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Concise Report

The relationship between glycated haemoglobin levels and the risk of giant cell arteritis – a case–control study

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Abstract

Objectives The EULAR core dataset for observational studies in GCA does not include glycated haemoglobin (HbA_{1c}). A multivariable score to stratify the pre-test probability of GCA also does not include HbA_{1c}. There have been contradictory reports about diabetes mellitus being a risk factor for GCA. We report the first study analysing the relationship of pre-diagnosis HbA_{1c} 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 two age- and sex-matched controls. The primary outcome measure was the glycaemic status (HbA_{1c} categorized into euglycaemia, pre-diabetes or diabetes mellitus) at diagnosis between cases and controls. The HbA_{1c} was compared between two groups using the Mann–Whitney *U* test. The glycaemic categorization was compared using the χ^2 test.

Results One hundred and twelve cases and 224 controls were included. The median (interquartile range) of HbA_{1c} of cases and controls was 40 (37, 43) and 41 (39, 47) mmol/mol ($P < 0.001$), respectively. Ten of 112 cases and 52 of 224 controls had diabetes mellitus. The χ^2 test demonstrated a significant interaction between glycaemic state and GCA ($P = 0.006$). Individuals with diabetes mellitus had an odds ratio (95% CI) of 0.32 (0.13, 0.74) ($P = 0.008$) of having GCA compared with euglycaemic individuals.

Conclusion HbA_{1c} in the diabetic range reduces the probability of GCA. HbA_{1c} should be considered in any multivariable score to calculate the risk of GCA, and in future development of diagnostic and classification criteria. There is a need for an epidemiological study looking at the possibility of a protective nature of diabetes mellitus against GCA or whether it is only a mimic.

Key words: giant cell arteritis, diabetes mellitus, glycated haemoglobin, case–control study, risk stratification

CLINICAL SCIENCE

Introduction

GCA is a primary systemic vasculitis, which most commonly affects women in the eighth decade of life [1]. High-dose glucocorticoid therapy remains the cornerstone of treatment and is typically tapered over ~2 years [2, 3]. EULAR recommends that the core dataset for observational studies and routine clinical care should include the laboratory markers of haemoglobin, ESR and CRP [4]. It also recommends recording the presence or absence of diabetes mellitus, but not glycated haemoglobin (HbA_{1c}). HbA_{1c} is the measure of prevailing plasma glucose concentrations over the preceding 3 months. A multivariable score to stratify the pre-test probability for GCA includes CRP as the only laboratory marker [5].

The global prevalence of diabetes mellitus in the adult population has been estimated to be 463 million in 2019 and is calculated to reach 700 million by 2045 [6]. Diabetes is known to be a pro-inflammatory state, and individuals with the condition have a higher CRP

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Key messages

- Women >65 years of age are a common demographic for GCA and diabetes mellitus.
- People with glycated haemoglobin in the diabetes range are less likely to have GCA.
- Glycated haemoglobin should be considered in any multivariable score to calculate risk of GCA.

compared with the general population [7]. In addition, there is a distinct difference in the incidence of diabetes amongst different age groups and by sex, with the most common population for incident diagnosis of diabetes mellitus being women >65 years of age [8]. Finally, there is an increased risk of anterior ischaemic optic neuropathy in elderly individuals with diabetes mellitus, 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 had a sensitivity of ~40% for a diagnosis of GCA in two recent studies [10, 11]. Given that diagnostic US does not have widespread availability [12], there is a high probability of making a clinical diagnosis of GCA in this scenario, leading to long-term CS 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 h, and an US 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 US 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 HbA_{1c} as a method of glycaemic stratification for individuals who might find themselves on long-term prednisolone [13]. In this paper, we examine 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 in this study. Individuals were considered to have GCA (case) if they had a positive US scan as previously defined [14], a temporal artery biopsy demonstrating intramural inflammation or a positive PET. Individuals in whom CSs were stopped were considered as controls. Each case was assigned two age- (by decade) and sex-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 that analysed data acquired during the routine care of the patients.

Data

Age and HbA_{1c} (if available) at diagnosis of GCA were recorded. All individuals were also categorized as euglycemic [HbA_{1c} ≤42 mmol/mol (6.0%)], pre-diabetes [HbA_{1c} 43–47 mmol/mol (6.0–6.4%)] and diabetes [HbA_{1c} ≥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 Student's unpaired *t* test if the distribution was parametric or the Mann–Whitney *U* test if the distribution was non-parametric. The distribution of categorical variables was checked using the χ^2 test. This test measures whether the difference between the observed distribution and the expected distribution is statistically significant. Odds ratios were calculated using binary logistic regression. All statistics were calculated with IBM SPSS v.25 (IBM, Armonk, NY, USA).

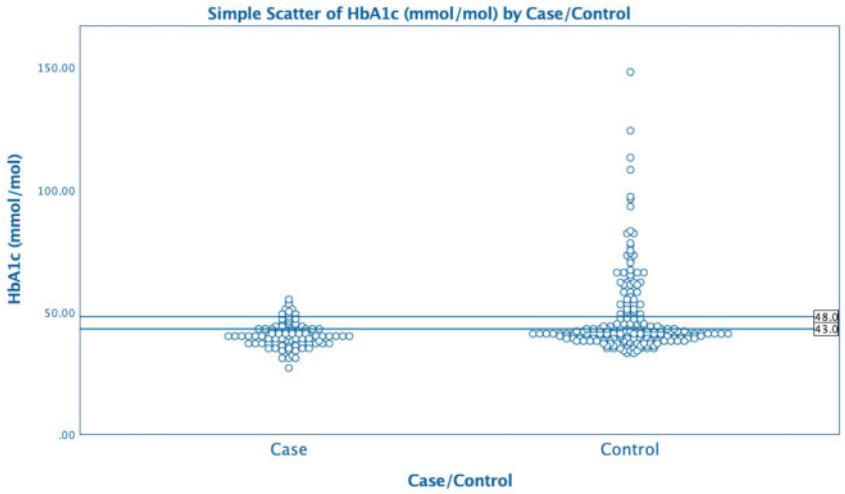
Results

Six hundred and two individuals between 10 January 2012 and 5 October 2019 were seen in our GCA service. The HbA_{1c} 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 sex controls. 36 pairs were male and 76 female. The mean (S.D.) 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 HbA_{1c} was not parametric (using the Shapiro–Wilk test). The median (interquartile range) HbA_{1c} of the cases and controls was 40 (37, 43) and 41 (39, 47) mmol/mol, respectively. The distribution is shown in Fig. 1. The Mann–Whitney *U* test indicated that the HbA_{1c} was greater for controls than for cases ($U = 15824.5$, $P < 0.001$).

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

Fig. 1 Glycated haemoglobin scatter of 336 patients divided into cases and controls



The horizontal lines demarcate the boundaries of euglycemia, pre-diabetes and diabetes mellitus. Cases: those with confirmed GCA; controls: those referred as GCA, where it was subsequently excluded; HbA_{1c}: glycated haemoglobin.

Table 1 Observed and expected numbers of cases and controls by glycaemic category and the odds of having GCA

Glycaemic groups (mmol/mol)	Cases, observed (expected)	Controls, observed (expected)
Euglycaemia, HbA_{1c} ≤42 mmol/mol	80 (72)	136 (144)
Pre-diabetes, HbA_{1c} 43–47 mmol/mol	22 (19.3)	36 (38.7)
Diabetes HbA_{1c} ≥48 mmol/mol	10 (20.7)	52 (41.3)

HbA_{1c}: glycated haemoglobin.

The odds of GCA in the three glycaemic groups was 0.59 (euglycaemic group), 0.61 (pre-diabetes group) and 0.19 (diabetes group). Individuals with diabetes (HbA_{1c} ≥48 mmol/mol) had an odds ratio (95% CI) of 0.32 (0.13, 0.74) ($P = 0.008$) of being diagnosed with GCA in comparison to the individuals with euglycaemia.

We noted and categorized anti-diabetes therapy into groups as in Supplementary Table S2 available at *Rheumatology Advances in Practice* online. Two cases and 37 controls were on anti-diabetes medicines. Although this difference was statistically significant on χ^2 analysis ($P < 0.001$), the numbers were too small to permit meaningful statistical analysis. All the patients on anti-diabetes medication had an HbA_{1c} ≥48 mmol/mol.

Discussion

Our study shows that in the population referred to our fast-track clinic, having an HbA_{1c} in the diabetes range is associated with lower odds of having GCA. Our study, which we believe is the first of its type, 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 had definite GCA established on a biopsy, US 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 sex on glycaemic status [8].

We also recognize the limitations of our study. It is a retrospective, single-centre study. We have focused 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 might be immunomodulatory and therefore protective against development of GCA. We have not been able to adjust for that variable in this observation. Likewise, we have not been able to control for other metabolic associations of diabetes mellitus, such as dyslipidaemia, or other medications, such as statins. However, our finding is in line with that of Ungprasert *et al.* [15], who have carried out a pooled analysis of five separate studies and shown that individuals with GCA had a statistically lower prevalence of diabetes mellitus than controls. Matthews *et al.* [16] carried out a smaller uncontrolled study looking at the prevalence of diabetes mellitus in patients who underwent a temporal artery biopsy and found

that there was a higher prevalence of diabetes mellitus in those with a negative biopsy. However, when insurance claims data were analysed from the USA, individuals with diabetes mellitus 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].

Diabetes mellitus might have a protective effect on GCA and perhaps even some of its complications. Robson *et al.* [19] 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 diabetes mellitus. 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 diabetes mellitus offers against GCA. There are two possible mechanisms for this protection. The first possibility is that poorly controlled diabetes might be associated with impairment of immune responses, which are relied upon to cascade inflammation in GCA. The second possibility is that microangiopathy associated with diabetes mellitus might involve the vasa vasorum in the adventitia, which might not allow the leakage of pro-inflammatory cells into the arterial wall. It is also possible that diabetes mellitus might cause no modification of the disease process of GCA and that this is an observation related to the shared demographic between type 2 diabetes mellitus and GCA (i.e. women >65 years of age 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 HbA_{1c} as a significant factor. There is a current international effort to formulate diagnostic and classification criteria for various vasculitides [20]. We would recommend that HbA_{1c} 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 diabetes mellitus and compare that with the incidence of GCA in the general population. The added advantage of testing HbA_{1c} in this population is the increased awareness of the risk of developing diabetes in those on long-term high-dose CSs [13].

In summary, we have shown in a controlled study that HbA_{1c} in the diabetic range should be taken into account to form a pre-test probability for GCA. Diabetes mellitus might be protective against GCA, and taking our study into account will reduce the numbers of individuals who might otherwise be treated needlessly with prolonged courses of CSs to their great detriment.

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Supplementary data

Supplementary data are available at *Rheumatology Advances in Practice* online.

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