Comments on "The Response of GHb to Stepwise Plasma Glucose Change Over Time in Diabetic Patients"

In their recent letter, Tahara and Shima (1) report on the response of GHb to stepwise lowering of blood glucose over 4–12 weeks. According to their data, during the first 4 weeks after therapeutic blood glucose lowering, the decline rate of glycosylated hemoglobin (GHb) is at its maximum of ~0.1% per day. Later on, the rate of fall of GHb leveled off, as did the rate of fall of glycemia. This is in line with previous observations on the decay of GHb in response to a sudden and sustained lowering of glycemia in healthy subjects (2) and insulin-dependent diabetes mellitus (IDDM) patients (3). From 32 diabetic patients, we obtained the following equation for the maximum possible decay of GHb (y, in percentage of total hemoglobin) over time (x, number of days): $y = -0.160 + 0.099x$; $P < 0.0001$), which is very similar to earlier data (3) and to the data from Tahara and Shima (1). Knowledge of this feature may be useful in some clinical situations, e.g., when a glycemic level has been lowered only recently and the actual GHb is still elevated. We had such a case in a 23-year-old woman with IDDM, who presented with nearly normal glycemia (day-profile around 6–8 mM) and an elevated GHb of 9.6% (equivalent to an average glycemia of 13 mM according to Nathan et al. [4]). Because she knew 2 weeks before that she was pregnant, she improved her glycemic control drastically to the level on her first visit to our department. From the maximum decay rate of GHb as described above, it can be inferred that her GHb 2 weeks earlier must have been around 11%, a figure which might have consequences with respect to pregnancy counselling.

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Plasma Endothelin in Diabetic Autonomic Neuropathy

Emerging evidence suggests that both endothelium cells and neurons in the paraventricular nucleus of the hypothalamus synthesize the vasoconstrictor peptide endothelin (1,2). Activation of the baroreceptor reflex (passive upright tilt) induces the release of endothelin into plasma, and this may contribute to maintenance of blood pressure (BP) during upright posture (3). Diabetes causes widespread damage of the autonomic nervous system, and diabetic patients are frequently exposed to the risk of orthostatic dysregulation (4).

We have measured the plasma concentrations of endothelin and noradrenaline before and during active orthostatic maneuvers in normal subjects, type II diabetic patients without autonomic cardiovascular neuropathy (ACN) and type II diabetic patients with ACN. The clinical characteristics of the three groups of subjects are given in Table 1. No subject had clinical or biological signs of intrinsic heart, vascular, or lung disease. Any drug known to affect cardiovascular function was withdrawn at least 3 weeks before the study. ACN was defined by the presence of a pathological value of deep breathing test (5). Heart rate and finger arterial pressure were continuously recorded with a noninvasive computerized technique (Finapress, Ohmeda 2300, Englwood, CA) during all maneuvers. Blood samples for hormone assay were withdrawn during the squatting test. Briefly, in this test, subjects were invited to hold upright posture for at least 3 min (phase I), then to squat down for 1 min (phase II), and finally to stand up during the inspiratory phase (phase III). Plasma endothelin was determined by radioimmunoassay (RIA). Blood was collected in prechilled tubes containing aprotinin and 6% EDTA and immediately centrifuged at 4°C; the resulting plasma was separated by Sep-Pak C-18 cartridges. The eluate was evaporated in a speed vacuum concentrator and stored at 4–8°C until RIA (Endothelin1/2, Biomedica, GES mbH, Diviuschgassey, Germany). Noradrenaline was measured by high-performance liquid chromatography with electrochemical detection after alumina extraction.

In both normal and diabetic subjects, an immediate and significant ($P < 0.001$, paired Student's t test) decrease of plasma endothelin concentration was observed at the end of phase II (passage

Table 1—*Characteristics of normal subjects and diabetic patients*

	Control subjects	Diabetic patients	
		Without ACN	With ACN
n	10	10	10
Age (years)	46 ± 8	53 ± 7	56 ± 5
Sex (M/F)	6/4	7/3	6/4
BMI (kg/m^2)	25.4 ± 1.2	26.2 ± 1.6	26 ± 1.3
HbA_{1c} (%)	4.7 ± 0.4	7.3 ± 0.6	6.9 ± 0.65
Deep breathing (E/I ratio)	1.3 ± 0.06	1.28 ± 0.07	1.07 ± 0.03*
Postural hypotension (mmHg)	14 ± 4	16 ± 4	45 ± 6*
Endothelin (pM)			
Phase I	0.62 ± 0.34	0.5 ± 0.28	0.34 ± 0.24
Phase II	0.032 ± 0.038	0.03 ± 0.06	0.02 ± 0.013
Phase III	1.6 ± 1.1†	1.62 ± 0.94‡	0.86 ± 0.36‡§
Noradrenaline (pg/ml)			
Phase I	252 ± 36	256 ± 38	234 ± 35
Phase II	154 ± 41	153 ± 34	220 ± 30
Phase III	534 ± 64‡	502 ± 52‡	293 ± 60‡§

Data are means ± SD. Postural hypotension represents the integrated BP fall during phase III of the squatting test.

*P <0.01 versus normal subjects and diabetic patients without ACN.

†P <0.02 versus phase I.

‡P <0.01 versus phase I.

§P <0.05 versus normal subjects and diabetic patients without ACN.

from standing to squatting) without difference among groups. In both normal subjects and diabetic patients without ACN, the passage from squatting to standing (orthostatic load) was associated with a twofold increase of noradrenaline (P <0.01) and a threefold rise of endothelin above prestimulatory values (P < 0.01). In diabetic patients with ACN, endothelin and noradrenaline increases were still greater than baseline, although significantly lower than those of normal subjects and diabetic patients without ACN (P < 0.01). BP fall after standing (phase III) was similar between normal and diabetic patients without ACN, but significantly greater in diabetic patients with ACN (P <0.01).

Our data showing important and rapid changes in plasma endothelin levels after orthostatic maneuvers suggest a role for this peptide in BP regulation during upright posture. It seems that endothelin release is activated by increased sympathetic drive and reduced during its inhibition. The reduced plasma endothelin and noradrenaline response in diabetic patients with authonomic neuropathy may contribute to their orthostatic hypotension.

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