HSP27 Concentrations Are Lower in Patients With Type 1 Diabetes and Correlate With Large Nerve Fiber Dysfunction

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There is a lack of knowledge about neuroprotective factors in diabetes. Heat shock protein 27 (HSP27) acts as a filament stabilizer and inhibits apoptotic pathways (1). Thus, HSP27 may be important as a neuroprotective factor (2). Our aims were to study whether HSP27 concentrations differ between individuals with and without type 1 diabetes and to evaluate the relationship between the progression of neuropathy and HSP27 concentration.

Type 1 diabetic patients ($n = 27$, 41% women; mean age 41 $\pm$ 8 years) were recruited in 1992 with a follow-up in 2005. Serum HSP27 concentrations were determined in baseline and follow-up samples and compared with nondiabetic control subjects ($n = 397$, 34% women; mean age 43 $\pm$ 14 years). The type 1 diabetic patients underwent nerve conduction studies and thermal and vibration perception threshold tests at baseline and at follow-up. Reference data were used to standardize results for age, height, and sex by calculating the *z* scores. Changes in HSP27 (follow-up HSP27 – baseline HSP27) and small and large nerve fiber function were used for correlation analyses.

At baseline, type 1 diabetic patients were middle-aged and had more than 20 years' duration of the disease (Table 1). Their glucose control was acceptable and weight and blood pressure were close to normal. Few of them had antihypertensive or lipid-lowering medication prescriptions. There were no major changes in body weight, systolic blood pressure, HbA_{1c}, and HSP27 concentrations from baseline to follow-up (Table 1).

Type 1 diabetic patients had lower HSP27 concentrations at baseline (geometric mean HSP27 547 pg/mL, 95% CI 421–711) and at follow-up (geometric mean HSP27 538 pg/mL, 95% CI 417–693) compared with healthy control subjects (geometric mean HSP27 785 pg/mL, 95% CI 732–842; $P < 0.05$ for both comparisons). Progression of large nerve fiber dysfunction correlated with a relative decrease in HSP27 concentrations during the follow-up period ($r_s = 0.50$, $P = 0.01$).

We report that patients with type 1 diabetes had lower HSP27 concentrations than nondiabetic healthy control subjects. The correlation between progression of large nerve fiber dysfunction and a relative decrease in serum HSP27 concentrations during the follow-up period could be indicative of an association between neuropathy and HSP27. One study showed higher HSP27 concentrations in type 1 diabetic patients with neuropathy than in those without neuropathy (3). Our diverging finding could be due to different assessment of nerve function, different study design, and choice of control subjects. HSP27 could be related to other diseases than diabetes and not necessarily related to peripheral nerves (4). However, we found no association between HSP27 and other factors, such as antihypertensive medication, lipids, blood pressure, and BMI. It has been shown in animal models that experimental upregulation of HSP27 is related to neuronal protection (5). This neuroprotective role has further been suggested in animal models, where experimental overexpression of HSP27 prior to diabetes resulted in protection from a range of sensory abnormalities (2). Regardless of the mechanism behind our findings, HSP27 might play a neuroprotective role in humans. Our results suggest an insufficient neuroprotection in type 1 diabetic patients.

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Table 1—Clinical characteristics of the type 1 diabetic population at baseline and follow-up

	Baseline 1992 ($n = 27$)	Follow-up 2005 ($n = 27$)
Age (years)	41 ± 8	53 ± 8
Diabetes duration (years)	22 ± 8	34 ± 8
Height (cm)	175 ± 10	175 ± 10
Weight (kg)	72 ± 9	75 ± 10
HSP27 (pg/mL)[a]	547 (421–711)	538 (417–693)
HbA_{1c} (%)	7.1 (6.5−7.7)	7.4 (6.6−8.1)
HbA_{1c} (mmol/mol)	53 (48−61)	57 (49−65)
Systolic blood pressure (mmHg)	128 ± 16	130 ± 11
Diastolic blood pressure (mmHg)	79 ± 8	72 ± 9*
Antihypertensive medication, *n* (%)	0 (0)	11 (41)*
Statin medication, *n* (%)	—	7 (26)
LDL (mmol/L)	—	2.6 ± 0.7
HDL (mmol/L)	—	1.4 ± 0.3
Triglycerides (mmol/L)	—	1.0 (0.7−1.2)
Total cholesterol (mmol/L)	—	4.7 ± 0.7
Creatinine (μmol/L)	—	71 (59−76)
Current smoking, *n* (yes/no)	9/18	7/20
Peroneal conduction velocity	−2.3 (−4.1 to −1.1)	−3.28 (−10.27 to −2.02)*
Sural conduction velocity	−1.21 (−1.86 to −0.92)	−2.30 (−2.54 to −0.86)
Sural amplitude	−1.58 (−2.20 to −0.33)	−2.47 (−2.80 to −0.91)
Composite *z* score	−1.79 (−2.51 to −1.00)	−2.42 (−4.32 to −1.32)*
Vibration perception threshold	1.21 (0.06−2.52)	2.5 (0.67−3.96)*
Heat perception threshold	0.68 (0.03−1.45)	6.84 (6.00−7.60)*
Cold perception threshold	0.49 (0.02−1.49)	1.58 (0.41−3.19)

Data are shown as mean ± SD or median (interquartile range [IQR]), unless stated otherwise. [a]HSP27 concentrations are shown as geometric means and 95% CI (alternative median HSP27 concentrations and IQR were 388 pg/mL, IQR 312–890 [baseline] and 368 pg/mL, IQR 312–762 [follow-up]). *z* Scores for the peripheral nerve functions tests are presented. *$P < 0.005$ for follow-up vs. baseline by paired samples *t* test or Wilcoxon paired signed rank test, where appropriate.

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