Association of cigarette smoking with organ damage in primary systemic vasculitis

Aladdin J. Mohammad[1, 2] and Mårten Segelmark[1]

[1]Department of Nephrology, Lund University and Skåne University Hospital, Lund, Sweden; [2]Department of Internal Medicine, Division of Rheumatology, Helsingborg Hospital, Helsingborg, Sweden.

Correspondence to:

Aladdin J. Mohammad, MD, PhD

Department of Nephrology, Skåne University Hospital, Lund

S-221 85 Lund, Sweden

E-mail: aladdin.mohammad@med.lu.se

Objectives. To study the association between late organ damage in patients with primary systemic vasculitis [PSV: Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), Churg-Strauss syndrome (CSS), and polyarteritis nodosa (PAN)] and cigarette smoking.

Methods. The pattern and extent of organ damage according to the Vasculitis Damage Index (VDI) was analyzed for 86 prevalent cases with PSV retrieved from a geographically defined population in southern Sweden (WG: 46, MPA: 27, CSS: 4 and PAN: 9). Data on clinical findings, laboratory results and smoking habits were collected from case records from the time of diagnosis. The patients were stratified into two main groups according to their smoking habits: smokers (subdivided into active and ex-smokers) and non-smokers (patients who had never smoked).

Results. Data on smoking habits were available for 77 patients (90%). Thirty-three (38%) patients were categorized as smokers and 44 (51%) were non-smokers. Smoking was more common in men (61.5% *vs.* 23.6% in women, p=0.001). There were no differences in smoking habits between the main diagnostic groups (WG 40% smokers, MPA 45%). Ear, nose, and throat (ENT) damage was significantly more prevalent in non-smokers (p=0.001). Myocardial infarction and end-stage renal disease (ESRD) were more common in the current smokers (p=0.04) than in the non-smokers.

Conclusions. We found ENT damage to be significantly less prevalent in smokers. This is the first report on a possible modifying effect of cigarette smoking on the development of organ damage in PSV, but more studies are needed before any firm conclusions can be made.

KEY WORDS: VASCULITIS, ANCA, SMOKING, DAMAGE, WEGENER'S GRANULOMATOSIS

Introduction

Autoimmune diseases are believed to be caused by complex interactions between environmental factors and genes, which together induce changes in immune and inflammatory responses initiating or activating a diseases process. One of the environmental factors that may play an important role in the development of these diseases is smoking. Cigarette smoking is a leading cause of cardiovascular diseases and cancer. According to the World Health Organization (WHO) cigarette smoking is the number one cause of preventable death in western countries. Epidemiological studies have demonstrated significant associations between cigarette smoking and a number of inflammatory diseases. Smoking increased the risk of developing seropositive rheumatoid arthritis (RA) (1-3) and systemic lupus erythematosus (SLE) (4). There are also some other studies demonstrating cigarette smoking as an important risk factor for the development of giant cell arteritis (GCA) (5, 6). Studies on the effect of smoking in RA demonstrated a possible association between smoking and development of extraarticular manifestations (7) and rheumatoid nodules (8). In patients with SLE, cigarette smoking was associated with higher disease activity, higher prevalence of vasculitis and a tendency to increased damage score (9).

The association of cigarette smoking with inflammatory bowel diseases is complex. While ulcerative colitis is a non-smokers disease, smoking increases the risk of developing Crohn's disease and worsens its course (10). However, it is reported that smoking might have a "beneficial" effect on some other inflammatory diseases. Smokers with Sjögren's syndrome had less severe disease measured by the focus score on salivary gland lip biopsy (11). Cessation of cigarette smoking can activate the mucocutaneous symptoms, especially oral aphthous lesions, in patients with Behçet's disease (12).

Wegener's granulomatosis (WG), microscopic polyangiitis (MPA), and Churg-Strauss syndrome (CSS) are small vessel vasculitis associated with antineutrophil cytoplasmic antibodies (ANCA) and are subsequently referred to as ANCA-associated small vessel vasculitis (AASV). PAN is a rare disease characterized by inflammation of medium size vessels. Because of clinical and pathologic similarities, AASV and PAN are commonly studied together, and often collectively referred to as PSV (primary systemic vasculitis) (13). In a case control study on patients with AASV with biopsy proven glomerulonephritis, no significant differences in the exposure rate to smoking (both previous or current) was found between the patients and their matched controls (14). However, a recently published study from two German referral centers for AASV reported a significantly lower prevalence of smoking in patients, at onset of vasculitis symptoms, as compared with the general population (15). This finding of possibly reduced risk of AASV in smokers awakened our interest to study the relationship between smoking at onset and subsequent irreversible organ damage among our prevalent patients with PSV.

The aim of this study was to describe the association of cigarette smoking at diagnosis with the development of permanent organ damage measured by the vasculitis damage index (VDI) in prevalent cases with WG, MPA, CSS and PAN retrieved from a defined population in southern Sweden.

Patients and methods

Data on 86 prevalent cases with PSV (42 females) from a geographically defined population in southern Sweden were collected retrospectively. The retrieval of cases, case ascertainment, classification, demographic features, clinical and serology data of the study patients have previously been described in detail (16). All the cases were verified by a medical record review, and the patients were classified according to an algorithm developed by support from the European Medicines Agency (EMEA) (17). The EMEA algorithm was based on the American College of Rheumatology classification criteria 1990 and the Chapel Hill Consensus Conference definitions 1994 (18-21).

The extent of irreversible organ damage was determined in each patient using the Vasculitis Damage Index (VDI) score (22).. Only irreversible damage present for at least 3 months is scored in VDI. A score of one is given for each item of damage, the total VDI score is the summation of all items registered for each patient. The VDI was registered for all the patients at the day of point prevalence (pp); January 1, 2003. In the absence of information on a given item of damage it was considered not be present. The source of data collection in determining the VDI, the treatment of patients as well as the details regarding the registration of items of damage have previously been described (23). In addition, data on smoking habits at the time of diagnosis were extracted from available case records. Smoking is in the vast majority of cases similar with cigarette smoking, but often the medical records do not distinguish between cigarettes, cigar's and pipe smoking. However, smoking never refers to other forms of tobacco use such as chewing tobacco and Swedish snuff. Only cases with available information on smoking habits were included in the analysis. The patients were stratified into two major groups according to their smoking habits; non-smokers (never smoked) and smokers, the smokers were in some analyses

subdivided into current smokers, and ex-smokers (stopped smoking for more than 6 months).

Statistical analysis. Statistical analysis was performed using the Statistical Package for the Social Sciences; SPSS 12.0.1 for Windows (SPSS inc., Chicago, IL, USA). The differences between groups were compared using the non-parametric Mann-Whitney U-test and chi square (χ^2) test when appropriate. The p-value of ≤ 0.05 is considered to be significant. Data are presented as median and range unless stated otherwise.

Ethics. The study was approved by the local Ethical Committee at the Faculty of Medicine, Lund University (LU 283-02).

Results

Data on smoking habits were available for 77 patients (13 active smokers; 20 ex-smokers; 44 non-smokers). The median age at VDI assessment was 66 yrs. (range 35.5-84.8) for smokers and 65.1 yrs. (15-84 yrs.) for non-smokers (p=0.980). The median time from diagnosis to VDI assessment was 10 yrs. (2-26) in smokers *vs.* 9.5 yrs. (1-37) in non-smokers, (p=0.171). There were 38 women and 39 men. Smoking was more common at diagnosis among the men (n= 24; 61.5%) than the women (n=9; 23.6%); p=0.001. There were no differences in smoking habits between the two largest groups of patients [WG 40% smokers and MPA 45% smokers, p=0.672].

Thirty-three patients had positive PR3-ANCA, among them 3 were active smokers (9%) and 13 (39%) were ex-smokers. The corresponding figures for the patients with MPO-ANCA were 17% for both smokers and ex-smokers.

Organ damage. A detailed list of organ damage registered in all the patients according to VDI and smoking habits is given in Table 1. The median VDI score was 3 (range 0-14) for smokers and 3(range 0-13) for non-smokers (p=0.649). Seven patients were not assigned any item of damage, 5 (71 %) of them were smokers. Ear, nose and throat (ENT) damage was recorded for a total of 17 patients (WG: 16; MPA: 1). The MPA patient with a VDI score in the ENT area had hearing loss. Among those patients who were active smokers at diagnosis, none had developed ENT damage. The only ex-smoker who had developed ENT damage was a WG patient who had hearing loss as the only ENT damage item. Accordingly, ENT damage was significantly more common in the non-smokers (p=0.001), Figure 1. All items of ENT damage recorded in our patients are shown in Table 2. Twelve of the 15 non-smoker WG patients who later developed ENT damage were ANCA-positive at diagnosis, 9 PR3-ANCA (60%) and 3 MPO-ANCA (20%).

Malignancy was recorded for 7 patients, 5 (71%) were smokers at diagnosis. Urinary bladder carcinoma had been diagnosed in two patients (one WG and one MPA), another WG patient had prostate cancer and there was one MPA each with colon cancer and malignant melanoma.

There were no statistically significant differences between the smokers and the non-smokers in the prevalence of hypertension or other items of cardiovascular damage except for myocardial infarction (MI) which was significantly more prevalent among the smokers (p=0.048), figure 1.

Renal damage tended to develop more often among the smokers (45 %) as compared with non-smokers (32 %, p=0.176). This was more pronounced with regard to severe renal damage. The development of end-stage renal disease (ESRD) was statistically more common among those who were current smokers than those who had never smoked (p=0.045, Figure 1). No statistically significant differences between smokers and non-smokers have been found in the other organ system damage as shown in Table 1.

WG patients who had developed renal damage, did not (with only one exception) exhibit damage in the ENT-area. When comparing patients with renal damage with those who had developed ENT-damage we found significant differences in smoking habits (Table 3). ENT-damage patients also tended to be younger at onset and have longer diagnosis delay, but these differences were not statistically significant.

Discussion

This is the first study addressing the possible correlation between smoking habits at diagnosis and the subsequent development of organ damage in patients with AASV and PAN (=PSV). Previous studies on environmental factors have reported on effects of different factors on the incidence of PSV; however, no studies have looked specifically at the possible effect on the outcome with respect to organ damage. Our study was not designed to address a possible effect of smoking on the development of vasculitis as described in previous studies (14, 15). Even though the retrospective nature our study and the use VDI which is a relatively blunt instrument, we find a negative association between cigarette smoking and the development of irreversible organ damage in the ear nose and throat (ENT) region among patients with PSV. Nasal damage occurred exclusively in non-smokers and that renal and cardiovascular damage tended to develop more frequently in both current and previous smokers.

In our study, ENT damage in non-smokers involved mainly the nasal area. Previous studies have shown a protective or "beneficial" effect of smoking on the development and/or severity of different inflammatory and granulomatous diseases such as ulcerative colitis (10), Sjögren's syndrome (11) and sarcoidosis (24, 25).

Another way to interpret our results is that smoking might affect the balance between localized and systemic inflammation. A local "beneficial" effect has been shown previously in studies on patients with other vasculitides such as Behçet's disease. Nicotine, one of the major components in cigarette smoke, has a direct effect on human nasal epithelium by the presence of functional nicotinic acetylcholine receptors (26). The nicotine and biochanin A have been shown to have a specific anti-inflammatory effect on keratinocytes and endothelial cells which may explain a positive effect of smoking on oral aphthae (27),

hence the cessation of smoking can activate the oral aphthous lesions (12). Bergström et al demonstrated that vascular reaction associated with dental plaque induced gingivitis is suppressed in smokers, possibly due to a constrictive effect of tobacco smoke on gingival vascularity (28). Cigarette smoke contains abundant potentially toxic components that might alter the immune response, inducing abnormalities in, for instance, T cell functions and numbers. Results have been published showing elevated levels of (CD8+)T-cytotoxic lymphocytes leading to a decrease in CD4+/CD8+ ratio and hence an immunosuppressive effect (29).

Cardiovascular disease is a major cause of long-term morbidity in vasculitis (30). The vascular inflammation caused by the disease might be of importance, but most likely traditional risk factors add a substantial likelihood of acquiring such complications. The importance of traditional risk factors have actually been shown in giant cell arteritis (31), and our findings regarding smoking at onset and the subsequent development of myocardial infarction are coherent with this notion. In a similar fashion our finding of a higher prevalence of ESRD in smokers is in line with the findings in previous studies. Smoking increases the risk of ESRD in men with inflammatory and non-inflammatory primary renal disease (32). A Swedish nation-wide population based study illustrates the association between smoking and the development of chronic renal failure in patients with nephrosclerosis and patients with glomerulonephritis (33).

Our data on the development of cancer in our patients were too small to be analyzed. Knight et al did not find smoking as a strong risk factor in the development of urinary bladder cancer in WG; according to the author, the limitation of this suggestion was the scarcity of the smoking data in their study (34).

We previously reported an almost complete dissociation between ENT and renal damage in patients with WG (23), an observation that raises questions regarding the present separation

between WG and MPA. The disease entity we today call WG represents a spectrum ranging from disease with dominating granulomatous manifestations to disease with mainly vasculitic features. Maybe those who subsequently develop ENT damage represent a distinct disease variety, separated from those who develop renal damage with respect to etiology and/or pathogenesis. If this assumption is correct, smoking (and maybe also other environmental factors), have opposite effects on the incidence of the different disease varieties.

The present study has some important limitations. The study is retrospective and looked at the effect of smoking only from the VDI perspective. Data on smoking were not available for all the patients. It is hard to extract data on the duration of time since cessation of smoking in the ex-smokers. Only damage data available in the case records were registered. Questions on the predictive value of smoking on damage extent cannot be answered by this study alone. What is needed is a large prospective study that collects detailed data on smoking habits by means of interviews, and that also comprises an active search for damage.

In conclusion, considering the harmful effect of smoking in the general population there seem to be special circumstances rendering some protective effect of smoking on the development of ENT damage in patients with PSV. This is the first report on a possible modifying effect of cigarette smoking on the development of organ damage in PSV, and more studies are needed before any firm conclusions can be reached.

Table 1. Organ damage in 77 patients with PSV according to smoking habits

Organ system Selected items of damage	Non-smokers (n. 44) n. patients assigned damage (%)	Ex-smokers (n.20) n. patients assigned damage (%)	Smokers (n. 13) n. patients assigned damage (%)	p-value	p-value (n vs. x)	p-value (n vs. s)	p-value (x vs. s)
Musculoskeletal	12 (27)	3 (15)	2 (15)	0.485			
Osteoporosis/Vertebral collapse	9 (20)	2 (10)	1 (8)	0.507			
Skin/mucous membranes	5 (11)	1 (5)	0	0.604			
Ocular	7 (16)	1 (5)	4 (31)	0.145			
ENT	16 (36)	1 (5)	0	0.001	0.012	0.011	1
Pulmonary	9 (20)	3 (15)	3 (23)	0.854			
Cardiovascular	19 (43)	12 (60)	10 (77)	0.085			
Myocardial infarction	0	3 (15)	2 (15)	0.013	0.027	0.048	1
Hypertension	17 (39)	9 (45)	7 (54)	0.599			
Peripheral vascular	2 (5)	2 (10)	0	0.623			
Gastrointestinal	3 (7)	2 (10)	1 (8)	0.851			
Renal	14 (32)	7 (35)	8 (62)	0.176			
ESRD	3 (7)	3 (15)	4 (31)	0.058	0.366	0.045	0.392
GFR<50%	14 (32)	7 (35)	7 (54)	0.374			
Neuropsychiatric	13 (30)	5 (25)	4 (31)	0.943			
Peripheral neuropathy	9 (20)	2 (10)	3 (23)	0.605			
Others	13 (30)	7 (35)	6 (46)	0.506			

ENT: ear nose throat; ESRD: End Stage Renal Disease. If p-value is significant further

analysis using Fisher's exact test between the following sub-groups was done: n vs. x: non-

smokers vs. ex-smokers; n vs. s: non-smokers vs. smokers; x vs. s: ex-smokers vs. smokers

Table 2. Items of ENT[1] damage in 77 patients with PSV[2]

Type of damage	No. of registered items
Non-smokers	
Nasal blockage /chronic nasal discharge	12
Chronic sinusitis/radiological evidence of bone destruction	6
Nasal bridge collapse/nasal perforation	4
Hearing loss	2
Smokers	
Hearing loss	1

[1]ENT: ear, nose and throat; [2]PSV: primary systemic vasculitis

Table. 3. Data from the time of diagnosis on 42 patients with WG divided into groups according to pattern of subsequent damage.

	ENT damage (n=15)	Renal damage[1] (n=11)	No ENT or no renal damage (n=16)	p value[#]
Sex F/M	9/6	6/5	4/12	1.00
Age at diagnosis yrs, median (range)	45 (1-74)	56 (28-74)	58.5 (18-69)	0.264
Diagnosis delay, mo, median (range)	9 (0.5-96)	3 (0.5-36)	3.5 (1-13)	0.183
Time from diagnosis to damage estimates, yrs., median (range)	10 (2-20)	9 (1-27)	10.5 (2-17)	0.876
Positive ANCA				
PR3 % (n)	64% (9/14)	90% (9/10)	75% (12/16)	0.341
MPO % (n)	21% (3/14)	10% (1/10)	0	0.615
Smoking habit				*0.048*
Active smokers % (n)	0	27% (3)	6% (1)	
Ex-smokers % (n	7% (1)	18% (2)	63% (10)	
Never-smoked % (n	93% (14)	55% (6)	31% (5)	

[1]one patient with renal damage also had ENT damage (nasal blockage and chronic sinusitis)
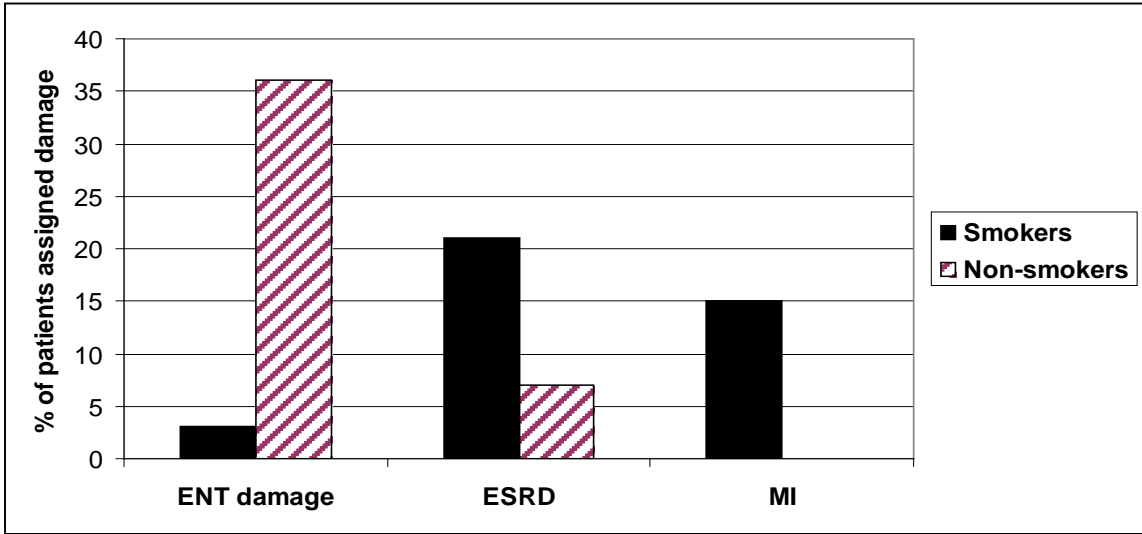[#]p value between patients with ENT and Renal damage

Figure 1. Damage recorded in smokers vs. non-smokers according to vasculitis damage index (VDI). ENT: ear, nose and throat; ESRD: end stage renal disease; MI: myocardial infarction

Figure legend:

Figure 1

Damage recorded in smokers vs. non-smokers according to vasculitis damage index (VDI).

ENT: ear, nose and throat; ESRD: end stage renal disease; MI: myocardial infarction

Table's legend:

Table 1:

ENT: ear nose throat; ESRD: End Stage Renal Disease. If p-value is significant further analysis using Fisher's exact test between the following sub-groups was done: n vs. x: non-smokers vs. ex-smokers; n vs. s: non-smokers vs. smokers; x vs. s: ex-smokers vs. smokers

Table 2:

[1]ENT: ear, nose and throat; [2]PSV: primary systemic vasculitis

Table 3:

[1]one patient with renal damage also had ENT damage (nasal blockage and chronic sinusitis)

[#]p value between patients with ENT and Renal damage

References:

1.	Hernandez Avila M, Liang MH, Willett WC, Stampfer MJ, Colditz GA, Rosner B, et al. Reproductive factors, smoking, and the risk for rheumatoid arthritis. Epidemiology. 1990 Jul;1(4):285-91.

2.	Heliovaara M, Aho K, Aromaa A, Knekt P, Reunanen A. Smoking and risk of rheumatoid arthritis. J Rheumatol. 1993 Nov;20(11):1830-5.

3.	Stolt P, Bengtsson C, Nordmark B, Lindblad S, Lundberg I, Klareskog L, et al. Quantification of the influence of cigarette smoking on rheumatoid arthritis: results from a population based case-control study, using incident cases. Ann Rheum Dis. 2003 Sep;62(9):835-41.

4.	Ghaussy NO, Sibbitt WL, Jr., Qualls CR. Cigarette smoking, alcohol consumption, and the risk of systemic lupus erythematosus: a case-control study. J Rheumatol. 2001 Nov;28(11):2449-53.

5.	Duhaut P, Pinede L, Demolombe-Rague S, Loire R, Seydoux D, Ninet J, et al. Giant cell arteritis and cardiovascular risk factors: a multicenter, prospective case-control study. Groupe de Recherche sur l'Arterite a Cellules Geantes. Arthritis Rheum. 1998 Nov;41(11):1960-5.

6.	Larsson K, Mellstrom D, Nordborg E, Oden A. Early menopause, low body mass index, and smoking are independent risk factors for developing giant cell arteritis. Ann Rheum Dis. 2006 Apr;65(4):529-32.

7.	Turesson C, O'Fallon WM, Crowson CS, Gabriel SE, Matteson EL. Extra-articular disease manifestations in rheumatoid arthritis: incidence trends and risk factors over 46 years. Ann Rheum Dis. 2003 Aug;62(8):722-7.

8.	Nyhall-Wahlin BM, Jacobsson LT, Petersson IF, Turesson C. Smoking is a strong risk factor for rheumatoid nodules in early rheumatoid arthritis. Ann Rheum Dis. 2006 May;65(5):601-6.

9.	Ghaussy NO, Sibbitt W, Jr., Bankhurst AD, Qualls CR. Cigarette smoking and disease activity in systemic lupus erythematosus. J Rheumatol. 2003 Jun;30(6):1215-21.

10.	Birrenbach T, Bocker U. Inflammatory bowel disease and smoking: a review of epidemiology, pathophysiology, and therapeutic implications. Inflamm Bowel Dis. 2004 Nov;10(6):848-59.

11.	Manthorpe R, Benoni C, Jacobsson L, Kirtava Z, Larsson A, Liedholm R, et al. Lower frequency of focal lip sialadenitis (focus score) in smoking patients. Can tobacco diminish the salivary gland involvement as judged by histological examination and anti-SSA/Ro and anti-SSB/La antibodies in Sjogren's syndrome? Ann Rheum Dis. 2000 Jan;59(1):54-60.

12.	Soy M, Erken E, Konca K, Ozbek S. Smoking and Behcet's disease. Clin Rheumatol. 2000;19(6):508-9.

13.	Watts RA, Lane S, Scott DG. What is known about the epidemiology of the vasculitides? Best Pract Res Clin Rheumatol. 2005 Apr;19(2):191-207.

14.	Hogan SL, Satterly KK, Dooley MA, Nachman PH, Jennette JC, Falk RJ. Silica exposure in anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and lupus nephritis. J Am Soc Nephrol. 2001 Jan;12(1):134-42.

15.	Haubitz M, Woywodt A, de Groot K, Haller H, Goebel U. Smoking habits in patients diagnosed with ANCA associated small vessel vasculitis. Ann Rheum Dis. 2005 Oct;64(10):1500-2.

16.	Mohammad AJ, Jacobsson LT, Mahr AD, Sturfelt G, Segelmark M. Prevalence of Wegener's granulomatosis, microscopic polyangiitis, polyarteritis nodosa and Churg-Strauss syndrome within a defined population in southern Sweden. Rheumatology (Oxford). 2007 Aug;46(8):1329-37.

17.	Watts R, Lane S, Hanslik T, Hauser T, Hellmich B, Koldingsnes W, et al. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis. 2007 Feb;66(2):222-7.

18.	Jennette JC, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, et al. Nomenclature of systemic vasculitides. Proposal of an international consensus conference. Arthritis Rheum. 1994 Feb;37(2):187-92.

19.	Leavitt RY, Fauci AS, Bloch DA, Michel BA, Hunder GG, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Wegener's granulomatosis. Arthritis Rheum. 1990 Aug;33(8):1101-7.

20.	Lightfoot RW, Jr., Michel BA, Bloch DA, Hunder GG, Zvaifler NJ, McShane DJ, et al. The American College of Rheumatology 1990 criteria for the classification of polyarteritis nodosa. Arthritis Rheum. 1990 Aug;33(8):1088-93.

21.	Masi AT, Hunder GG, Lie JT, Michel BA, Bloch DA, Arend WP, et al. The American College of Rheumatology 1990 criteria for the classification of Churg-Strauss syndrome (allergic granulomatosis and angiitis). Arthritis Rheum. 1990 Aug;33(8):1094-100.

22.	Exley AR, Bacon PA, Luqmani RA, Kitas GD, Gordon C, Savage CO, et al. Development and initial validation of the Vasculitis Damage Index for the standardized clinical assessment of damage in the systemic vasculitides. Arthritis Rheum. 1997 Feb;40(2):371-80.

23.	Mohammad AJ, Bakoush O, Sturfelt G, Segelmark M. The extent and pattern of organ damage in small vessel vasculitis measured by the Vasculitis Damage Index (VDI). Scand J Rheumatol. 2009 Mar 18:1-8.

24.		Musellim B, Kumbasar OO, Ongen G, Cetinkaya E, Turker H, Uzaslan E, et al. Epidemiological features of Turkish patients with sarcoidosis. Respir Med. 2009 Jan 30.

25.		Murin S, Bilello KS, Matthay R. Other smoking-affected pulmonary diseases. Clin Chest Med. 2000 Mar;21(1):121-37, ix.

26.		Blank U, Ruckes C, Clauss W, Weber WM. Effects of nicotine on human nasal epithelium: evidence for nicotinic receptors in non-excitable cells. Pflugers Arch. 1997 Sep;434(5):581-6.

27.		Kalayciyan A, Orawa H, Fimmel S, Perschel FH, Gonzalez JB, Fitzner RG, et al. Nicotine and biochanin A, but not cigarette smoke, induce anti-inflammatory effects on keratinocytes and endothelial cells in patients with Behcet's disease. J Invest Dermatol. 2007 Jan;127(1):81-9.

28.		Bergstrom J, Persson L, Preber H. Influence of cigarette smoking on vascular reaction during experimental gingivitis. Scand J Dent Res. 1988 Feb;96(1):34-9.

29.		Moszczynski P, Zabinski Z, Moszczynski P, Jr., Rutowski J, Slowinski S, Tabarowski Z. Immunological findings in cigarette smokers. Toxicol Lett. 2001 Jan 3;118(3):121-7.

30.		Faurschou M, Mellemkjaer L, Sorensen IJ, Svalgaard Thomsen B, Dreyer L, Baslund B. Increased morbidity from ischemic heart disease in patients with Wegener's granulomatosis. Arthritis Rheum. 2009 Apr;60(4):1187-92.

31.		Gonzalez-Gay MA, Pineiro A, Gomez-Gigirey A, Garcia-Porrua C, Pego-Reigosa R, Dierssen-Sotos T, et al. Influence of traditional risk factors of atherosclerosis in the development of severe ischemic complications in giant cell arteritis. Medicine (Baltimore). 2004 Nov;83(6):342-7.

32.		Orth SR, Stockmann A, Conradt C, Ritz E, Ferro M, Kreusser W, et al. Smoking as a risk factor for end-stage renal failure in men with primary renal disease. Kidney Int. 1998 Sep;54(3):926-31.

33.		Ejerblad E, Fored CM, Lindblad P, Fryzek J, Dickman PW, Elinder CG, et al. Association between smoking and chronic renal failure in a nationwide population-based case-control study. J Am Soc Nephrol. 2004 Aug;15(8):2178-85.

34.		Knight A, Askling J, Granath F, Sparen P, Ekbom A. Urinary bladder cancer in Wegener's granulomatosis: risks and relation to cyclophosphamide. Ann Rheum Dis. 2004 Oct;63(10):1307-11.