Hematocrit and Risk of NIDDM

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There is limited evidence that raised hematocrit levels may be associated with insulin resistance, which links cardiovascular disease with NIDDM. The association between hematocrit level at screening and the subsequent development of physician-diagnosed NIDDM during 12.8 years of follow-up was examined in a prospective study of 7,735 middle-aged men drawn at random from general practice in 24 British towns. With the exclusion of men with missing hematocrit data and men with diabetes at screening, data were available for 7,193 men, in whom there were 187 new cases of NIDDM during follow-up. The risk of NIDDM increased significantly with increasing hematocrit levels. There was more than a fourfold increase in relative risk (RR) of diabetes among men with a hematocrit of ≥48% relative to those with a hematocrit <42%, adjusted for age and BMI (RR 4.5; 95% CI 2.5–6.3). On further adjustment for predictors of NIDDM with which hematocrit is correlated, there remained a strong linear association with the risk of diabetes. There was a nearly fourfold increased risk of NIDDM in the highest relative to the lowest hematocrit group in the fully adjusted proportional hazard model (RR 3.6; 95% CI 1.7–7.6). The strong positive association between hematocrit level and risk of diabetes was seen even after exclusion of men with preexisting ischemic heart disease. The findings suggest that a raised hematocrit level, which is a major determinant of whole blood viscosity, should be added to the cluster of risk factors that link NIDDM with atheromatous vascular disease. *Diabetes* 45:576–579, 1996

There is increasing evidence that in some populations NIDDM and atherosclerotic vascular disease share a number of common genetic and environmental risk factors (1,2). It is proposed that these factors are linked via an insulin resistance syndrome (3). A number of studies (4–6), including our own (7), have reported that vascular risk factors such as obesity, hypertension, and dyslipidemia, which are regarded as elements of the insulin resistance syndrome, predict NIDDM in longitudinal studies (4–7). In our earlier report on predictors of NIDDM, we focused on lifestyle factors that had previously been implicated in the etiology of this condition and on biological factors that are well-established components of the insulin resistance syndrome (7). In this report we examine the role of hematocrit, a novel potential risk factor for NIDDM. There is evidence that hematocrit levels are increased in patients with established diabetes, as one of a range of hemorheological abnormalities that enhance the risk of vascular disease in this condition (8), and there are limited prospective data suggesting that high hemoglobin levels (highly correlated with hematocrit) predict subsequent glucose intolerance (9) and diabetes (10). In cross-sectional data from the Tecumseh Study, raised hematocrit levels were associated with major components of the insulin resistance syndrome, such as obesity, hyperglycemia, hyperinsulinemia, hypertension, and hypertriglyceridemia in healthy nondiabetic men ages 18–42 years (11). These observations raise the possibility that an elevated hematocrit level might predict NIDDM, thereby forming part of the common soil (2) linking NIDDM and cardiovascular disease. We report on a prospective study of the association between hematocrit level and the subsequent risk of physician-diagnosed NIDDM in a general population sample of middle-aged British men.

RESEARCH DESIGN AND METHODS

The British Regional Heart Study is a large prospective study of cardiovascular disease comprising 7,735 men ages 40–59 years selected from the age-sex registers of one group general practice in each of 24 towns in England, Wales, and Scotland. The criteria for selecting the town, the general practice, and the subjects as well as the methods of data collection have been reported (12). Research nurses administered to each man a standard questionnaire that included questions on smoking habits, alcohol intake, physical activity, and medical history. Several physical measurements were made, and nonfasting blood samples were taken for measurement of biochemical and hematological variables. Details of blood pressure measurement and classification methods for smoking status, alcohol consumption, occupation (social class), and BMI have been reported (12,13). The men were asked to indicate their usual pattern of physical activity, and a score was derived for each man based on frequency and type (intensity) of leisure activity (14). The men were grouped into six broad categories based on their total score: inactive, occasional, light, moderate, moderately vigorous, and vigorous. Forced expiratory volume in 1 s (FEV_1) was measured in the seated position with a Vitalograph spirometer, and the values were for standardized height.

Triglyceride. Triglyceride estimations were introduced after the survey had been completed in six towns, and data on triglyceride are therefore only available for 18 towns (5,675 men). Adjustments have been made for the marked diurnal variation in triglyceride measurements using a simple mathematical approach that makes no assumptions about the form of the association between triglyceride and time of sampling. The method involved used the mean log triglyceride level for each hour. Each value was adjusted to one an equal distance away from the grand mean as it was from the mean for the hour in which it was measured [i.e., adjusted log triglyceride = (unadjusted log triglyceride − the mean log triglyceride for the hour of sampling) + the grand mean log triglyceride level] (15,16).

Hematocrit. Blood samples (nonfasting) were taken into evacuated tubes for measurement of biochemical and hematological variables. All samples reached the Department of Haematology, Queen Elizabeth Hospital, Birmingham, by the following morning, and estimations were completed by noon of that day. Hematocrit was estimated using a Coulter S electronic particle counter (Coulter, Luton, U.K.) calibrated daily with Coulter $C. Internal quality control was achieved using an algorithm based on patient-derived hematology data modified from Bull

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FEV_1, forced expiratory volume in 1 s; IHD, ischemic heart disease; RR, relative risk; WHO, World Health Organization.

et al. (17) and external quality assurance by participation in the National External Quality Assurance Scheme. Hematocrit and hemoglobin concentrations were strongly correlated (r = 0.93), and only the hematocrit findings are presented in this paper. Data on hematocrit were missing for 389 men.

Preexisting ischemic heart disease (IHD). The men were asked whether a doctor had ever told them that they had angina or myocardial infarction (heart attack or coronary thrombosis), stroke, or a number of other disorders. The World Health Organization (WHO) (Rose) chest pain questionnaire was administered to all men at the initial examination (18) and a three orthogonal-lead electrocardiogram was recorded at rest. Men with evidence of IHD were defined as those with a recall of doctor diagnosis of angina or heart attack, WHO (Rose) questionnaire responses indicating angina (definite or possible) or possible myocardial infarction, or electrocardiographic evidence of definite or possible myocardial ischemia or myocardial infarction.

Follow-up. All men were followed up for all-cause mortality, cardiovascular morbidity, and the development of NIDDM up to December 1991, a mean period of 12.8 years (range 11.5–13.0 years) (19). New cases of NIDDM were ascertained by means of *1*) a postal questionnaire sent to the men at year 5 of their follow-up, *2*) systematic reviews of primary care records in 1990 and 1992, *3*) a further questionnaire to 6,483 surviving members of the cohort resident in the U.K. in 1992, and *4*) review of all death certificates for any mention of diabetes. On the questionnaire at year 5 a response rate of 98% was achieved, and on the 1992 questionnaire a response rate of 91% was achieved. A diagnosis of diabetes was not accepted on the basis of questionnaire data unless confirmed in the primary care records.

Statistical analysis. The Cox proportional hazards model (20) was used to obtain the relative risks for the five hematocrit groups adjusted for age, smoking, physical activity, BMI, lung function, preexisting IHD, uric acid, heart rate, blood glucose, and systolic blood pressure. Age, BMI, lung function, uric acid, heart rate, blood glucose, and systolic blood pressure were fitted as continuous variables. Smoking (five levels), physical activity (six levels), and preexisting IHD (yes/no) were fitted as categorical variables. Hematocrit was fitted as four dummy variables for the five hematocrit groups. Tests for trend were carried out, fitting hematocrit in its original continuous form. Differences in the hematocrit-NIDDM relationship between men with and without preexisting IHD were assessed by fitting a hematocrit-preexisting IHD interaction term in the model.

RESULTS

Data on hematocrit were available for 7,346 men. Known diabetic subjects at screening (n = 118), those with nonfasting glucose concentrations at screening in the diabetic range (≥11.1 mmol/l, n = 22), and men in whom diabetes was diagnosed within the same calendar year in which they were screened (n = 13) were excluded. Hence the analysis is based on 7,193 men. After a mean follow-up period of 12.8 years (to December 1991), there were 187 new cases of NIDDM in the 7,193 men, an incidence of 2.15 per 1,000 person-years of follow-up.

Because of the nonlinear relationship with IHD and stroke events and the differing threshold effect of hematocrit on risk of IHD and stroke (21,22), the men were divided into five groups based on absolute levels of hematocrit: <42.0% = 1,183 men, 42.0–43.9% = 1,623 men, 44.0–45.9% = 1,974 men, 46.0–47.9% = 1,388 men, and ≥48.0% = 1,025 men.

Hematocrit and risk of NIDDM. Table 1 shows the diabetes incidence rate per 1,000 person-years by the five hematocrit groups in the 7,193 men. The risk of diabetes increased significantly with increasing hematocrit levels. BMI was the strongest determinant of NIDDM in this cohort (7) and was significantly associated with hematocrit levels (23). The strong positive association persisted even after adjustment for age and BMI.

Multivariate analysis. Hematocrit was associated with many of the cardiovascular risk factors known to be associated with NIDDM (23). We further adjusted for risk factors shown to be associated with NIDDM, viz., physical activity, smoking, systolic blood pressure, blood glucose, heart rate, uric acid, HDL cholesterol (7), and FEV_1 (24). This reduced the association, but a hematocrit level of ≥48% was still associated with a nearly fourfold increase in the risk of NIDDM.

TABLE 1
Hematocrit and adjusted RR (95% CI) of NIDDM

Hematocrit level	No. men	No. cases	Rate/1,000 person-years	Adjusted RR +	Adjusted RR ++
<42	1,183	11	0.8	1.0	1.0
42–	1,623	31	1.6	1.9 (0.9, 3.8)	1.9 (1.0, 3.9)
44–	1,974	56	2.4	2.6 (1.9, 5.1)	2.6 (1.3, 5.0)
46–	1,388	34	2.1	2.3 (1.2, 4.5)	1.9 (1.0, 3.9)
48–	1,025	55	4.7	4.5 (2.5, 6.3)	3.9 (2.0, 7.7)
Test for trend				$P < 0.0001$	$P < 0.001$

+, adjusted for age and BMI; ++, adjusted for age, BMI, smoking, alcohol intake, physical activity, preexisting IHD, FEV_1, HDL cholesterol, heart rate, uric acid, blood glucose, and systolic blood pressure. The analysis was based on 6,688 men (171 cases) with complete data on all covariates.

Triglyceride. Hematocrit was significantly associated with triglyceride levels (r = 0.15; $P < 0.0001$), which have also been shown to be an independent predictor of NIDDM in this cohort (7). Triglyceride measurements were only available for 5,292 men. To assess the effects of adjustment for triglyceride, the analysis was performed on this subgroup of men after adjustment first for all the risk factors presented in Table 1 and then in addition for triglyceride. Further adjustment for triglyceride reduced the association only slightly (Table 2).

Preexisting IHD. Since the presence of IHD may be associated with an increase in hematocrit levels (25), we also examined the relationship separately in men with and without preexisting IHD (Table 3). The positive association between hematocrit and risk of NIDDM was apparent in men without preexisting IHD. No consistent association was seen in men with preexisting IHD. This may have been because of the relatively small number of subjects. A test for difference in trend between the two groups was not significant (P = 0.12).

Multivariate prediction. To assess the potential role of hematocrit in identifying men at high risk for subsequent development of NIDDM, we examined the effect of adding hematocrit to multivariate predictive models (risk scores) for this condition (26) (Table 4). In a risk score based on age, BMI, and blood glucose, 58% of cases of NIDDM occurred

TABLE 2
Hematocrit and adjusted RR (95% CI) of NIDDM in a subgroup of men with available data on triglycerides

Hematocrit level	No. men	No. cases	Adjusted RR ++	Adjusted RR Triglyceride
<42	851	9	1.0	1.0
42–	1,117	23	1.9 (0.9, 4.1)	1.9 (0.9, 4.1)
44–	1,374	36	2.2 (1.1, 4.6)	2.1 (1.0, 4.5)
46–	1,002	20	1.6 (0.7, 3.6)	1.6 (0.7, 3.5)
48–	682	36	3.9 (1.8, 8.2)	3.6 (1.7, 7.6)
Test for trend			$P < 0.0001$	$P < 0.001$

++, adjusted for age, BMI, smoking, alcohol intake, physical activity, preexisting IHD, FEV_1, HDL cholesterol, heart rate, uric acid, blood glucose, and systolic blood pressure. The analysis included 5,026 men (124 cases) with complete data for all covariates.

TABLE 3
Hematocrit and RR (95% CI) of NIDDM in men with and without preexisting IHD

Hematocrit level	RR	
	No evidence of IHD	Preexisting evidence of IHD
<42	1.0	1.0
42–	2.5 (1.0, 6.0)	1.4 (0.4, 4.3)
44–	2.9 (1.2, 7.2)	2.3 (0.8, 6.2)
46–	2.8 (1.1, 7.1)	1.0 (0.3, 3.3)
48–	5.5 (2.2, 13.5)	2.7 (0.9, 7.8)
Test for trend	$P < 0.0001$	NS

Data were adjusted for age, BMI, smoking, alcohol intake, physical activity, FEV_1, HDL cholesterol, heart rate, uric acid, blood glucose, and systolic blood pressure. The analysis included 6,688 men (171 cases: 5,054 with no IHD, 113 cases; 1,634 with preexisting IHD, 58 cases) with complete data for all the covariates (excluding triglyceride).

among men in the upper 20% of the distribution of the score. Addition of hematocrit to this risk score was associated with a further 5 percentage point increase in the absolute yield of cases in the top fifth of the distribution. Further inclusion of eight additional risk factors for NIDDM in the model was associated with only a 0.5 percentage point improvement in the yield of cases in the top fifth of the distribution (Table 4).

DISCUSSION

Hematocrit was a strong and independent predictor of NIDDM in this cohort. With adjustment for age and BMI, there was more than a fourfold increased risk of diabetes among the 14% of men with a hematocrit of ≥48% relative to those with a hematocrit <42%. In full multivariate analysis, there remained a greater than threefold increased risk in the highest hematocrit group. BMI index and blood glucose were the dominant predictors of NIDDM. Inclusion of hematocrit in a multivariate prediction score based on BMI and blood glucose increased the yield of cases by 5 percentage points, whereas further inclusion of other known risk factors for NIDDM provided little improvement in yield. It should be noted, however, that the contribution of factors such as hematocrit to predictive models is heavily influenced by the reliability of measurement, which may be higher for hematocrit than for other biological markers of increased risk of diabetes, thereby increasing the apparent importance of hematocrit.

Although ascertainment bias is an issue in studies of NIDDM incidence that rely on physician-diagnosed cases, the association with hematocrit was independent of factors that might increase the probability of a NIDDM diagnosis such as obesity, hypertension, and prevalent coronary heart disease at screening. Indeed, the high risk of NIDDM among men with a hematocrit ≥48% who were without evidence of preexisting IHD at screening suggests that ascertainment bias is not a factor in this association. Obesity and hematocrit are highly intercorrelated, and it may be that the hematocrit-NIDDM association is confounded by the duration or distribution of obesity. This is unlikely given the minimal attenuation of the association on adjustment for BMI, and it is unlikely that adjustment for body fat distribution (which is highly correlated with BMI and not necessarily a better predictor of NIDDM [27]) would have altered the findings. Physical training has been shown to decrease hematocrit levels (28), and in the British Regional Heart Study there is an inverse association between self-reported physical activity and hematocrit (23). Although we adjusted for physical activity in this study, there may have been residual confounding because of random measurement error (i.e., the adjustment for physical activity may have been incomplete).

The mechanisms that underlie this association between hematocrit and the risk of NIDDM are unclear. Clearly a single unifying mechanism is unlikely. We need to consider both physiological effects of insulin, which are likely to influence the hematocrit level and fundamental causal factors in the development of insulin resistance and NIDDM. For example, it has been reported that intravenous infusion of insulin in doses that increase plasma insulin to physiological levels is associated with an increased transcapillary escape rate of albumin and reduced plasma volume (29). This may partially explain the association between hematocrit and hyperinsulinemia reported in the Tecumseh Study (11) and the association between hematocrit and insulin sensitivity as described by Moan et al. (30).

In the Tecumseh Study, hematocrit levels were associated with markers of increased sympathetic tone such as higher heart rate and more specifically elevated plasma norepinephrine levels after mental arithmetic exercises (11). There are plausible mechanisms linking psychosocial stress and increased sympathetic tone with obesity (particularly central obesity), insulin resistance, and NIDDM (31). Direct evidence linking psychosocial stress and increased sympathetic activity with NIDDM is lacking. However, in the British Regional Heart Study, higher heart rate, which has also been shown to be associated with hematocrit (23), was an independent predictor of NIDDM in multivariate analysis (7). Hence, it may be that increased sympathetic tone is one of the mechanisms linking hematocrit with an increased risk of diabetes.

The absence of an association between duration of NIDDM and the risk of death from coronary heart disease in

TABLE 4
Comparison of yield and rate per 1,000 person-years of risk in the top fifth of the distribution of the basic scoring system with and without hematocrit and in the full score

All men	Score derived from		
	Basic model	Basic model + Hct	Full model
Proportion of all NIDDM events in top fifth (%)	57.9 (99/171)	63.2 (108/171)	63.7 (109/171)
NIDDM rate/1,000 person-years in top fifth	6.5	7.1	7.3

n = 6,688 (171 cases). Basic score includes age, BMI, and blood glucose. Full model includes age, BMI, blood glucose, hematocrit (Hct), preexisting IHD, smoking, physical activity, FEV_1, heart rate, HDL cholesterol, uric acid, and systolic blood pressure.

the Whitehall Study led Jarrett and Shipley (1) to argue that NIDDM and coronary heart disease are not causally linked but share common antecedents. The findings presented in this paper add to the accumulating evidence in support of this hypothesis in white populations.

We have found a strong, independent, and largely linear association between hematocrit level and the risk of NIDDM during 12 years of follow-up in a general population sample of middle-aged men. There are data from clinical and epidemiological studies suggesting that insulin resistance is associated with hemorheological derangements including raised hematocrit, which is a major determinant of whole blood viscosity. Hence, these findings suggest that an elevated hematocrit level should be added to the insulin resistance syndrome, which links NIDDM with atheromatous vascular disease.

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REFERENCES

1. Jarrett RJ, Shipley MJ: Type 2 (non-insulin-dependent diabetes and cardiovascular disease: putative association via common antecedents; further evidence from the Whitehall study. *Diabetologia* 31:737–740, 1988
2. Stern MP: Diabetes and cardiovascular disease: the common soil hypothesis. *Diabetes* 44:369–374, 1995
3. Laws A, Reaven GM: Insulin resistance and risk factors for coronary heart disease. *Baillière's Clin Endocrinol Metab* 7:1063–1078, 1993
4. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK: Cardiovascular risk factors in confirmed prediabetic individuals: does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA* 263:2893–2898, 1990
5. McPhillips JB, Barrett-Connor E, Wingard DL: Cardiovascular disease risk factors prior to the diagnosis of impaired glucose tolerance and non-insulin-dependent diabetes mellitus in a community of older adults. *Am J Epidemiol* 131:443–453, 1990
6. Mykkanen L, Kuusisto J, Pyorala K, Laakso M: Cardiovascular disease risk factors as predictors of type 2 (non-insulin-dependent)) diabetes mellitus in elderly subjects. *Diabetologia* 36:553–559, 1993
7. Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH, Shaper AG: A prospective study of risk factors for non-insulin-dependent diabetes in middle-aged British men. *Br Med J* 310:560–564, 1995
8. MacRury SM, Lowe GDO: Blood rheology in diabetes mellitus. *Diabetic Med* 7:285–291, 1990
9. Wilson PW, McGee DL, Kannel WB: Obesity, very low density lipoproteins and glucose intolerance over fourteen years: the Framingham Study. *Am J Epidemiol* 114:697–704, 1981
10. Medalie JH, Papier CM, Goldbourt U, Herman JB: Major factors in the development of diabetes mellitus in 10,000 men. *Arch Intern Med* 135:811–817, 1975
11. Smith S, Julius S, Jamerson K, Amerena J, Schork N: Haematocrit levels and physiologic factors in relationship to cardiovascular risk in Tecumseh, Michigan. *J Hypertens* 12:455–462, 1994
12. Shaper AG, Pocock SJ, Walker M, Cohen NM, Wale CJ, Thomson AG: British Regional Heart Study: cardiovascular risk factors in middle-aged men in 24 towns. *Br Med J* 283:179–186, 1981
13. Bruce NG, Shaper AG, Walker M, Wannamethee G: Observer bias in blood pressure studies. *J Hypertens* 6:375–380, 1988
14. Shaper AG, Wannamethee G: Physical activity and ischaemic heart disease in middle-aged British men. *Br Heart J* 66:384–394, 1991
15. Thelle DS, Shaper AG, Whitehead TP, Bullock DG, Ashby D, Patel I: Blood lipids in middle-aged British men. *Br Heart J* 49:205–213, 1983
16. Phillips AN: *Statistical Issues in Prospective Studies of Risk Factors for Ischaemic Heart Disease.* PhD Thesis, London, 1986
17. Bull BS, Elashoff RM, Heilbron DC, Couperus J: A study of various estimators for the derivation of quality control procedures from patient erythrocyte indices. *Am J Clin Pathol* 61:473–481, 1974
18. Cook DG, Shaper AG, Macfarlane PW: Using the WHO (Rose) angina questionnaire in cardiovascular epidemiological studies. *Int J Epidemiol* 18:607–613, 1989
19. Walker M, Shaper AG: Follow-up of subjects in prospective studies based in general practices. *J R Coll Gen Pract* 34:365–370, 1984
20. Cox DR: Regression models and life tables (with discussion). *J R Stat Soc (B)* 34:187–220, 1972
21. Wannamethee G, Shaper AG, Whincup PH: Ischaemic heart disease: association with haematocrit in the British Regional Heart Study. *J Epidemiol Community Health* 48:112–118, 1994
22. Wannamethee G, Perry IJ, Shaper AG: Haematocrit, hypertension and risk of stroke. *J Intern Med* 235:163–168, 1994
23. Wannamethee G, Shaper AG: Haematocrit relationships with blood lipids, blood pressure and other cardiovascular risk factors. *Thromb Haemostasis* 72:58–64, 1994
24. Paffenbarger RS Jr, Wing AL: Chronic disease in former college students: early predictors of adult-onset diabetes mellitus. *Am J Epidemiol* 97:314–323, 1973
25. Lowe GD, Drummond MM, Lorimer AR, Hutton I, Forbes CD, Prentice, CR, Barbenel JC: Relation between extent of coronary artery disease and blood viscosity. *Br Med J* 1:673–674, 1980
26. Stern MP, Morales PA, Valdez RA, Monterrosa A, Haffner SM, Mitchell BD, Hazuda HP: Predicting diabetes: moving beyond impaired glucose tolerance. *Diabetes* 42:706–714, 1993
27. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willett WC: Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. *Diabetes Care* 17:961–969, 1994
28. Suzuki T, Yamauchi K, Yamada Y, Furumichi T, Furui H, Tsuzuki J, Hayashi H, Sotobata I, Saito H: Blood coagulability and fibrinolytic activity before and after physical training during the recovery phase of acute myocardial infarction. *Clin Cardiol* 15:358–364, 1992
29. Hilsted J, Christensen NJ: Dual effect of insulin on plasma volume and transcapillary albumin transport. *Diabetologia* 35:99–103, 1992
30. Moan A, Nordby G, Os I, Birkeland KI, Kjeldsen SE: Relationship between haemorrheologic factors and insulin sensitivity in healthy young men. *Metabolism* 43:423–427, 1994
31. Bjorntorp P: Visceral fat accumulation: the missing link between psychosocial factors and cardiovascular disease? *J Intern Med* 230:195–201, 1991