Hematocrit and the Incidence of Type 2 Diabetes in the Pima Indians

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Several prospective studies have shown that a high hematocrit (or hemoglobin) predicts type 2 diabetes (1–6). However, the reasons for this association have not been fully explored.

Hematocrit has been positively correlated with hyperinsulinemia and conditions associated with insulin resistance such as high blood pressure, elevated serum triglycerides, low HDL cholesterol, and central obesity and could therefore be associated with insulin resistance (7,8). On the other hand, hematocrit is also a major determinant of blood viscosity (9). An elevated blood viscosity is thought to contribute to the development of insulin resistance by reducing blood flow to skeletal muscle, thereby interfering with insulin-mediated glucose uptake in this tissue (10).

The aim of this study was to examine the association between hematocrit and type 2 diabetes incidence in the Pima Indians and to determine whether any association between hematocrit and diabetes incidence was altered by adjustment for fasting insulin.

**RESEARCH DESIGN AND METHODS** — The population studied was part of an ongoing epidemiological study of diabetes that has been conducted in the Gila River Indian community since 1965 (11). Subjects selected for analysis were ≥20 years old; had height, weight, and hematocrit measurements; and were free of diabetes at their baseline examination. Subjects were classified as nonsmokers, former smokers, and current smokers based on responses to a smoking questionnaire. Hematocrit was measured using an Autocrit centrifuge from venous blood collected in EDTA anticoagulant and stored at 4–10°C until processing. Fasting insulin was measured by radioimmunoassay (Concept 4; ICN Biomedicals, Horsham, PA) in nondiabetic individuals. Diabetes was diagnosed if the 2-h postload glucose from a 75-g oral glucose tolerance test was ≥11.1 mmol/l or if a diagnosis of diabetes had been made during the course of routine medical care because ~60% of the subjects included in the sample (predominantly subjects with their first examination before 1975) did not have a fasting glucose measurement at their baseline examination. Impaired glucose tolerance (IGT) was defined as a 2-h glucose value of 7.8–11.1 mmol/l after a 75-g oral glucose tolerance test.

Proportional hazards models were used to determine the effect of baseline hematocrit on type 2 diabetes risk. Fasting insulin, waist circumference, HDL cholesterol, and triglycerides were not all routinely measured until 1993. Therefore, a second sample, a subset of the original cohort, was generated. Spearman’s correlation coefficient was used to test the relationship between hematocrit and blood pressure, lipids, waist circumference, and insulin in this subset. Hazard rate ratios (HRRs) and 95% CIs for both baseline and for restricting the analysis to subjects with hematocrit measurements within the normal range (41–53% in men and 36–46% in women).

In the subset, significant correlations were noted between the baseline hematocrit and systolic blood pressure ($r = 0.31$, $P < 0.01$), diastolic blood pressure (0.30, $P < 0.01$), fasting triglycerides (0.18, $P < 0.01$), and fasting insulin (0.14, $P < 0.01$). Hematocrit was not correlated with waist circumference (0.04, $P = 0.18$) and was inversely correlated with HDL cholesterol ($–0.07$, $P = 0.03$). The hematocrit was also positively associated with the incidence of type 2 diabetes in this subset, adjusted for age and sex (HRR 1.29 [95% CI 1.02–1.63]); however, with adjustment for fasting insulin, hematocrit no longer predicted diabetes risk (0.97 [0.82–1.15]) (Table 1).

**CONCLUSIONS** — Hematocrit is correlated with fasting insulin and predicts diabetes incidence in Pima Indians independent of age, sex, BMI, time, serum.
creatinine, IGT, and cigarette smoking. The effect of hematocrit on diabetes incidence was no longer significant after adjustment for fasting insulin.

Insulin stimulates the proliferation of erythroid progenitor cells in culture (12). In addition, intravenous infusion of insulin increases the transcapillary escape of albumin, thereby reducing the plasma volume and increasing hematocrit (13). Thus a high hematocrit, in the absence of an underlying hematological or medical disorder, may be the result of elevated insulin levels and reflect insulin resistance.

We are uncertain as to whether an independent effect might have been noted if plasma viscosity, a measure determined not only by hematocrit but also by serum proteins (such as fibrinogen and γ-globulins), red cell deformity, and red cell aggregation, had been measured (9).

In conclusion, elevated hematocrit measurements are associated with higher risk of developing type 2 diabetes in the Pima population, possibly mediated through an association with insulin resistance.

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References

Table 1—HRRs (with 95% CIs) for the development of type 2 diabetes per 5% difference in blood hematocrit

<table>
<thead>
<tr>
<th>Model covariates</th>
<th>Total population (n = 3,513)</th>
<th>Subgroup (n = 993)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age and sex</td>
<td>1.37 (1.26–1.48)</td>
<td>0.97 (0.82–1.15)</td>
</tr>
<tr>
<td>Age, sex, exam date, BMI, smoking, serum creatinine, and IGT</td>
<td>1.40 (1.28–1.53)</td>
<td>1.07 (0.88–1.30)</td>
</tr>
</tbody>
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Age is included as a continuous and quadratic variable in all equations.