The relationship between glycated haemoglobin levels and the risk of Giant Cell Arteritis – A case-control study

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Key Words

Giant Cell Arteritis
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Risk stratification

Abstract

Objectives

The EULAR core dataset for observational studies in giant cell arteritis (GCA) does not include glycated haemoglobin (HbA1c). A multivariable score to stratify pre-test probability of GCA also does not include HbA1c. There have been contradictory reports about Diabetes Mellitus (DM) being a risk factor for GCA. We report the first study analysing the relationship of pre-diagnosis HbA1c with the risk of GCA.

Methods

This was a single centre retrospective case-control study conducted in Norfolk, UK. All GCA cases were diagnosed with imaging or biopsy. Each case was assigned 2 age and gender-matched controls. The primary outcome measure was the glycaemic status (HbA1c categorised into euglycaemia, pre-diabetes, DM) at diagnosis between cases and controls. HbA1c between two groups was compared using the Mann-Whitney U test. The glycaemic categorisation was compared using the Chi-squared test.

Results

112 cases and 224 controls were included. The median (IQR) of HbA1c of cases and controls was 40 (37, 43) and 41 (39, 47) ($p<0.001$) respectively. 10/112 cases and 52/224 controls had DM. Chi-square test demonstrates significant interaction between glycaemic state and GCA ($p=0.006$). Individuals with DM had an odds ratio (95% CI) of 0.32 (0.13,0.74) ($p=0.008$) of having GCA compared to euglycaemic individuals.

Conclusion

HbA1c in the diabetic range reduces probability of GCA. HbA1c should be considered in any multivariable score to calculate risk of GCA, and in future development of diagnostic and classification criteria. There is need for an epidemiological study looking at the possibility of a protective nature of DM against GCA or whether it is just a mimic.

Introduction

Giant Cell Arteritis (GCA) is a primary systemic vasculitis which most commonly affects women in the 8th decade of life (1). High dose glucocorticoid therapy remains the cornerstone of treatment and typically tapered over about 2 years (2, 3). The European League Against Rheumatism (EULAR) recommends that the core data set for observational studies and routine clinical care should include the laboratory markers of haemoglobin, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) (4). It also recommends recording the presence or absence of diabetes mellitus (DM), but not glycated haemoglobin (HbA1c). HbA1c is the measure of prevailing plasma glucose concentrations over the preceding three months. A multi-variable score to stratify the pre-test probability for GCA includes CRP as the only laboratory marker (5).

The global prevalence of DM in the adult population has been estimated to be 463 million in the year 2019 and is thought to reach 700 million by the year 2045 (6). Diabetes is known to be a pro-inflammatory state; individuals with the condition having a higher CRP compared to the general population (7). In addition, there is a distinct difference in the incidence of diabetes amongst different age groups and by gender; the most common population for incident diagnosis of DM being women above the age of 65 (8). Finally, there is an increased risk of anterior ischaemic optic neuropathy (AION) in elderly individuals with DM, which would be non-arteritic (9). Therefore, if someone from this demographic were to present with a headache, GCA would be among the differential diagnoses. Temporal artery biopsy (TAB) had a sensitivity of about 40% for a diagnosis of GCA in two recent studies (10, 11). Since diagnostic ultrasound does not have wide-spread availability (12), there is a high probability of making a clinical diagnosis of GCA in this scenario, leading to long-term corticosteroid treatment.

Our centre runs a dedicated fast-track pathway for the diagnosis and management of suspected GCA. Individuals referred from primary care are assessed clinically within 48 hours and an ultrasonographic examination is performed within 7 days of starting prednisolone. All individuals in whom the clinical suspicion of GCA is retained are commenced on the Norwich regimen of prednisolone as published previously (3). While waiting for the ultrasonographic examination As part of the routine baseline laboratory tests, and in line with national guidance it is standard of care at our institution to include HbA1c as a method of glycaemic stratification for individuals who might find themselves on long-term prednisolone (13). This paper examines the interplay between the glycaemic state and GCA.

Methods

Cases and Controls

The records of individuals referred to the GCA clinic of the Norfolk and Norwich University Hospital were reviewed for inclusion into this study. Individuals were considered to have GCA (Case) if they had a positive ultrasound scan as previously defined (14), a TAB demonstrating intramural inflammation or a positive Positron Emission Tomogram (PET).

Individuals in whom corticosteroids were stopped were considered as controls. Each case was assigned two age (by decade) and gender matched controls. If there was more than one eligible case or control, preference for inclusion was given to those with the nearest age matching. Ethical approval was not sought for this project because it was a retrospective study which analysed data acquired during the routine care of the patients.

Data

Age and HbA1c (if available) at diagnosis of GCA were recorded. All individuals were also categorised into euglycemic (HbA1c ≤42 mmol/mol [6.0%]), pre-diabetes (HbA1c 43-47 mmol/mol [6.0-6.4%]), and diabetes (HbA1c ≥48 mmol/mol [6.5%]). Details of the medication for diabetes were recorded.

Statistics

The distribution of the variables was checked using the Shapiro-Wilk test and the variance was checked using Levene's test. The difference in distributions of continuous variables was checked using either t-test if the distribution was parametric, or Mann-Whitney U test if the distribution was non-parametric. The distribution of categorical variables was checked using the Chi-Squared test. This test measures whether the difference between the observed distribution and expected distribution is statistically significant. Odds ratios were calculated using Binary Logistic Regression. All statistics were done on IBM SPSS Version 25 (IBM, New York, USA).

Results

602 individuals between 10/01/2012 and 05/10/2019 were seen in our GCA service. HbA1c at diagnosis was available for 422 individuals. 154 of these had GCA and 268 had GCA excluded. We matched 112 cases to 224 age (by decade) and gender controls. 36 pairs were male and 76 were female. The mean (SD) age in years of the cases and controls was 72.9 (7.6) and 73.1 (8.2) respectively (p=0.08). The age distribution of the cases and controls by decade is available in Supplementary Table S1, available at *Rheumatology Advances in Practice* online.

The distribution of HbA1c was not parametric (using Shapiro-Wilk test). The median (IQR) HbA1c of the cases and controls was 40 (37, 43) mmol/mol and 41 (39, 47) mmol/mol respectively. The distribution is shown in Figure 1. The Mann-Whitney U test indicated that the HbA1c was greater for controls, than for cases, U=15824.5, p<0.001.

The categorisation of the cases and controls into their glycaemic status groups is as in Table 1. A chi-square test of independence was calculated based on this distribution. It demonstrates a significant interaction between glycaemic state and having GCA, $\chi^2(2) = 10.14$, p=0.006.

The odds of GCA in the three glycaemic groups is 0.59 (euglycaemic group), 0.61 (pre-diabetes group) and 0.19 (diabetes group). Individuals with diabetes (HbA1c ≥48mmol/mol) had an odds ratio (95% CI) of 0.32 (0.13, 0.74) (p=0.008) of being diagnosed with GCA as compared to the individuals with euglycaemia.

We noted and categorised anti-diabetes therapy into groups as in Supplementary Table S2 available at *Rheumatology Advances in Practice* online. 2 cases and 37 controls were on anti-diabetes medicines. While this difference is statistically significant on Chi-Squared analysis (p<0.001), the numbers were too small to do meaningful statistical analysis. All the patients on anti-diabetes medication had an HbA1c ≥48 mmol/mol.

Discussion

Our study shows that in the population referred to our fast-track clinic, having an HbA1c in the diabetes range is associated with lower odds of having GCA. Our study, which we believe is the first of its kind, has many strengths. All the patients were referred and managed according to our hospital guidelines and these data were collected at the time of assessment. All the cases have definite GCA established on a biopsy, ultrasonography or PET scan. Likewise, all controls had at least one negative imaging or biopsy and oral prednisolone had been stopped. To avoid false negatives, all patients had open access to the GCA clinic to attend in case of further suspicion of GCA. The case-control methodology has eliminated the effect of age and gender on glycaemic status (8).

We also recognise the limitations of our study. It is a retrospective, single-centre study. We have focussed on the glycaemic categories for our analysis, but there were a statistically higher number of individuals on anti-diabetic medication amongst the control arm. It is possible that the anti-diabetic medication may be immunomodulatory and therefore protective against development of GCA. We have not been able to adjust for that variable in this observation. Similarly, we have not been able to control for other metabolic associations of DM like dyslipidaemia or other medications like statins. However our finding is in line with that of Ungprasert et al who have done a pooled analysis of 5 separate studies and shown that individuals with GCA had a statistically lower prevalence of DM than controls (15). Matthews et al did a smaller uncontrolled study looking at the prevalence of DM in patients who underwent a TAB and found that there was a higher prevalence of DM in those with a negative biopsy (16). However, when insurance claims data were analysed from the United States of America, individuals with DM were more likely to have developed GCA than a comparative cohort (17). However, in that study the diagnosis of GCA relied on coding data and was not verifiable. There is some evidence that coding data does not translate to verifiable diagnosis for GCA (18).

DM may have a protective effect on GCA and perhaps even some of its complications. Robson et al showed that individuals with GCA have a twofold increase in the risk of aortic aneurysms, but this risk is reduced by the presence of concurrent DM (19). The unadjusted protection for this event was an odds ratio (95% CI) of 0.32 (0.19, 0.56), which is almost exactly the odds ratio in our study of the level of protection that DM offers against GCA. There are two possible mechanisms of this protection. It is possible that poorly controlled diabetes may be

associated with impairment of immune responses which are relied upon to cascade inflammation in GCA. The second is the possibility that microangiopathy associated with DM may involve the vasa vasora in the adventitia which may not allow the leakage of pro-inflammatory cells into the arterial wall. It is also possible that DM may have no modification of the disease process of GCA and that this is an observation related to the shared demographic between Type 2 DM and GCA – women over 65 with raised CRP. Even in that scenario, this observation will be helpful to prevent over-diagnosis of GCA in individuals with diabetes.

Current strategies to form a pre-test probability for GCA have not considered HbA1c as a significant factor. There is a current international effort to formulate diagnostic and classification criteria for various vasculitides (20). We would recommend that HbA1c be considered as a possible variable in formulating criteria. We are going to use these data to study the prevalence of verifiable GCA in individuals with DM and compare that to the incidence of GCA in the general population. The added advantage of testing HbA1c in this population is the increased awareness of the risk of developing diabetes in those on long term high dose corticosteroids (13).

In summary, we have shown in a controlled study that HbA1c in the diabetic range should be taken into account to form a pre-test probability for GCA. DM may be protective against GCA and taking our study into account will reduce the numbers of individuals who might otherwise be needlessly treated with prolonged courses of corticosteroids to their great detriment.

Key Messages

1. Women over 65 are a common demographic for GCA and DM
2. People with HbA1c in the diabetes range are less likely to have GCA.
3. HbA1c should be considered in any multivariable score to calculate risk of GCA

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Figure legend

Figure 1 HbA1c scatter of 336 patients divided into cases and controls Cases: those with confirmed GCA; controls: those referred as GCA, where it was subsequently excluded. The horizontal lines demarcate the boundaries of euglycemia, pre-diabetes and Diabetes mellitus.

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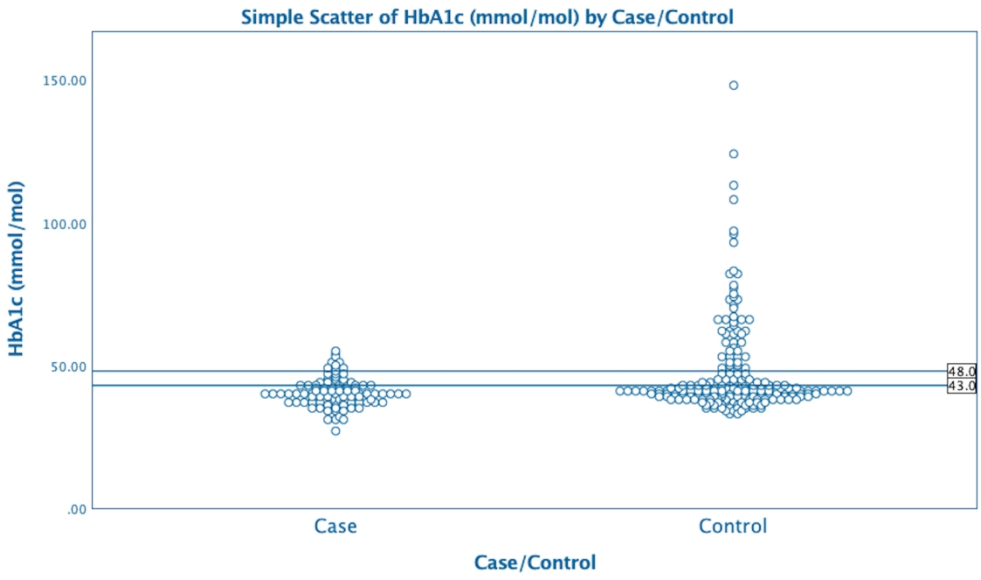
Glycaemic groups (mmol/mol)	Cases (expected)	Controls (expected)
Euglycaemia (HbA1c ≤42)	80 (72)	136 (144)
Pre-diabetes (HbA1c 43-47)	22 (19.3)	36 (38.7)
Diabetes (HbA1c ≥48)	10 (20.7)	52 (41.3)

Table 1 Observed and Expected Numbers of cases and controls by glycaemic categories and the odds of having GCA



HbA1c scatter of 336 patients divided into cases (those with confirmed GCA) and controls (those referred as GCA, where it was subsequently excluded). The horizontal lines demarcate the boundaries of euglycemia, pre-diabetes and Diabetes mellitus.