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

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Heat shock protein 27 concentrations are lower in patients with type 1 diabetes mellitus than in healthy controls and correlates with large nerve fibre dysfunction.

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There is a lack of knowledge about neuroprotective factors in diabetes mellitus. 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 progression of neuropathy and HSP27 concentration.

Type 1 diabetes patients (n=27, 41% women; mean age 41±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 to non-diabetic controls (n=397, 34% women; mean age 43±14 years). The type 1 diabetes patients underwent nerve conduction studies and thermal and vibration perception threshold tests at baseline and at follow-up. Reference data was used to standardise results for age, height and sex by calculating the Z-scores. Delta changes in HSP27 (follow-up HSP27 – baseline HSP27) and small and large nerve fibre function were used for correlation analyses.

At baseline, type 1 diabetes patients were in their middle-age, and had more than 20 years duration of the disease (Table 1). Their glucose control was acceptable, and the weight and blood pressure was close to normal. Few of them had anti-hypertensive or lipid lowering medication. There were no major changes in body weight, systolic blood pressure, HbA1c, and HSP27 concentrations from baseline to follow-up (Table 1).

Type 1 diabetes 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 to healthy controls (geometric mean HSP27 785 pg/ml, 95% CI 732, 842; $p<0.05$ for both comparisons). Progression of large nerve fibre 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 non-diabetic healthy controls. The correlation between progression of large nerve fibre 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 T1DM patients with neuropathy than in T1DM patients without neuropathy (3). Our diverging finding could be due to different assessment of nerve function, different study design and choice of controls. 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 factors, such as antihypertensive medication, lipids, blood pressure and BMI. It has been shown in animal models that experimental up-regulation 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 diabetes patients.

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K.P. wrote the manuscript and analyzed data. H.S, L.B.D and O.R contributed to the discussion and reviewed/edited the manuscript. O.R is the guarantor of this work, had full access to all the data, and takes full responsibility for the integrity of data and the accuracy of data analysis. All authors approved the final version to be published.

The authors declare that there is no duality of interest associated with this manuscript.

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Tables

Table 1 – Clinical characteristics of the type 1 diabetes 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)
HbA1c (%)	7.1 (6.5−7.7)	7.4 (6.6−8.1)
HbA1c (mmol/mol)	53 (48−61)	57 (49−65)
Systolic blood pressure (mm Hg)	128 ± 16	130 ± 11
Diastolic blood pressure (mm Hg)	79 ± 8	72 ±9[*]
Anti-hypertensive 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 CV	-2.3 (-4.1−-1.1)	-3.28 (-10.27−-2.02)[*]
Sural CV	-1.21 (-1.86−-0.92)	-2.30 (-2.54−-0.86)
Sural amplitude	-1.58 (-2.20−-0.33)	-2.47 (-2.80−-0.91)
Composite Z-score	-1.79 (-2.51−-1.00)	-2.42 (-4.32−-1.32)[*]
VPT	1.21 (0.06−2.52)	2.5 (0.67−3.96)[*]
HPT	0.68 (0.03−1.45)	6.84 (6.00−7.60)[*]
CPT	0.49 (0.02−1.49)	1.58 (0.41−3.19)

Data are shown as mean ± SD or median (interquartile range, IQR), or 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. CV, conduction velocity; VPT, vibration perception thresholds; HPT, heat perception thresholds; CPT, cold perception thresholds. [*]$p<0.005$ for follow-up vs. baseline by paired samples t-test or Wilcoxon-paired signed rank test, where appropriate.