54) | 0.001 |
| ANCA negative[a] | 21 (15) | 239 (22) | 0.10 | 4 (5) | 84 (11) | 0.06 | 2 (7) | 7 (5) | 0.67 | 15 (72) | 148 (65) | 0.64 |
| MPO positive[a] | 62 (45) | 282 (25) | <0.001 | 30 (34) | 88 (12) | <0.001 | 26 (87) | 116 (85) | 0.89 | 6 (29) | 78 (34) | 0.79 |
| PR3 positive[a] | 56 (40) | 591 (53) | 0.02 | 54 (62) | 575 (77) | 0.004 | 2 (7) | 14 (10) | 0.69 | 0 (0) | 2 (1) | 0.78 |
| Constitutional | 111 (78) | 911 (77) | 0.75 | 74 (80) | 607 (78) | 1.00 | 22 (73) | 107 (76) | 0.81 | 15 (65) | 197 (76) | 0.31 |
| ENT | 106 (73) | 931 (79) | 0.10 | 84 (90) | 668 (87) | 0.41 | 4 (13) | 32 (23) | 0.45 | 18 (78) | 231 (89) | 0.17 |
| Cutaneous | 42 (29) | 392 (33) | 0.30 | 20 (21) | 235 (30) | 0.06 | 9 (30) | 30 (21) | 0.34 | 13 (57) | 127 (49) | 0.52 |
| Musculoskeletal | 82 (56) | 671(57) | 0.86 | 56 (60) | 498 (64) | 0.42 | 15 (50) | 59 (42) | 0.42 | 11 (48) | 114 (44) | 0.83 |
| Ocular | 27 (18) | 273 (23) | 0.20 | 26 (28) | 243 (31) | 0.55 | 1 (3) | 10 (7) | 0.69 | 0 (0) | 20 (8) | 0.39 |
| Cardiac | 8 (5) | 104 (9) | 0.21 | 4 (4) | 26 (3) | 0.55 | 0 (0) | 8 (6) | 0.35 | 4 (17) | 70 (27) | 0.46 |
| Gastrointestinal | 2 (1) | 70 (6) | 0.02 | 0 (0) | 22 (3) | 0.16 | 1 (3) | 8 (6) | 1.00 | 1 (4) | 40 (15) | 0.22 |
| Pulmonary | 102 (70) | 862 (73) | 0.48 | 63 (68) | 535 (69) | 0.72 | 18 (60) | 86 (61) | 1.00 | 21 (91) | 241 (93) | 0.67 |
| Renal | 82 (56) | 580 (49) | 0.09 | 54 (58) | 432 (56) | 0.66 | 24 (80) | 120 (86) | 0.77 | 4 (17) | 28 (11) | 0.31 |
| Nervous system | 39 (27) | 379 (32) | 0.22 | 19 (20) | 181 (23) | 0.54 | 5 (17) | 29 (21) | 0.80 | 15 (65) | 169 (65) | 1.00 |
| Venous thromboembolism | 20 (14) | 102 (8) | 0.05 | 16 (17) | 72 (9) | 0.03 | 3 (10) | 13 (9) | 0.74 | 1 (4) | 17 (7) | 1.00 |

[a]Percentage reported among patients with testing available.

**Table 4** Summary of published literature evaluating hypothyroidism in patients with vasculitis

| Study | Year | Population studied | Total number of patients | Number of patients with hypothyroidism | Risk of hypothyroidism |
|---|---|---|---|---|---|
| GCA | | | | | |
| Nicholson *et al.* [20] | 1984 | GCA, PMR and comparison population | 98 GCA/PMR (number with each diagnosis not available) and 392 controls | 3% with GCA/PMR *vs* 2% controls | Not increased Relative risk 1.7 (95% CI 0.4, 6.7) |
| Wiseman *et al.* [23] | 1989 | GCA, PMR | 20 GCA, 16 PMR | 30% with GCA, 56% with PMR | NA |
| Dasgupta *et al.* [17] | 1990 | GCA, PMR | 8 patients with GCA, 69 patients with PMR | 0 | NA |
| Bowness *et al.* [16] | 1991 | GCA, PMR | 98 GCA, 269 PMR | 4.9% all patients (data by diagnosis not available) | NA |
| Myklebust *et al.* [19] | 1997 | GCA, PMR | 41 GCA, 150 PMR | 5 of 142 tested (3.5%) (data by diagnosis not available) | NA |
| Duhaut P, *et al.* [18] | 1999 | GCA and comparison population | 285 GCA and 222 controls | 4.2% with GCA *vs* 7.7% controls | NA |
| Mohammad *et al.* [13] | 2017 | GCA and comparison population | 768 GCA and 3066 from general population | 16% with GCA *vs* 11% controls | Increased OR 1.55 (95% CI 1.25, 1.91) |
| Yavne *et al.* [15] | 2017 | GCA and comparison population | 5663 GCA and 23 308 from general population | 18% GCA *vs* 7% controls | Increased OR 1.3 (95% CI 1.19, 1.42) |
| Current study | 2021 | GCA and 5 other forms of vasculitis | 427 GCA, 1658 with other forms of vasculitis | 12% GCA *vs* 10% other vasculitides | Decreased compared with other forms of vasculitis OR 0.61 (95% CI 0.41, 0.90) |
| TAK | | | | | |
| Ohta Y *et al.* [21] | 2003 | TAK | 36 patients | 1 patient, 3% | NA |
| Current study | 2021 | TAK and 5 other forms of vasculitis | 225 TAK, 1860 with other forms of vasculitis | 6% TAK *vs* 11% other vasculitides | Not increased compared with other forms of vasculitis OR 0.57 (95% CI 0.31, 1.03) |

(continued)

**Table 4** Continued

| Study | Year | Population studied | Total number of patients | Number of patients with hypothyroidism | Risk of hypothyroidism |
|---|---|---|---|---|---|
| PAN | | | | | |
| Current study | 2021 | PAN and 5 other forms of vasculitis | 108 PAN, 1977 with other forms of vasculitis | 6% PAN *vs* 11% other vasculitides | Not increased compared with other forms of vasculitis OR 0.59 (95% CI 0.25, 1.38) |
| AAV | | | | | |
| Lionaki *et al.* [12] | 2007 | AAV with renal involvement and comparison population | 158 patients (13% GPA, 55% MPA, 32% renal limited vasculitis) and 99 controls | Thyroid disease (not characterized) present in 20% cases and 7% controls | NA |
| Englund *et al.* [9] | 2016 | AAV and comparison population | 186 patients (49% GPA, 45% MPA, 6% EGPA) and 744 from general population | 27 (15%) with thyroid disease (hypothyroidism not specified) | Increased Rate ratio 2.1 (95% CI 1.3, 3.3) |
| Li *et al.* [11] | 2018 | GPA and comparison population | 570 GPA and 5389 from general population | 7% GPA *vs* 4% general population at study entry | Not increased Hazard ratio 1.41 (95% CI 0.84, 2.37) |
| Prednecki *et al.* [14] | 2018 | AAV | 279 patients (clinical diagnosis not available) | 49 (18%) | NA |
| Kim *et al.* [10] | 2019 | AAV | 186 patients, 25% GPA, 53% MPA, 22% EGPA | 27 (15%) | NA |
| Sarica *et al.* [22] | 2021 | AAV and comparison population | 543 AAV (58% GPA, 29% MPA, 12.5% EGPA, 0.4% missing), 2672 general population | New cases hypothyroidism in 4% AAV, 1.3% general population during median follow-up 5.1 years | Increased Incidence rate ratio 3.4 (95% CI 2, 6) |
| Current study | 2021 | AAV and 3 other forms of vasculitis | 1325 AAV (66% GPA, 13% MPA, 21% EGPA), 760 other vasculitides | 11% GPA, 18% MPA, 8% EGPA *vs* 9% other vasculitides | Increased for GPA OR 1.51 (95% CI 1.12, 2.05) Increased for MPA OR 1.81 (95% CI 1.18, 2.80) Not increased for EGPA OR 0.82 (95% CI 0.52, 1.30) |

NA, not available; MPO, anti-MPO antibodies.

possible explanation is that the inflammatory process in GCA further compounds the baseline risk from hypothyroidism. This finding deserves further study in this population. No conclusions could be drawn about the association with stroke due to the small number of events. There were no differences in vasculitic manifestations between patients with thyroid disease in patients with TAK, PAN or AAV. Given the multiple manifestations of vasculitis compared in patients with and without hypothyroidism, any significant differences should be considered preliminary and require confirmation in an independent cohort.

The strengths of this study include the large number of patients with each of the six forms of vasculitis. There was systematic data collection at centres expert in the care of patients with vasculitis on the presence of thyroid disease and disease manifestations attributed to vasculitis.

This study also has several limitations to consider. This study evaluated the risk of hypothyroidism across the different forms of vasculitis and did not address risk compared with the general population. Information on thyroid function testing, antithyroid antibodies and specific forms of thyroid disease (e.g. Hashimoto's thyroiditis, etc.) was not available. Since this is not an inception cohort, the timing of thyroid disease in relation to the onset of vasculitis could not be determined. Finally, the number of patients with thyroid disease in TAK and PAN were small, limiting the ability to draw definitive conclusions in these diseases.

In conclusion, similar to the general population, age and female sex are risk factors for hypothyroidism in patients with vasculitis. Among patients with vasculitis, patients with GPA and MPA have the highest risk of hypothyroidism and there is a strong association of hypothyroidism with MPO-ANCA in patients with AAV. The potential mechanisms accounting for the differential risk among the different forms of vasculitis and the association in patients with MPO positivity warrants further study.

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## Data availability statement

The data underlying this article will be shared on reasonable request to the corresponding author.

## Supplementary data

Supplementary data are available at *Rheumatology* online.

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