PAPERS AND ORIGINALS

Chlorpropamide-alcohol flushing and large-vessel disease in non-insulin-dependent diabetes

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Summary and conclusions

A total of 220 non-insulin-dependent diabetics aged over 45 (139 with a history of chlorpropamide-alcohol flushing and 81 without such a history) were examined for the prevalence of large-vessel disease.

Large-vessel disease was significantly more common in the group without a history of flushing (41% *v* 24% of the two groups respectively; $p < 0.05$). A history of myocardial infarction was found in 14 (17%) of the patients without flushing but in only 10 (7%) patients with flushing. Similar differences were detected in the prevalences of angina, intermittent claudication, and absent foot pulses. There were, however, no significant differences in the prevalence of cerebrovascular disease or hypertension between the two groups.

These results suggest that patients with non-insulin-dependent diabetes who flush in response to chlorpropamide and alcohol are significantly less likely to develop large-vessel disease than those who do not. Hence such flushing is probably related to the pathogenesis not only of small-vessel but also of large-vessel disease.

Introduction

Patients with non-insulin-dependent diabetes treated with chlorpropamide often show facial flushing after taking even a small amount of alcohol (chlorpropamide-alcohol flushing).¹ The latter is dominantly inherited and occurs in 30-60% of such diabetic patients, particularly those with a first-degree family history of diabetes.¹⁻³ We found that those patients with non-insulin-dependent diabetes who flush are less susceptible to diabetic retinopathy, especially severe retinopathy, than those who do not.⁴

We therefore conducted a retrospective study to see whether the same was true for large-vessel (macrovascular) disease—namely, myocardial infarction, angina, intermittent claudication, absent foot pulses, cerebrovascular disease, and hypertension.

Patients and methods

We studied 220 patients with non-insulin dependent diabetes aged over 45 years attending the diabetic clinic at this hospital. The presence or absence of chlorpropamide-alcohol flushing had already been determined in these patients by a single challenge test of 250 mg chlorpropamide and 40 ml sherry.¹ We are gradually putting the essential clinical features of all our diabetic patients on to a computer recording, and a complete record was available for 204 of the 220 patients (93%). As well as reviewing the clinical notes the observers who completed the clinical records had made an assessment of each patient, including asking specific questions about myocardial infarction, angina, cerebrovascular accident, and intermittent claudication and recording foot pulses and blood pressure. They did not know whether the patient was negative or positive for flushing.

Of the 16 patients for whom a computer record had not been completed, 11 had adequate clinical records. In the other five cases no specific questions about ischaemic heart disease had been asked and it was assumed to be absent; for these five patients there was also no record of the presence or absence of arterial foot pulses, which were assumed to be present. Hypertension was recorded if the patient was taking antihypertensive treatment or had a diastolic blood pressure of over 100 mm Hg. All results were analysed by the χ^2 test.

Results

Of the 220 patients, 139 were positive for flushing and 81 were not. At the time of examination the mean age of the two groups was similar (64 and 66 years respectively). The groups were also comparable for duration of diabetes ($14 \pm (\text{SD}) 7$ years in the positive group and 13 ± 6 years in the negative group).

Evidence of macrovascular disease was significantly more common in patients in the negative group (33, 41%) than in patients in the positive group (33, 24%; $p < 0.05$, table I). The same was true for each type of disease considered separately (myocardial infarction, angina, intermittent claudication, and absent foot pulses). Myocardial infarction had occurred in 14 patients (17%) in the negative group

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and in 10 patients (7%) in the positive group ($p < 0.05$). Angina was also more common in the negative group (11 patients, 14%) than in the positive group (13 patients, 9%), although this difference was not significant. Intermittent claudication was more common in the negative group (7 patients, 9% *v* 6 patients, 4%) but the numbers were small and the difference was not significant; absence of both dorsalis pedis and post-tibial pulses, in one or both feet, was also more common in the negative group (17, 21% *v* 15, 11%; $p < 0.05$). In contrast, there was no significant difference in the prevalence of cerebrovascular accident or hypertension between the two groups (table I).

TABLE I—Prevalence of large-vessel disease in positive and negative groups

Disease	No (%) in negative group (n = 81)	No (%) in positive group (n = 139)	Significance
All	33 (41)	33 (24)	< 0.05
Myocardial infarction	14 (17)	10 (7)	< 0.05
Angina	11 (14)	13 (9)	NS
Intermittent claudication	7 (9)	6 (4)	NS
Absent foot pulses	17 (21)	15 (11)	< 0.05
Cerebrovascular accident	6 (8)	8 (6)	NS
Hypertension	18 (22)	41 (29)	NS

NS = Not significant

TABLE II—Numbers of patients with large-vessel disease according to duration of diabetes, age at examination, and group

Duration (years)	Age	No (%) in negative group	No (%) in positive group	Significance
< 15	45-64	7/25 (28)	5/49 (10)	< 0.05
	≥ 65	20/32 (63)	10/43 (23)	< 0.001
> 15	45-64	0/8	6/18 (33)	NS
	≥ 65	6/16 (38)	12/29 (41)	NS

NS = Not significant

The patients were classified according to age and duration of diabetes (table II): among diabetics aged under 65, 7 (28%) out of 25 in the negative group and 5 (10%) out of 49 in the positive group had evidence of macrovascular disease; for patients aged over 65 the respective figures were 20 out of 32 (63%) and 10 out of 43 (23%). In patients who had been diabetic for over 15 years, however, there was no significant difference in prevalence between the two groups.

As microvascular and macrovascular disease may occur in the same patients we wondered if the increased prevalence of macrovascular disease in the negative group was caused only by the increased prevalence of severe retinopathy in that group. When diabetics with severe retinopathy (proliferative retinopathy or maculopathy) were excluded, however, the difference between the two groups was unchanged: 20 out of 48 (42%) in the negative group and 28 out of 129 (22%) in the positive group had macrovascular disease ($p < 0.05$).

Obesity—There was no significant difference in mean body weight between the two groups. Mean body weight at diagnosis of diabetes or at first clinic attendance was $75 \pm$ (SD) 15.5 kg in the positive group and 77 ± 16.1 kg in the negative group.

Smoking—Information on cigarette smoking was incomplete. The number recorded as smoking, however, was similar in the two groups; 12 out of 26 in the negative group and 14 out of 35 in the positive group.

Plasma lipids concentrations were not measured.

Discussion

Our results show that chlorpropamide-alcohol flushing in patients with non-insulin-dependent diabetes is associated with relative freedom from large-vessel (macrovascular) disease, as we have shown for microvascular disease (retinopathy).⁴ Nearly twice as many patients negative for flushing compared with patients positive for flushing showed evidence of macrovascular

disease. As chlorpropamide-alcohol flushing is an inherited trait^{1,2} we conclude that susceptibility to microvascular and macrovascular disease is also inherited to some extent.

The "protective" effect of flushing against macrovascular disease is not as strong as that against microvascular disease, especially severe retinopathy. The prevalence of macrovascular disease in the negative and positive groups was 41% and 24% respectively, compared with prevalences of 34% and 4% respectively for severe retinopathy.⁴

The differences between the positive and negative groups might be a result of differences in diabetic control, although this is notoriously difficult to assess. We, however, failed to detect any such differences between the two groups. Nor was there any difference in two risk factors for macrovascular disease (obesity and smoking) between the two groups. Interestingly, the prevalence of hypertension and cerebrovascular accident was similar in the two groups.

The association between chlorpropamide-alcohol flushing and lower susceptibility to macrovascular disease was seen only in the first 15 years of diabetes. After this the prevalence of large-vessel disease was almost the same in the two groups, being slightly higher in the group positive for flushing, although the numbers were small. We cannot explain why the protective effect of flushing should stop after about 15 years of diabetes.

We have already suggested that as diabetic retinopathy can now be treated it is important to identify those diabetics at special risk, and that as diabetics who do not flush in response to chlorpropamide and alcohol are at high risk they should be kept under close observation.⁴ We now think that this is also true for macrovascular disease. Patients with non-insulin-dependent diabetes who are negative for flushing are at greater risk than those who are positive for flushing for both microvascular and macrovascular complications of the disease.

We believe that patients with non-insulin-dependent diabetes who show chlorpropamide-alcohol flushing are significantly less susceptible to macrovascular disease than those who do not. This implies that chlorpropamide-alcohol flushing in patients with non-insulin-dependent diabetes is related to the pathogenesis not only of small-vessel disease but also of large-vessel disease, a striking finding in view of the differences between the two conditions.

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Requests for reprints should be addressed to AHB.

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ONE HUNDRED YEARS AGO The German government has recently bought the secret for a new preservative fluid. It is stated that human bodies and animal tissues generally, even after years, retain their colour, form, and flexibility. Decay is entirely prevented, and the muscles even keep their natural colour. The bodies are saturated in a liquid made as follows: alum, 100 parts; chloride of sodium, 25; nitrate of potash, 12; carbonate of potash, 60; arsenic acid, 10; and water, 1000 parts. This solution is cooled, and filtered. There are then added to ten litres of the fluid four litres of glycerine and one litre of methylic alcohol. From two to five litres of the liquid are used in saturating the body to be preserved. (*British Medical Journal*, 1880.)