Blood rheology and cognition in the Edinburgh Type 2 Diabetes Study

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Abstract

Background: the association between the rheological factors haematocrit and plasma viscosity and cognitive ability has not been extensively studied. It is possible that blood viscosity affects cerebral blood flow and cognitive function. This study...
Blood rheology and cognition in type 2 diabetes

tested the contemporaneous associations between these two markers of rheology and cognitive ability and estimated lifetime cognitive change in an elderly population with type 2 diabetes.

Methods: A cross-sectional cohort of 1,066 men and women with type 2 diabetes (Edinburgh Type 2 Diabetes Study) was used for the analysis. Plasma viscosity and haematocrit were measured in venous blood samples at baseline. Contemporaneously, a battery of seven cognitive tests was administered to all participants. These data were used to derive a general intelligence factor, g. A vocabulary-based test was also administered as an estimate of prior intelligence, and adjustment for scores on this test was used to estimate lifetime cognitive decline.

Results: Increased plasma viscosity was associated with poorer age- and sex-adjusted scores on the cognitive domains of processing speed, mental flexibility and general intelligence, g, with standardised regression coefficients −0.092 (P < 0.01), −0.077 (P < 0.05) and −0.093 (P < 0.01), respectively. After adjusting for vocabulary, education level, cardiovascular dysfunction, duration of diabetes and glycaemic control, the associations remained significant for the measure of processing speed and g, with standardised regression coefficients −0.059 (P < 0.05) and −0.051 (P < 0.05). Increased haematocrit was significantly associated with better age- and sex-adjusted cognitive scores on the majority of the tests and with g. However, significant associations were not retained after adjustments for additional covariates.

Conclusions: Increased plasma viscosity is associated with decreased cognitive ability and increased estimated lifetime cognitive decline. The relationship between haematocrit and cognitive ability requires further study.

Keywords: cognition, rheology, type 2 diabetes mellitus

Introduction

Haematological factors affect the clotting and the viscosity of blood, which in turn may affect cerebral blood flow [1]. Despite evidence for an association between haematological factors and cerebrovascular disease [1, 2], few studies have related these factors to cognitive function in ageing populations. Two such studies investigated the associations between haematocrit and plasma viscosity and late-life cognitive ability [3, 4].

A study by Elwood et al. found cross-sectional U-shaped associations between haematocrit and reaction times but not general intelligence in 2,154 elderly Welsh men from the Caerphilly study [3]. Raised plasma viscosity associated inversely and significantly with both reaction times and general intelligence. Assessment of fibrinogen yielded null findings. Marioni et al. analysed 2,359 elderly men and women from central Scotland participating in the Aspirin for Asymptomatic Atherosclerosis (AAA) trial [4]. They found no association between haematocrit and six measures covering the main domains of cognitive function. Significant findings were reported for both plasma viscosity and fibrinogen with increased levels associating with decreased cognitive ability. The associations were most pronounced for measures of processing speed, mental flexibility and general ability although the magnitude of the associations were typically small (standardised regression coefficients did not exceed 0.10). In contrast to the main Caerphilly study analysis, the AAA trial cohort had blood samples for marker measurements taken 5 years prior to cognitive testing. Nonetheless, the Caerphilly study also repeated their calculations using marker measures from 5 years prior to cognitive testing, finding a similar but slightly weaker pattern of results compared to the cross-sectional analysis. However, they argued in favour of taking a cross-sectional approach given that previous studies found venesection to reduce high haematocrit levels, resulting in an immediate improvement in cerebral blood flow and cognitive function [5, 6].

The aim of this study was to further examine the relationship between markers of rheology and cognitive function using cross-sectional data on over 1,000 persons with type 2 diabetes.

Methods

Study population

The Edinburgh Type 2 Diabetes Study (ET2DS) is a population based study of 1,066 men and women aged 60–75 years with type 2 diabetes living in Lothian, Scotland, established to investigate the role of inflammation, glucocorticoids and microvascular disease in the aetiology of cognitive impairment in type 2 diabetes. Cross-sectional baseline data were used for the current analysis. Cognitive testing was undertaken, a health questionnaire was administered and blood was extracted for biomarker and other relevant biological measures between 2006 and 2007. Assays were performed in the University Department of Medicine, Glasgow Royal Infirmary. Plasma viscosity was assayed in a fresh blood sample anticoagulated with K₂EDTA in a capillary viscometer (Coulter) at 37°C [4]. In the same sample, haematocrit was measured using a microcentrifuge and optical reader (Hawksley) [4]. All subjects were living independently in the community and provided written, informed consent to take part in the study. Ethical approval for the ET2DS was granted by the Lothian Research Ethics Committee. A full description of the cohort recruitment and examination process has been published [7].
Cognitive assessment

Cognitive ability was assessed using tests of non-verbal memory (Faces and Family Pictures Subtest (FACES), Logical Memory I (LM) from the Wechsler Memory Scale III uk [8]); working memory, non-verbal reasoning, processing speed (Letter–Number Sequencing (LNS), Matrix Reasoning (MR), Digit Symbol Test (DST) from the Wechsler Adult Intelligence Scale (WAIS) III uk [9]); executive function (Verbal Fluency Test (VFT) [10]); and mental flexibility (Trail Making Test, Part B (TMT) [11]). Vocabulary (‘crystallised’ intelligence) was measured in this group using the combined Junior and Senior Mill Hill Vocabulary Scale (MHVS) synonyms [12].

Adjustment variables

The following were included as covariates in the multivariate linear regression models: age at time of cognitive testing in 2006/07; sex; depressed mood — assessed using the Hospital Anxiety and Depression Scale (HADS) [13]; total cholesterol; body mass index (BMI); ankle brachial index (ABI); diastolic brachial blood pressure (BP); smoking — current, ex or non-smoker; self-reported duration of diabetes; coronary heart disease — myocardial infarction or angina; stroke; self-reported best level of education, which was split into four categories — primary, secondary, professional qualification or university/college degree; and glycated haemoglobin (HbA1c). Finally, adjustments were also made for scores on the MHVS in the models of estimated lifetime cognitive change. As results on vocabulary tests such as the MHVS vary little with ageing, they can be used to approximate peak prior cognitive ability [14]. It has been shown that late-life cognitive test scores adjusted for a measure of vocabulary correlate highly with actual cognitive change over a lifetime [15]. Two additional descriptive measures that were assessed at baseline included the proportion of persons receiving insulin treatment and the Scottish Index of Multiple Deprivation [16] (a measure of deprivation assigned to each subject according to post-code of residence).

Statistical analysis

The haematocrit and plasma viscosity measures and all of the cognitive test scores were found to follow a Normal distribution with the exception of the TMT scores, which were positively skewed and therefore transformed using natural logarithms. Scores from the seven cognitive tests were used to obtain a general cognitive ability factor, g, via a principal components analysis. Scree slope analysis indicated a single principal component, which accounted for 44.0% of the variance. Each individual test was found to load strongly on g (range 0.454–0.794); the loading for the TMT was negative (−0.794) due to a high score on this test reflecting lower cognitive ability.

Age- and sex-adjusted linear regression was used to analyse the association between the cognitive scores and rheological markers. Further adjustments were made for the MHVS to enable an estimate of relative lifetime cognitive change, and for additional covariates to control for mood (HADS depression score), duration of diabetes and glycaemic control (HbA1c), cardiovascular risk factors (total cholesterol, BMI, diastolic BP, smoking, ABI), cardiovascular disease (myocardial infarction, angina and stroke) and level of education. The modelling approach used a three-tiered process. Initially, we focussed on an age- and sex-adjusted model before controlling for MHVS to obtain an estimate of lifetime cognitive change. Finally, we ran a fully adjusted model, which controlled for these three factors in addition to other covariates that may have confounded the association between rheological factors and estimated lifetime cognitive change. The regression analysis was powered at over 90% for a two-sided significance test (a = 0.05) to detect a standardised regression coefficient of 0.10. All analyses were performed using R version 2.7.0 [17].

Results

The mean age of the ET2DS was 67.9 years (s.d. 4.2), and approximately half of the sample was male (n = 547, 51.3%). The study descriptives (Table 1) show a relatively healthy ageing cohort with slightly lowered mean cholesterol and BP, which are most likely a consequence of the medication being taken to control for cardiovascular risk factors. The mean values for the rheological markers were 1.31 mPa s (s.d. 0.086) for plasma viscosity and 0.41 (s.d. 0.042) for haematocrit. Splitting the cohort by gender showed males to have a higher mean haematocrit measure (0.42 versus 0.39).

Table 2 shows the linear regression results for the cross-sectional associations between the rheological markers and cognition and also the results for the estimated lifetime cognitive change models. For the age- and sex-adjusted models, plasma viscosity associated significantly with DST, TMT and g, with standardised coefficients −0.092 (P < 0.01), −0.077 (P < 0.05) and −0.093 (P < 0.01). In the estimated lifetime change models, adjustment for the MHVS scores reduced the magnitude of the associations although all remained statistically significant, with standardised coefficients −0.074 (P < 0.01), −0.064 (P < 0.05) and −0.063 (P < 0.05). In the fully adjusted model, only the associations with TMT and g remained statistically significant, with standardised coefficients −0.059 (P < 0.05) and −0.053 (P < 0.05). The DST results showed a trend toward association, with a standardised coefficient of −0.056 (P = 0.057). The associations were all in the direction of increased plasma viscosity relating to decreased cognitive ability and cognitive decline. The TMT coefficients were in the opposite direction from the other cognitive tests due to increased scores (time to task completion) reflecting poorer cognitive ability.

For the models investigating haematocrit levels with cognitive ability, several significant findings were found in the
Blood rheology and cognition in type 2 diabetes

Table 1. Baseline characteristics of the ET2DS population

<table>
<thead>
<tr>
<th>ET2DS population (n = 1,066)</th>
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<tbody>
<tr>
<td>Age (years)</td>
<td>67.9 (4.20)</td>
</tr>
<tr>
<td>Male — n (%)</td>
<td>547 (51.3)</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>8.1 (4.46)</td>
</tr>
<tr>
<td>Duration of diabetes — n (%)</td>
<td>550 (51.6)</td>
</tr>
<tr>
<td>Up to 5 years</td>
<td>516 (48.4)</td>
</tr>
<tr>
<td>≥ 5 years</td>
<td>550 (51.6)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.4 (1.12)</td>
</tr>
<tr>
<td>Insulin treatment — n (%)</td>
<td>185 (17.4)</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>133.3 (16.44)</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
<td>69.1 (9.02)</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>4.31 (0.90)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>31.4 (5.69)</td>
</tr>
<tr>
<td>Smoker — n (%)</td>
<td>153 (14.4)</td>
</tr>
<tr>
<td>Current</td>
<td>499 (46.8)</td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>414 (38.8)</td>
</tr>
<tr>
<td>Never smoked</td>
<td>185 (17.4)</td>
</tr>
<tr>
<td>HADS depression</td>
<td>3 (1, 6)</td>
</tr>
</tbody>
</table>

Values are mean (standard deviation), median (interquartile range) or n (%). ET2DS, Edinburgh Type 2 Diabetes Study; BP, blood pressure; HbA1c, glycated haemoglobin; ankle brachial index, ABI; BMI, body mass index; HADS, Hospital Anxiety and Depression Scale; SIMD, Scottish Index of Multiple Deprivation; CHD, coronary heart disease (myocardial infarction or angina).

*Self-reported highest education level attained.

Table 2. Multivariate associations between rheological markers and late-life cognition, and estimated cognitive change

<table>
<thead>
<tr>
<th></th>
<th>MR</th>
<th>LNS</th>
<th>VFT</th>
<th>DST</th>
<th>−ln(TMT)</th>
<th>FACES</th>
<th>LM</th>
<th>g</th>
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<tr>
<td></td>
<td>Standardised beta coefficient (s.e.)</td>
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<tr>
<td><strong>Plasma viscosity</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex</td>
<td>−0.056 (0.031)</td>
<td>0.049 (0.032)</td>
<td>−0.032 (0.032)</td>
<td>−0.092 (0.031)**</td>
<td>−0.077 (0.031)*</td>
<td>−0.047 (0.031)</td>
<td>−0.009 (0.032)</td>
<td>−0.093 (0.031)**</td>
</tr>
<tr>
<td>MHVS</td>
<td>−0.038 (0.028)</td>
<td>−0.030 (0.029)</td>
<td>−0.009 (0.029)</td>
<td>−0.074 (0.026)**</td>
<td>−0.064 (0.029)*</td>
<td>−0.035 (0.029)</td>
<td>0.008 (0.029)</td>
<td>−0.063 (0.025)*</td>
</tr>
<tr>
<td>MHVS and adjustment variables</td>
<td>−0.040 (0.029)</td>
<td>−0.016 (0.031)</td>
<td>0.002 (0.030)</td>
<td>−0.056 (0.029)</td>
<td>−0.059 (0.030)*</td>
<td>−0.028 (0.032)</td>
<td>0.017 (0.032)</td>
<td>−0.051 (0.026)*</td>
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<tr>
<td><strong>Haematocrit</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age and sex</td>
<td>0.068 (0.033)*</td>
<td>0.074 (0.033)*</td>
<td>0.052 (0.034)</td>
<td>0.068 (0.032)*</td>
<td>0.094 (0.033)**</td>
<td>0.075 (0.033)*</td>
<td>−0.022 (0.033)</td>
<td>0.082 (0.033)*</td>
</tr>
<tr>
<td>MHVS</td>
<td>0.029 (0.030)</td>
<td>0.044 (0.031)</td>
<td>0.014 (0.030)</td>
<td>0.039 (0.030)</td>
<td>0.060 (0.030)</td>
<td>0.052 (0.032)</td>
<td>−0.051 (0.031)</td>
<td>0.039 (0.027)</td>
</tr>
<tr>
<td>MHVS and adjustment variables</td>
<td>0.030 (0.032)</td>
<td>0.030 (0.030)</td>
<td>0.011 (0.032)</td>
<td>0.033 (0.032)</td>
<td>0.055 (0.032)</td>
<td>0.035 (0.034)</td>
<td>−0.068 (0.034)*</td>
<td>0.016 (0.028)</td>
</tr>
</tbody>
</table>

*Adjustment variables*: HADS depression score, duration of diabetes, HbA1c, total cholesterol, BMI, diastolic BP, smoking, myocardial infarction, angina, stroke, ABI and level of education. **P < 0.05, ***P < 0.01, MR, Matrix Reasoning; LNS, Letter–Number Sequencing; VFT, Verbal Fluency Test; DST, Digit Symbol Test; TMT, Trail Making Test, Part B; FACES, Faces and Family Pictures Subtest; LM, Logical Memory; g, general intelligence factor; MHVS, Mill Hill Vocabulary Scale.

Discussion

This cross-sectional study of the two main determinants of blood viscosity (plasma viscosity and haematocrit) and cognition showed reasonably strong evidence for an association between plasma viscosity and several measures of cognition in later life: processing speed, mental flexibility and general intelligence. There was also evidence relating raised levels of plasma viscosity to increased estimated cognitive decline. By contrast, there was weak evidence to suggest that increased haematocrit levels associated with decreased estimated cognitive decline.

Finally, age- and sex-adjusted linear regression analyses showed haematocrit but not plasma viscosity to be associated with the MHVS, with standardised coefficients of 0.071 (P = 0.043) and −0.048 (P = 0.13).
Comparing the magnitude and direction of the effects with the results from the Caerphilly study is difficult given that Elwood et al. split the marker data into quartiles prior to analysis [3]. However, comparison with the AAA trial data [4], which was analysed in a near identical way, showed consistent findings for plasma viscosity with both cognitive ability and estimated cognitive decline. The standardised effect sizes from both studies were similar and did not exceed 0.10. There was also support for replication of the AAA trial findings with the plasma viscosity associations being strongest for the processing speed/mental flexibility domains and with the general intelligence factor. In contrast to the AAA trial findings, which yielded no significant associations between haematocrit and cognition, and also to the Caerphilly study findings, the ET2DS data suggested a positive association between haematocrit and cognition. However, all bar one of these associations disappeared after adjustment for the MHVS score. Reverse causation has been presented previously to explain the relationship between plasma C-reactive protein (CRP) and fibrinogen levels and cognitive ability [18]. As haematocrit was significantly associated with MHVS, such a mechanism may provide an explanation for the findings presented here. However, given the small size and weakly significant nature of the effect sizes, the addition of any covariate that correlates relatively highly with the cognitive scores (range for the MHVS and cognitive scores was 0.28–0.57) to the age- and sex-adjusted models is likely to render these associations non-significant.

Unlike the AAA trial, which had prospective data, the ET2DS analysis was based on cross-sectional associations. This is a limitation of the study as we were only able to estimate cognitive change rather than measure it directly from tests performed at two different time points. In addition, we would ideally have had more than a single evaluation of rheology, an issue which we will address in future follow-up phases of the ET2DS. In total, 48 tests were conducted in the course of this analysis, raising the possibility of false positive findings. However, we reduced the dimensionality of the cognitive dataset by creating a g-factor, which resulted in only six major tests being performed. The results for the individual cognitive tests were included in order to try and pin-point the specific cognitive domains that were behind the main associations.

Whilst the methodology used here is identical to that of the AAA trial (linear regression), the Caerphilly study reported a U-shaped relationship between haematocrit and cognition and thus inserted a quadratic term into their models. Such an approach was investigated here, but there was no strong evidence to favour its use (results not shown). Comparison of the marker levels in the three studies showed lower plasma viscosity readings for the AAA trial and the ET2DS than the Caerphilly cohort and slightly lower haematocrit measures in the ET2DS males (mean plasma viscosity AAA trial: 1.27, ET2DS: 1.31, Caerphilly cohort: 1.70 mPa s and mean haematocrit 0.42 (0.45 for males), 0.41 (0.42 for males), 0.46 (all males), respectively). However, plasma viscosity was measured at 25°C in the Caerphilly cohort and at 37°C in the AAA trial and ET2DS. Upon application of the standard correction factor for these differences, plasma viscosity values were similar in all three studies. There were no significant (P < 0.05) marker:gender interactions in any of the models for either plasma viscosity or haematocrit (results not shown). The increased haematocrit levels in the Caerphilly study compared to the ET2DS may explain the non-significant inclusion of a quadratic term to the modelling. Furthermore, these differences may also provide an explanation for the positive associations that were uncovered. Had the range of haematocrit values been greater in the ET2DS then it is entirely possible that U-shaped associations would have been uncovered. Mechanistically, a U-shaped association between haematocrit and cognitive impairment is plausible with higher haematocrit increasing blood viscosity, but lower haematocrit reducing oxygen delivery.

The main strengths of this study include extensive phenotyping that enabled comprehensive adjustments to be made for indicators of cardiovascular disease, education, lifestyle, diabetes control and duration of diabetes. Whilst the sample size was smaller than the two previous large-scale studies in this area, it was still sufficiently large to detect small associations between the markers and cognitive ability. To our knowledge, it is also the first study to investigate rheology and cognition in a population with type 2 diabetes. Our study did not set out to determine whether there is any differential effect of plasma viscosity or haematocrit on cognition in people with diabetes compared to those without diabetes, which would have required a non-diabetic comparator population. However, it is possible to speculate that there may indeed be some differential effect, not least due to the large number of complications, co-morbidities, alterations in circulating biomarkers and medication use associated with the diabetic condition, many of which are likely to interact with each other and with factors such as plasma viscosity, in the development of cognitive change [19]. In addition, plasma viscosity and haematocrit are found to be elevated in persons with or at risk from type 2 diabetes [20, 21], and any effect of these factors on cognitive ability may therefore be accentuated in the diabetic population.

Due to different findings from the AAA trial and a different methodological approach to the Caerphilly study, it is difficult to draw firm conclusions for haematocrit when combining results from the ET2DS and the two previous studies. However, the plasma viscosity results are consistent across the studies. Combined with a growing body of evidence to associate increased plasma fibrinogen (a major determinant of plasma viscosity) with decreased cognition and cerebrovascular disease, this suggests that there is a consistent link between blood flow and cognitive ability [22–25].

In conclusion, there is consistent evidence for an association between plasma viscosity and both cognitive ability and cognitive change. However, these relationships need to be examined further via additional large-scale prospective
cohort data or, potentially, through randomised controlled trials of plasma viscosity reduction (e.g. by statins) [26]. Further studies are also required to assess the associations between haematocrit and cognitive function.

**Key points**

- Increased plasma viscosity is associated with decreased cognitive ability in later life.
- Increased plasma viscosity is associated with increased estimated lifetime cognitive decline.
- There is potentially a U-shaped relationship between haematocrit and cognitive ability although this requires further study.

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**Conflicts of interest**

None.

**References**


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