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Original article

Negative associations for fasting blood glucose, cholesterol and triglyceride levels with the development of giant cell arteritis

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Abstract

Objectives. To investigate metabolic features that may predispose to GCA in a nested case–control study.
Methods. Individuals who developed GCA after inclusion in a population-based health survey (the Malmö Preventive Medicine Project; $N = 33\ 346$) were identified and validated through a structured review of medical records. Four controls for every validated case were selected from the database.
Results. A total of 76 cases with a confirmed incident diagnosis of GCA (61% female, 65% biopsy positive, mean age at diagnosis 70 years) were identified. The median time from screening to diagnosis was 20.7 years (range 3.0–32.1). Cases had significantly lower fasting blood glucose (FBG) at baseline screening compared with controls [mean 4.7 *vs* 5.1 mmol/l (S.D. overall 1.5), odds ratio (OR) 0.35 per mmol/l (95% CI 0.17, 0.71)] and the association remained significant when adjusted for smoking [OR 0.33 per mmol/l (95% CI 0.16, 0.68)]. Current smokers had a reduced risk of GCA [OR 0.35 (95% CI 0.18, 0.70)]. Both cholesterol [mean 5.6 *vs* 6.0 mmol/l (S.D. overall 1.0)] and triglyceride levels [median 1.0 *vs* 1.2 mmol/l (S.D. overall 0.8)] were lower among the cases at baseline screening, with significant negative associations with subsequent GCA in crude and smoking-adjusted models [OR 0.62 per mmol/l (95% CI 0.43, 0.90) for cholesterol; 0.46 per mmol/l (95% CI 0.27, 0.81) for triglycerides].
Conclusion. Development of GCA was associated with lower FBG and lower cholesterol and triglyceride levels at baseline, all adjusted for current smoking, suggesting that metabolic features predispose to GCA.

Key words: giant cell arteritis, epidemiology, lipids

CLINICAL SCIENCE

Rheumatology key messages

- Cases who subsequently developed GCA had significantly lower glucose and lipids levels compared with controls.
- The results are compatible with previous findings of reduced prevalence of diabetes at GCA diagnosis.
- Metabolic factors may predispose to GCA, with new implications for disease pathogenesis.

Introduction

GCA is the most common vasculitis among individuals >50 years of age in northern European countries, with the highest reported incidence in Scandinavian countries and Minnesota (USA) [1–5]. It has a distinct pathology and mainly affects large and medium-sized arteries [6]. About 70% of patients with GCA are women [3, 4, 6]. Although ethnic factors, age and sex clearly play a role, the aetiology of the disease is largely unknown. Current treatment recommendations include glucocorticoids, with IL-6 inhibition added in severe and refractory cases [7]. Further insights on aetiology and pathogenesis may be helpful for optimal therapy.

A limited number of studies have investigated predictors of GCA. A retrospective case–control study from Gothenburg of 49 women showed that low BMI and several hormone-related factors were associated with

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GCA [8]. In a recent nested case–control study, our group confirmed the finding of a lower BMI earlier in life as a predictor for developing GCA [9]. However, we did not find any associations with hormone-related factors such as the duration of breastfeeding and age at menopause [9]. A systematic review on the relation between BMI and the risk of subsequent development of GCA found only three studies on this subject. In a meta-analysis based on these three studies, Ungprasert *et al.* [10] found a significant inverse association between BMI and the risk of GCA. In addition, a more recent cohort study from Iceland found a negative association between obesity and GCA among women [5]. There have been conflicting data on smoking and the risk of GCA. A recent meta-analysis by Brennan *et al.* [11] reported a statistically significant increased risk of GCA among smokers.

A meta-analysis of observational studies demonstrated that patients with GCA have a significantly reduced prevalence of diabetes at the time of diagnosis compared with the general population [12], but a subsequently published large register-based study came to the opposite conclusion [13]. It has been shown that during the first 2 years after GCA diagnosis, the incidence of diabetes is increased, most likely due to treatment with high doses of glucocorticoids [14].

There are no data on the relation between blood levels of glucose or lipids and the risk of GCA. The objective of the study was to investigate metabolic features prior to the diagnosis of GCA.

Methods

Source population

In this nested case–control study, individuals were identified who developed GCA after inclusion in a population-based health survey performed in the city of Malmö (current population slightly more than 300 000; during the screening period ~235 000) between 1974 and 1992 [the Malmö Preventive Medicine Project (MPMP)]. The MPMP had 33 346 participants (22 444 men and 10 902 women), with an overall response rate of 71%, with slight variations for different age groups (range 64–78%). The mean age at screening for the participants was 49 years for women and 44 years in men. During the first half of the period (1974–82), mostly men were invited to participate, but during the second half (1982–92) mostly women were invited. The vast majority of the participants were Caucasians of Scandinavian origin. More details on the cohort are described elsewhere [15].

Exposure information

Information regarding metabolic features and inflammation was based on blood tests obtained at inclusion in the MPMP: fasting blood glucose (FBG), total cholesterol (TC), triglycerides (TGs) and ESR. Blood samples were obtained in the morning, between 0800 and 1000, after an overnight fast. Serum TC and serum TG levels were immediately assessed using fresh samples by enzymatic methods in routine use at the local hospital laboratory. ESR was measured at screening according to the standard Westergren method.

FBG levels were automatically analysed using the glucose-oxidase method (1974–77) or the hexokinase-oxidase method (1977–87) at the local hospital laboratory. Because these two methods give rather similar results, we used the blood glucose data as reported, without applying a conversion factor [16].

Every participant in the MPMP completed a computer-based self-administered questionnaire on medical and personal history and underwent a physical examination. For this study, the following information was collected: information on smoking, BMI, blood pressure, medication for high blood pressure and triceps skinfold. Height (to the nearest centimetre) and weight (at intervals of 0.1 kg) were measured wearing indoor clothing and the BMI was calculated (kg/m^2). Blood pressure (mmHg) was measured twice after 10 min rest in the supine position and a mean figure was recorded. High blood pressure was defined as having a systolic pressure $\geq$140 mm or a diastolic pressure $\geq$90 mm at the time of screening or stating 'yes' in response to the question 'Do you use medication for high blood pressure?'. Triceps skinfold thickness was measured by callipers in the right brachial triceps 5 cm above the elbow. Values were later transformed into a log scale for use (triceps skinfold index) [17, 18].

Data on self-reported cancer, diabetes and cardiovascular disease (CVD; the latter classified as self-report of either hospitalization for stroke, physician diagnosis of angina pectoris or current use of heart medication) at baseline were extracted from the self-administered questionnaire.

Data on incident diabetes after inclusion in the MPMP were retrieved from the MPMP database and based on multiple sources [the Malmö HbA_{1c} Register, the Swedish National Diabetes Register, the Swedish Hospital Discharge Register, the Swedish Patient Register, the nationwide Swedish Prescription Drug Register (SPDR), the Diabetes 2000 Register of the Scania region and re-examinations of individuals in the MPMP cohort], as previously described [19].

Cases and controls

Patients were identified using a registered diagnosis code of GCA in the local outpatient clinic administrative register for Malmö University Hospital and the National Hospital Discharge Register (national patient register) [20] after inclusion in the MPMP and through 31 December 2011.

A structured review of all medical records of the identified patients was performed. For inclusion in the present study, a validated diagnosis of GCA, based on available medical records, was required. Cases were classified according to the ACR 1990 criteria for the classification of GCA [21]. The 1990 ACR classification criteria were not mandatory for inclusion in this study.

Some cases with typical clinical features but limited data regarding some parameters were included, based on expert opinion, even though they did not fulfil the classification criteria based on available information.

Four controls for every validated case, matched for sex, year of birth and year of screening, were selected from the MPMP cohort. The controls were alive and free from GCA when the index subject was diagnosed. Controls were randomly selected, using specially designed software, from those who fulfilled the matching criteria. The cases with GCA were in the pool of possible controls until the time they themselves became cases. This study was approved by the regional research ethics committee for southern Sweden. This research was done without patient involvement.

Clinical data regarding GCA at the time of diagnosis were extracted from the clinical records. These data included information used in the ACR criteria, i.e. age, new type of headache, abnormality on physical examination of the temporal arteries, ESR and pathology report of temporal artery biopsy (TAB). In addition, other data on blood sample analysis and symptoms were collected, including CRP, haemoglobin, platelet count, smoking history, symptoms of PMR at diagnosis, as well as visual manifestations at diagnosis (self-reported new onset of visual problems not explained by factors other than GCA) or permanent visual impairment. Information regarding the initial dose of glucocorticoids, family history of rheumatic diseases and documented large vessel involvement based on all vascular imaging performed in Malmö up to the date of record review was also retrieved.

Statistical analysis

Potential predictors of GCA were examined in conditional logistic regression models. Each case and its corresponding controls were given a group number that was entered in the logistic regression models as a categorical variable. For continuous variables, odds ratios (ORs) were calculated per S.D. to enable comparisons of effect sizes. Analyses were stratified by time from screening to GCA diagnosis (above *vs* below the median). In order to evaluate potential effect modification, analyses were also stratified by BMI category (normal *vs* high/obese) [22] and interaction between BMI category and each of FBG, TC and TGs was tested.

Correlation between the different covariates was tested by Spearman's rank test and Pearson's test, as appropriate. In the case of pairs with $r > 0.3$, the covariate with the weaker univariate association with GCA was excluded from the multivariate analysis. In a sensitivity analysis, all covariates with significant associations with GCA in the univariate analyses were included in the multivariate model.

All statistical analyses were performed using the Statistical Package for Social Sciences (version 24.0; IBM, Armonk, NY, USA) with $P < 0.05$ considered statistically significant.

Results

A total of 76 cases [46 females (61%)] with a confirmed clinical diagnosis of GCA were included in this study. The mean age at diagnosis was 70 years (range 56–83) and the median time from screening to diagnosis was 20.7 years (range 3.0–32.1). Sixty-five percent had a positive TAB and 95% fulfilled the ACR classification criteria for GCA (Table 1).

BMI at the time of screening was significantly lower in pre-GCA cases than controls [mean 23.6 *vs* 24.7 kg/m^2, OR 0.90 per kg/m^2 (95% CI 0.82, 0.98)] (Tables 2 and 3). In analysis stratified by sex, there was a significant negative association in women but not in men (Table 3).

Rates of self-reported cancer, diabetes and CVD comorbidities at baseline were low overall and somewhat lower among cases than controls (Table 2). Twelve cases (16%) and 73 controls (28%) had incident diabetes mellitus after inclusion in the MPMP and before the index date (date of diagnosis for the cases and the corresponding date for the controls). There were no major differences in baseline ESR or haemoglobin levels between cases and controls (Table 2)

The cases had significantly lower FBG at baseline screening compared with controls [mean 4.7 *vs* 5.1 mmol/l; OR 0.35 per S.D. (95% CI 0.17, 0.71)].

Current smokers at the time of screening had a significantly reduced risk of GCA [OR 0.35 (95% CI 0.18, 0.70)]. This association reached significance in men, but not in women, when stratified by sex (Table 3).

The negative association between baseline FBG and GCA remained significant in analysis adjusted for smoking [OR 0.33 per S.D. (95% CI 0.16, 0.68)] (Table 4). The effect was stronger in men compared with women [smoking-adjusted ORs per S.D. 0.05 (95% CI 0.01, 0.27)

TABLE 1 Characteristics of patients with GCA at diagnosis

Characteristics	Values
Patients, *N*	76
Female, *n* (%)	46 (61)
Age at GCA diagnosis, years, mean (S.D.; range)	70 (6.4; 56–83)
Time from screening to GCA diagnosis, years, median (range)	20.7 (3.0–2.1)
Positive biopsy, *n* (%)	49 (65)
Fulfilled the 1990 ACR criteria [21], *n* (%)	72 (95)
Documented visual symptoms at diagnosis, *n* (%)	31 (41)
Permanent visual loss, *n* (%)	4 (5)
ESR at diagnosis, mm/h, mean (S.D.)[a]	82 (24.8)
Initial glucocorticoid dose, mg prednisolone, median (IQR)[a]	50 (40–60)
CRP at diagnosis, mg/l, median (IQR)[a]	101 (52–159)
Large vessel involvement during follow-up, *n* (%)	13 (17)

[a]Data available for ESR in 70 cases, initial dose of glucocorticoids in 71 cases and CRP in 45 cases. IQR: interquartile range.

Table 2 Baseline characteristics of cases with later GCA diagnosis and controls, overall and stratified by sex

Characteristics	Total		Women		Men	
Cases, *N*	Cases 76	Controls 304	Cases 46	Controls 184	Cases 30	Controls 120
Age at screening, years, mean (S.D.)	50.2 (5.5)	50.0 (5.5)	52.2 (4.9)	52.1 (4.9)	47.0 (4.7)	46.7 (4.7)
Current smoking at screening, *n/N* (%)	17/70 (24)	120/283 (42)	10/41 (24	63/168 (38)	7/29 (24)	57/115 (50)
Ever smoking, *n/N* (%)	40/74 (54)	191/295 (65)	24/46 (52)	103/183 (56)	16/28 (57)	88/112 (79)
Body mass index, kg/m^2, mean (S.D.)	23.6 (3.2)	24.7 (4.0)	23.1 (2.5)	24.6 (4.4)	24.5 (3.9)	25.0 (3.3)
fB-glucose, mmol/l, mean (S.D.)	4.7 (0.6)	5.1 (1.6)	4.7 (0.6)	5.1 (1.9)	4.5 (0.5)	5.1 (1.0)
Cholesterol, mmol/l, mean (S.D.)[a]	5.6 (0.9)	6.0 (1.1)	5.7 (0.9)	6.1 (1.1)	5.5 (0.8)	5.9 (1.0)
Triglycerides, mmol/l, median (IQR)	1.0 (0.7–1.3)	1.2 (0.8–1.6)	0.9 (0.7–1.1)	1.0 (0.7–1.4)	1.3 (1.0–1.6)	1.4 (1.1–2.0)
ESR, mm/h, mean (S.D.)	8.9 (7.1)	8.6 (6.7)	10.2 (7.7)	10.3 (7.2)	6.9 (5.5)	6.2 (4.8)
Hypertension, *n/N* (%)	42/75 (56)	160/300 (53)	22/45 (49)	89/180 (49)	20/30 (67)	71/120 (59%)
Triceps skinfold index, mean (S.D.)[a]	211.1 (23.0)	210.8 (25.0)	222.6 (14.8)	223.9 (18.1)	193.7 (22.4)	191.2 (20.5)
Self-reported cancer, *n/N* (%)	0/74 (0)	6/294 (2)	0/46 (0)	5 /182 (2.7)	0/74 (0)	1/112 (0.9)
Self-reported diabetes, *n/N* (%)	0/75 (0)	7/293 (2.3)	0/75 (0)	3/183 (1.6)	0/30 (0)	3/120 (3.3)
Self-reported cardiovascular disease, *n/N* (%)	2/74 (2.7)	14/295 (4.7)	2/76 (4.3)	11/183 (6)	0/74 (0)	3/112 (2.7)

[a]Information missing: cholesterol (cases, 1; controls, 0), triceps skinfold index (cases, 3; controls, 7). Hypertension was defined as a systolic pressure ≥140 or a diastolic pressure ≥90 at the time of screening or a response of 'yes' to the question 'Do you use medication for high blood pressure?'. IQR: interquartile range.

Table 3 Potential predictors of GCA in bivariate analyses using conditional logistic regression models, stratified by sex

Variables		All			Women		Men	
		OR	95% CI		OR	95% CI	OR	95% CI
BMI (per kg/m^2)		0.90	0.82, 0.98		0.86	0.76, 0.98	0.95	0.82, 1.10
fB-glucose (per S.D.)		0.35	0.17, 0.71		0.67	0.35, 1.25	0.07	0.01, 0.30
Cholesterol (per S.D.)		0.58	0.42, 0.81		0.55	0.35, 0.85	0.63	0.38, 1.03
Triglycerides (per S.D.)		0.45	0.27, 0.74		0.34	0.15, 0.75	0.55	0.30, 1.01
Current smoking	No	1.00 (ref)			1.00 (ref)		1.00 (ref)	
	Yes	0.35	0.18, 0.70		0.48	0.19, 1.19	0.24	0.09, 0.70
Ever smoking	No	1.00 (ref)			1.00 (ref)		1.00 (ref)	
	Yes	0.57	0.32, 1.03		0.82	0.40, 1.68	0.29	0.11, 0.78
Hypertension	No	1.00 (ref)			1.00 (ref)		1.00 (ref)	
	Yes	1.15	0.64, 2.06		0.97	0.46, 2.04	1.52	0.58, 3.95
Triceps skinfold index (per S.D.)		1.04	0.72, 1.51	0.90		0.54, 1.51	1.21	0.71, 2.09

S.D. values: fB-glucose 1.5 mmol/l, cholesterol 1.0 mmol/l, triglycerides 0.8 mmol/l, triceps skinfold index 24.6.

and 0.68 (95% CI 0.36, 1.28), respectively] (Table 4). Both TC (mean 5.6 *vs* 6.0 mmol/l) and TG levels (median 1.0 *vs* 1.2 mmol/l) were lower among the cases at baseline screening, with significant negative associations with subsequent GCA [OR 0.58 per S.D. (95% CI 0.42, 0.81) and 0.45 per S.D. (95% CI 0.27, 0.74), respectively]

TABLE 4 Potential predictors of GCA in multivariate analyses adjusted for current smoking at screening

Variables	All		Women		Men	
	OR	95% CI	OR	95% CI	OR	95% CI
fB-glucose (per S.D.)	0.33	0.16, 0.68	0.68	0.36, 1.28	0.05	0.01, 0.27
Cholesterol (per S.D.)	0.62	0.43, 0.90	0.58	0.35, 0.95	0.68	0.40, 1.15
Triglycerides (per S.D.)	0.46	0.27, 0.81	0.42	0.18, 1.01	0.49	0.24, 1.00

S.D. values: fB-glucose 1.5 mmol/l, cholesterol 1.0 mmol/l, triglycerides 0.8 mmol/l.

TABLE 5 Potential predictors of GCA in multivariate analyses adjusted for all included variables

Variables	All		Women		Men	
	OR	95% CI	OR	95% CI	OR	95% CI
fB-glucose (per S.D.)	0.43	0.20, 0.89	0.77	0.47, 1.26	0.05	0.01, 0.31
Cholesterol (per S.D.)	0.71	0.48, 1.05	0.62	0.36, 1.06	0.69	0.36, 1.31
Triglycerides (per S.D.)	0.64	0.36, 1.14	0.56	0.23, 1.41	0.91	0.42, 1.95
Current smoking	0.32	0.15, 0.67	0.45	0.17, 1.20	0.18	0.06, 0.60

S.D. values: fB-glucose 1.5 mmol/l, cholesterol 1.0 mmol/l, triglycerides 0.8 mmol/l.

(Table 3). These associations remained significant with adjustment for smoking (Table 4).

There were no associations between hypertension or triceps skinfold index and GCA at baseline screening (Table 3).

In multivariate analysis, including FBG, TC, TG and smoking in the same model, the negative associations for FBG and current smoking with GCA at baseline remained significant [OR 0.43 per S.D. (95% CI 0.20, 0.89) for FBG and 0.32 (95% CI 0.15, 0.67) for current smoking] (Table 5). BMI had a strong correlation with FBG and TG levels ($r > 0.3$) and was therefore excluded from the multivariate analysis. The sensitivity analysis, which included BMI as a covariate in the multivariate model, gave similar results (Supplementary Table S1, available at *Rheumatology* online).

Patterns were similar when stratifying for time from screening to diagnosis over and above the median (20.7 years). The CIs were wider, likely reflecting the smaller number of cases (Table 6).

Analyses stratified by normal (18.5–25 kg/m^2) *vs* high (>25 kg/m^2) BMI (according to the World Health Organization definition [22]) gave similar estimates, with wider CIs (Supplementary Table S2, available at *Rheumatology* online). There was no significant interaction between the BMI category (normal *vs* overweight/obese) and FBG ($P = 0.55$), TC ($P = 0.16$) or TG ($P = 0.32$).

Discussion

In this study we confirmed previous results [5, 8–10] that lower BMI is associated with an increased risk for developing GCA. Furthermore, FBG levels were significantly lower at baseline in cases compared with controls and there were similar findings for TC levels and TG levels. These associations remained significant when adjusted for smoking. These findings suggest that a metabolic profile with a lack of overweight/obesity and better glucose tolerance and lipids may be associated with an increased risk of GCA.

In the multivariate analysis, FBG had the strongest effect of the metabolic factors on future risk of GCA. Among the cases who subsequently developed GCA, not a single individual had a history of diabetes at baseline, compared with 2.3% of the controls. This is in line with studies suggesting that GCA cases at the time of diagnosis have a lower prevalence of diabetes compared with controls [12], although there are conflicting results [13]. Methodological differences in diabetes ascertainment and possibly age-related effects of diabetes on the risk of GCA may explain such discrepancies. In the present study, the mean age at GCA diagnosis was 70 years, reflecting the age range of the source population and the length of follow-up.

The results are not likely to be explained by early effects of inflammation on BMI, glucose and lipids. First, baseline ESR levels were low for most individuals, with no difference between cases and controls. Second, the median time from inclusion in the health survey to GCA diagnosis was 20.7 years, and results were similar in stratified analysis of those with shorter *vs* longer time to diagnosis. The relatively long duration between screening and diagnosis may suggest that changes in metabolic features many years before diagnosis could make some individuals predisposed to GCA, whereas other factors may trigger disease development. It is also

Table 6 Potential predictors of GCA in bivariate analyses, stratified by time from screening to diagnosis

Variables	Less than median (<20.7 years)		Greater than median (>20.7 years)	
	OR	95% CI	OR	95% CI
BMI (per kg/m^2)	0.81	0.70, 0.95	0.96	0.86, 1.08
Current smoking (yes *vs* no)[a]	0.59	0.24, 1.46	0.19	0.06, 0.57
Ever smoking (yes *vs* no)[b]	0.72	0.32, 1.62	0.44	0.19, 1.03
fB-glucose (per S.D.)	0.48	0.20, 1.17	0.25	0.09, 0.70
Cholesterol (per S.D.)	0.57	0.36, 0.90	0.59	0.37, 0.96
Triglycerides (per S.D.)	0.41	0.19, 0.88	0.48	0.24, 0.94
Hypertension (yes *vs* no)	0.68	0.30, 1.54	1.98	0.85, 4.59
Triceps skinfold index (per S.D.)	0.86	0.50, 1.49	1.22	0.73, 2.03

S.D. values: fB-glucose 1.5 mmol/l, cholesterol 1.0 mmol/l, triglycerides 0.8 mmol/l, triceps skinfold index 24.6. [a]Current smoking defined by the question, 'Do you smoke daily?' (yes or no) or a quantification of the number of cigarettes/day. [b]Ever smoking defined by the question, 'Have you ever in your life smoked daily for half a year?' (yes or no).

possible that these findings reflect previously unknown early disease features that we cannot yet measure.

Recent studies have suggested that key mechanisms in GCA (i.e. defective checkpoint control of T cells) are regulated by metabolic factors on a cellular level, providing a biologic model that may be reflected in our findings. Researchers have shown higher expression of programmed cell death 1 receptor (PD-1) on T cells and lower expression of programmed death ligand 1 (PD-L1) on dendritic cells (DCs) in TABs from patients with GCA compared with non-inflamed human arteries. PD-1 is normally expressed on activated B and T cells and when binding to PD-L1 it disrupts kinase activity in the T cell receptor activation cascade, leading to immunosuppression [23, 24]. In addition, their results showed that *in vivo* blocking of PD-1 in human artery–severe combined immunodeficiency mice chimaeras, reconstituted with peripheral blood mononuclear cells from patients with GCA, led to more intense vascular inflammation [25]. Thus, defective checkpoint regulation of T cells is an important mechanism in GCA.

Another study from the same group reported a positive association between expression of PD-L1 on macrophages and the amount of glucose metabolites, e.g. pyruvate, in the mitochondria [26]. A recent follow-up study investigated how the glucose metabolism controls disease-specific signatures by comparing three cohorts, the first with GCA, the second with CVD and the third with healthy controls. Distinctive differences in both resting and activated macrophages in PD-L1 expression were found, whereby expression in GCA macrophages was profoundly suppressed. In addition, transcriptome analysis showed strong upregulation of the glycolytic machinery in CVD macrophages compared with GCA and controls. Specifically, the transcript concentrations for GLUT1, which is the dominant glucose transporter on macrophages, were multifold higher in CVD macrophages compared with the other groups [27]. By flow cytometric analysis they confirmed the same difference in surface induction of GLUT1. Serum glucose levels in the CVD group were higher than in the GCA group [28].

These studies are in line with our results of lower levels of FBG and related metabolic markers in cases who subsequently developed GCA than controls. This might imply that lower levels of serum glucose in our pre-GCA individuals associate with a lower expression of PD-L1 on the macrophages. Such downregulation of the PD-1/PD-L1 checkpoint would predispose to T cell activation and development of chronic vascular inflammation.

If relevant, such mechanisms must have a long-term effect to explain our findings. The long-term influence of metabolic features on the expression of PD-L1 and related mechanisms have not been investigated. There might also be other as yet unidentified factors that are associated with a long-term favourable metabolic profile and development of GCA that contribute to the results presented here.

In this study population we found a significant protective effect of current smoking at baseline for cases compared with controls. Previous studies on smoking have shown conflicting data, but a meta-analysis concluded that patients with recently diagnosed GCA were more likely to be smokers than were controls [11]. In a recent cohort study from Iceland, there was a lower risk of developing GCA among male smokers [5]. In the present study, the effect of smoking was stronger in men and in individuals screened >20 years before GCA diagnosis. Changes in smoking patterns over time and differences in other exposures related to smoking between studies may contribute to the conflicting results.

A limitation of our study is the relatively small sample size. Furthermore, data on exposures were only collected at a single time point, therefore we could not assess the effect of changes in exposures over time. As the vast majority of participants in the MPMP were Caucasians of Scandinavian heritage, our results may not apply to other ethnic groups or geographic settings.

The strengths of our study are related to the study design, with a community-based approach and a well-

defined cohort with a high participation and questionnaire response rate (71%). The high response rate indicates that our cases were representative of patients with GCA in the study area. The exposures were measured before GCA diagnosis in a standardized manner. Due to this prospective approach, there is no risk of recall bias.

The results of this study shed new light on the understanding of a possible disease mechanism for developing GCA. Our data are uniquely based on a cohort with blood samples taken from both cases and controls long before the onset of disease or the corresponding index date. As this is the first study to report on the relation between glucose, lipids and subsequent risk of GCA, confirmatory studies are needed.

Conclusion

Development of GCA, after a median of 20.7 years, was associated with lower FBG and lower TC and TG levels at baseline, all adjusted for current smoking. These findings are in line with the previous findings of a reduced prevalence of diabetes mellitus at the time of diagnosis of GCA. The findings provide clinical epidemiological support for recent studies suggesting that the PD-1/PD-L1 pathway may play an important role in disease pathology and that this pathway may be regulated by glucose metabolites, supporting the hypothesis that metabolic factors influence the development of GCA.

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Supplementary data

Supplementary data are available at *Rheumatology* online.

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