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Brief report

Increased red cell count in diabetes and pre-diabetes

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ABSTRACT

The aim of this study was to test whether an increased red cell count (RCC) is present in pre-diabetes, obesity and the metabolic syndrome. The results demonstrate that these diabetes precursor states are associated with an increased RCC. This relationship can be explained, in part, by an increased HbA1c.

1. Introduction

An increased haematocrit and blood viscosity are important determinants of blood rheology and are also associated with an increased risk of coronary heart disease [1,2]. Diabetic patients have been shown to respond normally to haematocrit variation, suggesting that a raised haematocrit would also be associated with an increased risk of macrovascular disease [3]. Haematocrit is dependent on the number and nature of erythrocytes and the question as to whether erythrocytes are "normal" in diabetes has arisen. Decreased erythrocyte deformability [4] and a 10% increase in red cell count (RCC) ("relative polycythaemia") have previously been shown [5]. Erythrocyte deformation is inversely related to HbA1c [6] and red cell number is positively correlated with the HbA1 [5]. More recently, RCC has been shown to be associated with insulin resistance [7]. We wondered if other pre-diabetic states also had an increased RCC.

2. Materials and methods

The "Crossroads study" was carried out between June 2001 and March 2003 across seven Australian towns as previously described [8–10]. Briefly, an initial census of 2376 randomly selected households (half in the regional centre, a twelfth in each of the six smaller towns) was undertaken. All usual (at least 6 months) residents aged ≥25 years who participated in the census were invited to attend a morning "clinic" fasting. Demographic, health, socioeconomic, anthropometric and blood pressure data were collected [8–10]. Glucose was collected and measured as previously described [8]. Diabetes,

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Table 1 – Adjusted red cell count ($\times 10^{11}$/L), haemoglobin (g/dl) and HbA1c (%) and glucose tolerance.

	N	Red cell count	Haemoglobin	HbA1c
Normal glucose tolerance	1168	47.4(47.2–47.6)	14.5(14.5–14.6)	5.15(5.13–5.18)
Impaired glucose tolerance/impaired fasting glucose	149	48.4(47.8–49.0)	14.7(14.5–14.9)	5.38(5.32–5.45)
New diabetes	31	49.6(48.3–51.0)	15.0(14.6–15.3)	6.32(6.17–6.47)
Known diabetes	106	46.6(45.9–47.4)	14.1(13.9–14.3)	6.59(6.51–6.67)
Diabetes with CKD III or more	32	44.3(42.5–46.0)	13.3(12.8–13.8)	6.60(6.17–7.02)
Diabetes without CKD III or more	105	48.2(47.3–49.0)	14.6(14.4–14.9)	6.56(6.35–6.78)
Diabetes excluded				
Metabolic syndrome	256	48.5(48.0–48.9)	14.7(14.6–14.9)	5.28(5.25–5.31)
No metabolic syndrome	1061	47.3(47.0–47.5)	14.5(14.4–14.6)	5.15(5.13–5.17)
Past gestational diabetes (women only)	40	45.6(45.5–46.7)	13.8(13.5–14.1)	5.22(5.15–5.29)
No past GDM	710	45.6(45.3–45.8)	13.9(13.8–14.0)	5.16(5.14–5.18)
Obese (BMI 30 + kg/m^2)[a]	341	48.1(47.7–48.5)	14.6(14.5–14.7)	5.27(5.24–5.30)
Not obese	971	47.3(47.1–47.6)	14.5(14.5–14.6)	5.14(5.13–5.16)
Smoker	223	47.8(47.3–48.3)	14.9(14.7–15.0)	5.21(5.17–5.24)
Not a smoker	1094	47.4(47.2–47.7)	14.5(14.4–14.5)	5.17(5.15–5.18)

Mean (95% confidence intervals) shown after adjusting for town, age, sex, ethnicity, socioeconomic status.
[a] 6 cases had missing data.

impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) were defined by World Health Organisation criteria [8], metabolic syndrome (MS) by ATPIII criteria [9] and chronic kidney disease (CKD III) as an estimated glomerular filtration rate <60 ml/min using MDRD criteria [11]. Biochemical analyses were undertaken using a Hitachi 917R auto-analyser (Hitachi, Tokyo, Japan). Full blood examination was undertaken by flow cytometry using an Abbott Cell-Dyn 400 (Abbott laboratories, Abbott Park, IL, USA). Total glycated haemoglobin analysis used high-performance liquid chromatography (Bio-Rad Variant Hemoglobin Testing System: Bio-Rad, Hercules, CA) with standardized conversion to HbA1c values. The study was approved by the Goulburn Valley Ethics Committee.

Data were analysed using SPSS v15 (SPSS Inc., IL, USA). Results shown are either mean (95% confidence intervals), mean ± standard deviation, median (range) or frequencies (percentages) with $p < 0.05$ taken as significant. All tests are 2 tailed. Unadjusted discrete variables were compared using Chi-squared test and continuous variables using analysis of co-variance. The logistic regression was undertaken using simultaneous, forward and backward entry of variables with little change in the result: only simultaneous entry is shown.

3. Results

The response rate was 61.3% overall. Of the 1454 subjects (56.3% women, 1.2% non-European, 16.4% smokers), mean age was 53 ± 16 years and BMI was 27.9 ± 5.2 kg/m^2.

Differences in haemoglobin and RCC are shown in Table 1. In particular, subjects with new diabetes and IGT/IFG had a higher RCC than normal subjects and those with pre-existing diabetes (Table 1). Those with diabetes and CKD had a lower RCC and haemoglobin than others with diabetes. Among those without diabetes, the RCC was higher in those with MS and obesity. Women with and without past gestational diabetes were similar.

Among men, an RCC above the median was more likely with IGT/IFG and new diabetes, while among women it was more likely with MS and being a smoker (Table 2). Repeating the logistic regressions including the MS non-glycaemic components instead of MS itself among women, a large waist (OR 1.61(1.18–2.21)), a high blood pressure (1.52(1.07–2.15)) and a low HDL (1.58(1.10–2.27)) were significant entrants. No significant relationship was shown among men (data not shown).

After adding HbA1c, having a higher RCC, was associated with haemoglobin and HbA1c. Repeating with the MS non-glycaemic components and waist replacing obesity, a large waist remained an entrant among women (1.62(1.078–2.43)) but not men (data not shown).

4. Discussion

Our study has confirmed the association between an increased RCC and diabetes [5], but only in the absence of CKD III. However, we now also show that RCC is increased in the diabetes precursor states of IGT/IFG, the metabolic syndrome and obesity. In these states, the HbA1c but not the haemoglobin is increased. The earlier hypothesis was that in diabetes, the HbA1c alters erythrocyte oxygen dissociation properties and membrane fluidity [5], thereby leading to relative hypoxia [8]. Alternatively, obstructive sleep apnoea (OSA) could be a common link between obesity and increased haemopoesis. Only 3 participants reported OSA, 2 of whom had diabetes. We did not ask direct questions about sleep or snoring and this is something for further studies to include. Some research has suggested that the adipokines leptin and adiponectin concentrations may also be associated with erythrocyte metabolism [12–16]: future studies should include measures of adipokines.

There were several limitations to our study. Firstly, this is a cross-sectional study rather than prospective and is exploratory and observational in nature. With the small number of new cases of diabetes found, our findings could be by chance, although they are supported by the earlier papers showing an

Table 2 – Logistic regression: odds ratios of having RCC above the median after adjusting for demographic and socioeconomic variables.

	Odds ratio	Significance
Men – model 1		
Normal	1.00	.005
IGT/IFG	2.06(1.15–3.68)	
New diabetes	6.90(1.27–37.6)	
Known diabetes	0.71(0.37–1.36)	
Model 2 = Model 1 variables then including haemoglobin		
Smoker – yes	2.36(1.27–4.40)	.007
Smoker – no	1	
Hb per g/dl	1.28(1.23–1.33)	<.001
Model 3 = Model 1 variables then including haemoglobin and HbA1c		
Smoker – yes	2.58(1.34–4.96)	.004
Smoker – no	1	
Hb per g/dl	1.28(1.23–1.33)	<.001
HbA1c (per 1%)	2.91(1.48-5.69)	.002
Women – Model 1		
Metabolic syndrome – yes	2.15(1.40–3.31)	.001
Metabolic syndrome – no	1	
Smoker – yes	1.64(1.09–2.47)	.017
Smoker – no	1	
Model 2 = Model 1 variables then including haemoglobin		
Smoker – yes	1.81(1.06–3.11)	.031
smoker – no	1	
Hb per g/dl	1.23(1.19–1.26)	<.001
Model 3 = Model 1 variables then including haemoglobin and HbA1c		
Hb per g/dl	1.24(1.20–1.28)	<.001
HbA1c per 1%	3.49(1.84–6.64)	<.001

Variable(s) entered on step 1: CKD III or worse, yes/no, higher education yes/no, European/non-European ethnic group, health insurance yes/no, metabolic syndrome (ATP III) yes/no, smoker yes/no, obese by BMI yes/no, regional town yes/no, glucose tolerance status, 10 year age group.

increased RCC in diabetes. We did not screen for haemoglobinopathies, although these were uncommon locally. We do not feel that identifying a marginally increased RCC will be of use clinically, but it may help explain why the impact of an elevated HbA1c may be greater than the effect of the tissue glycation that it reflects in some individuals.

5. Conclusion

We have shown that IGT, IFG, obesity and metabolic syndrome as well as diabetes (without CKD III) are associated with an increased RCC. This relationship can be explained, at least in part, by an increased HbA1c. A relationship between central adiposity and the RCC was also found among women, a finding warranting further study.

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Conflict of interest

There are no conflicts of interest.

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