Long-Term Glycemic Control and Neurological Function in IDDM Patients

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OBJECTIVE — To examine the relationship between sensory modalities of neurological function and antecedent glycemic control in IDDM patients.

RESEARCH DESIGN AND METHODS — Examinations were conducted on 220 IDDM patients (age at onset <25 yr, duration <18 yr) for the presence or absence of the right or left ankle reflex and determination of vibration perception threshold at each medial malleolus and great toe using biothesiometry. These parameters were related to the concurrent HbA_1 and to a mean of serial measurements (mean HbA_1) over the previous 6 yr.

RESULTS — Ankle reflexes were absent in 39 (right ankle) and 41 (left ankle) patients, respectively. Mean (right + left) ankle and toe VPTs were 8.7 ± 3.6 and 6.3 ± 4.2 (mean ± SD) (arbitrary units), respectively. Both the mean and concurrent HbA_1 were significantly different in patients with absent ankle reflexes (11.6 ± 1.9 and 12.2 ± 2.8%, respectively) compared with present ankle reflexes (10.3 ± 1.7, 10.3 ± 2.1%) ($P < 0.0001$). Similarly, a present ankle reflex was related to mean HbA_1 arbitrarily divided into groups <10, 10–12, >12% ($P = 0.0009$). In contrast, mean ankle VPT (8.0 ± 2.2, 8.8 ± 3.1, and 10.3 ± 6.2) and toe VPT (5.5 ± 2.2, 6.1 ± 2.9, and 8.5 ± 8.2) did not increase significantly with poor glycemic control ($P > 0.05$). Age, right ankle reflex, retinopathy, 24-h urinary albumin excretion rate, and erect systolic blood pressure were the only independent variables predicting the toe VPT using linear regression analysis.

CONCLUSIONS — These findings support a role for glycemic control in neurological dysfunction in IDDM patients, but also suggest that other unknown factors may be involved.

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IDDM, insulin-dependent diabetes mellitus; VPT, vibration perception threshold; CV, coefficient of variation; AER, albumin excretion rate; BP, blood pressure; sBP, systolic blood pressure; ANOVA, analysis of variance.

The role of long-term hyperglycemia in the development and progression of diabetic neuropathy is poorly understood. The lack of a reliable estimate of long-term glycemic control is a serious deficiency of many studies, which have reached conflicting conclusions (1–4). In contrast to sensory nerve conduction, motor conduction is rapidly reversible with improved metabolic control and therefore, may reflect a direct biochemical or physiological component of metabolism rather than a structural abnormality. This suggests that sensory conduction may be the more relevant clinical modality to relate to long-term glycemia. This study examines the relationship between several sensory modalities of neurological function and antecedent glycemic control in 220 IDDM patients.

RESEARCH DESIGN AND METHODS

— Patient identification and recruitment have been described previously (5). Questions were asked of 220 IDDM patients (age at onset <25 yr, duration <18 yr) for symptoms of somatic and autonomic neuropathy. None admitted to excess alcohol consumption or to solvent or toxin abuse. Examination included elicitation of lower limb reflexes, which were defined as absent, present, or present with reinforcement. The latter two groups were combined for the purpose of analysis.

VPTs (mean of 3 readings) were measured at each great toe and medial malleolus using a biothesiometer (Biomedical Instruments, Newbury, Ohio). The mean intraindividual CV of ankle and toe measurements was 7.8 and 12.1%, respectively. Readings range from 0 to 50 on a linear scale: low values indicate a weak stimulus. Retinopathy was assessed by retinal photography and graded by increasing severity from grade 0 (no retinopathy) to grade 6 (vasoproliferation) (6).

After the examination, venepuncture was obtained for HbA_1 estimation

Table 1—*Ankle reflex examined in relation to mean HbA_1*

	Right ankle reflex		Left ankle reflex	
	Absent*	Present†	Absent*	Present‡
Mean HbA_1 (%)				
<10	6	81	8	79
10–12	21	75	22	74
>12	12	24	11	25

*Degrees of freedom = 2.
†$P = 0.0009$.
‡$P = 0.0082$.

(agar gel electroendosmosis, Corning Medical, Halsted, England, UK) (normal range 3.6–7.2%). A single 24-h and a timed overnight urine sample were obtained at home from each patient immediately before the clinic visit for calculation of AER in μg/min. Microalbuminuria was defined as $20 \leq AER < 200$ μg/min.

Serial HbA_1 and plasma glucose values were abstracted from each patient's medical chart: HbA_1 values were measured routinely at our outpatient clinic since November 1980, and plasma glucose values (postprandial, usually midmorning, samples) were available from the time of diagnosis of diabetes. The mean number of HbA_1 measurements per patient was 14 (range 2–34) and of glucose was 33 (range 3–51). From these values, mean HbA_1 and mean glucose were calculated for each patient.

Statistical analysis

Parameters of long-term glycemia were examined by the ankle reflex (present/absent) using a Kruskall-Wallis one-way ANOVA and Spearman's correlation coefficient (SPSS). On clinical grounds, patients were divided arbitrarily into 3 groups: mean HbA_1 <10% (good control), 10–12% (intermediate), and <12% (poor control), for examination by the ankle reflex and VPT. Variables independently associated with toe VPT were determined by linear regression analysis.

RESULTS — Of the 220 patients, 5 admitted to persistent lower limb paraesthesia; 4 to frequent episodes of fainting or dizziness on standing; 2 had unexplained diarrhea, constipation, or micturitional difficulty; and 2 patients suffered from chronic leg or foot ulceration. Three of 109 males admitted to sexual difficulty. All of the symptomatic patients had absent ankle reflexes and the highest ankle and toe VPTs.

Ankle reflexes were absent in 39 (right) and 41 (left) patients, respectively (Table 1). Mean ± SD ankle and toe VPT were 8.7 ± 3.6 and 6.3 ± 4.2, respectively.

Mean HbA_1, concurrent HbA_1, and mean glucose were significantly higher in patients with an absent reflex (11.6 ± 1.9%, 12.2 ± 2.8%, and 11.6 ± 3.0 mM) compared with a present ankle reflex (10.3 ± 1.7%, 10.3 ± 2.1%, and 10.4 ± 3.0 mM) and a right ankle reflex ($P < 0.001$, $P < 0.0001$, $P < 0.05$), respectively. The 3 categories of mean HbA_1 were significantly associated with ankle reflex measurements (Table 1). In contrast, neither mean (right + left) ankle nor mean toe VPT rose significantly with increasing HbA_1 (Table 2). The orthostatic fall in BP (≤15 mmHg), as a possible reflection of subclinical autonomic neuropathy, was significantly correlated with both mean and concurrent HbA_1 ($P < 0.01$, $P < 0.05$), respectively. Mean HbA_1 correlated significantly with both mean ankle and toe VPT (ankle: $r = 0.14$, $r = 0.17$, $P < 0.05$), whereas the concurrent HbA_1 correlated only with toe VPT (toe: $r = 0.14$, $P < 0.05$). No correlation was found between mean glucose and VPT.

Patients with absent ankle reflexes had significantly higher 24-h and overnight AERs and more severe retinopathy. VPT also increased with severity of retinopathy ($P < 0.0001$), but the association with microalbuminuria was not significant ($P > 0.05$). Age ($P = 0.05$), retinopathy ($P = 0.01$), 24-h AER ($P = 0.04$), right ankle reflex ($P = 0.001$), and erect sBP ($P = 0.04$) were significant variables. These variables were independently associated with toe VPT using linear regression analysis, whereas age at onset of diabetes, diabetes duration, sex, mean and concurrent HbA_1, mean plasma glucose, supine sBP, number of episodes of ketosis, number of visits per year to the outpatient clinic, total daily insulin dose, family history of

Table 2—*Right and left ankle and toe VPTs examined in relation to mean HbA_1*

	n	Right and left ankle VPT*	Right and left toe VPT†
Mean HbA_1 (%)			
<10	88	8.0 ± 2.2	5.5 ± 2.2
10–12	96	8.8 ± 3.1	6.1 ± 2.9
>12	36	10.3 ± 6.2	8.5 ± 8.2

Data are means ± SD.
*$P = 0.2050$.
†$P = 0.0612$.

diabetes, cigarette consumption, and percentage of ideal body weight were not significant.

CONCLUSIONS — Collectively, the similar association of mean HbA_1 and concurrent HbA_1 with ankle reflex measurements, the weak correlation of ankle and toe VPT with glycemic control, and the nonsignificant association of mean HbA_1 with toe VPT using linear regression, although not denying a role for glycemia in the development of neurological dysfunction, suggests a limited role for hyperglycemia in its progression. Alternatively, these results could be interpreted as indicating that neurological dysfunction may be amenable to improved control. The association between glycemic control and a postural fall in sBP would support a role for hyperglycemia in the pathogenesis of autonomic neuropathy (6).

Although commonly used to assess vibration perception, inability to control applied pressure may reduce the objectivity of biothesiometry measurements. This variability may have limited our ability to demonstrate an association with glycemia, although the progressive increase in VPT with more severe retinopathy suggests that the thresholds do reflect subclinical neurological dysfunction. Other more recently designed instruments have been described (7) and should also be evaluated in relation to long-term glycemia and the natural history of diabetic neuropathy.

In summary, these findings add further support to the hypothesis that neurological dysfunction may not simply reflect a cumulative glycemic process. The relevance of other risk or perpetuating factors must also be considered.

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