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Acetyl-L-carnitine for symptomatic diabetic neuropathy

Dear Sir,

Diabetic neuropathy is a progressive disorder that causes functional and structural alterations of peripheral nerves. According to a recent survey in a hospital clinic population in the United Kingdom, the overall prevalence of diabetic peripheral neuropathy may be as high as 28.5% [1]. A beneficial effect of acetyl-L-carnitine (ALC) on nerve function has been demonstrated in animal models of diabetes [2, 3]; moreover, ALC levels are decreased in sciatic nerve from streptozotocin-diabetic rats [4]. ALC is an endogenous substance similar in structure to acetylcholine and is involved in uptake and oxidation of long-chain fatty acids in mitochondria [5].

We evaluated the therapeutic effectiveness of ALC in 20 (14 female/6 male) diabetic subjects (age 58 ± 3 years, mean \pm SD, diabetes duration 18 ± 6 years) with symptomatic peripheral diabetic neuropathy. Diabetic treatment was insulin for 13 patients and oral tablets for the other 7 diabetic subjects. All patients were troubled by symptoms of burning, shooting pain or tingling in the legs. After stopping any previous analgesic or anti-inflammatory drug, they entered a single-blind, randomized, placebo-controlled, cross-over study in which ALC (an intramuscular vial, 500 mg, twice a day), or placebo treatments lasted 15 days and were separated by a 2-week wash-out period. The patients who received ALC on the first occasion took the placebo later and vice versa. The severity of symptoms was assessed by a visual analogue scale graded from 0 to 10 (0 = no symptoms, 10 = very severe) (Table 1). A significant ($p < 0.01$) amelioration of symptoms occurred when patients took ALC as compared to placebo treatment. Vibration perception threshold (VPT), measured at the great toe and the external malleolus of the dominant leg, was above the upper limit of normal adjusted for age and did not show any significant change after ALC or placebo.

There are several ways by which ALC may exert beneficial effects on nerve function in diabetic patients. ALC has been shown to acutely increase the plasma concentration of the endogenous opioid peptide beta-endorphin in healthy volunteers (analgesic effect) [6]; ALC increases the number of nerve growth factor receptors on the brain and prevents substance P loss in the sciatic nerve and spinal cord of diabetic animals (neurotropic effect) [7]; ALC influences mitochondrial protein synthesis and transport and non-esterified fatty acid oxidation, thereby increasing the oxidative metabolism of neurons (metabolic effect) [5]; lastly, ALC enhances the activity of antioxidant factors, such as reduced glutathione, and protects

the cells against lipid peroxidation (free radical scavenging effect) [8]. Recent evidence suggests that oxidative injury may be the ultimate factor of aggression to the diabetic nerve [9]. Long-term controlled studies will tell us whether ALC has a role in the treatment of symptomatic diabetic neuropathy.

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Antihypertensives retarding progression of diabetic nephropathy

Dear Sir,

With interest I read the study of Elving et al. [1] comparing the effects of atenolol and captopril in retarding progression of diabetic nephropathy.

The authors fail to distinguish between results which are identical and those which are not statistically significantly different. For example, baseline values for blood pressure in the captopril-treated group and the atenolol-treated group were described as "identical" despite a 5 mm Hg difference in mean arterial pressure (MAP). In a meta-analysis of observational blood pressure studies involving 420,000 patients, a 5 mm Hg

Table 1. The effect of acetyl-L-carnitine (ALC) in symptomatic peripheral diabetic neuropathy

	Pain scale	VPT (volts)	
		Great toe	External malleolus
Basal	7.4 ± 1.1	19 ± 2.4	23 ± 3
Placebo	7.4 ± 1.3	19 ± 2.2	23.5 ± 2.8
ALC	3.6 ± 1.7^a	18 ± 2.1	23 ± 1.9

VPT, Vibration perception threshold. Great toe and external malleolus both at the dominant leg. ^a $p < 0.01$ vs placebo

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difference in diastolic pressure was associated with 34 % less stroke and 21 % less coronary heart disease [2]. Similarly, although MAP in the two groups fell to the same level, the difference in the fall (-10 mm Hg MAP in the captopril group vs -4 mm Hg MAP in the atenolol group) may well be biologically significant [3] even if it is not statistically significant.

Albuminuria was described as "identical" at baseline (1549 vs 933 mg/24 h in the two groups), and as being reduced to the "same extent" (1549 to 851 (-59 %) for captopril and 933 to 676 (-28 %) for atenolol. The differences may not have been statistically significant but can hardly be described as "identical". Indeed, when the authors eliminated several spurious outliers (a risky practice), there was a statistically significant difference in MAP and albuminuria in favour of the captopril-treated group (for MAP -10.6 vs -5.2 , $p < 0.05$ and for albuminuria -60 % vs -20 %, $p < 0.01$).

Was a power calculation performed before the study and if so, what difference in blood pressure was taken to be biologically significant? Given that very small differences in blood pressure have been found to be biologically significant [2, 3], the risk of a type II error in this study must be high. To conclude that ACE-inhibitors and beta-blockers are equally effective in retarding progression of diabetic nephropathy on the basis of these data is an overstatement.

Yours sincerely,
Dr. K. J. Hardy

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Response from the authors

Dear Sir,
We thank Dr. Hardy for his comment. We did not perform a power calculation based on blood pressure differences. Our study was designed to examine a possible beneficial effect of ACE-inhibitors, compared to beta-blockers, on the progression of diabetic nephropathy (measured as decline in glomerular filtration rate) independent of blood pressure control. In that regard it was important to attain similar levels of blood pressure during the study in both treatment groups. We certainly feel that we have succeeded in this respect. The mean \pm SD of all blood pressure measurements during the 2-year follow-up (17 visits in each patient) was 100.9 ± 6.0 and

100.8 ± 8.5 mm Hg in the captopril- and atenolol-treated patients, respectively. To detect a 50 % difference in the effects of captopril and atenolol on the decline in glomerular filtration rate with a power of 80 %, 16 patients in each treatment group would have been needed. The actual number of patients (29, instead of 32) is within an acceptable margin. As we mentioned in our paper, from our data it can be calculated that the chance that captopril is 50 % better than atenolol is 4.8 %. It is therefore unlikely that we have missed such a difference. We agree that smaller differences (in either direction) might go undetected in our study. To prove this, studies with more patients or studies of longer duration will be needed.

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Use of terminology related to fetal insulin secretion

Dear Sir,
I enjoyed reading Hughes' paper [1] which reports some useful new information relating to insulin secretion by fetal as compared to neonatal rat pancreatic islets. My purpose in writing is to suggest a change in perception and terminology in this field. Fetal insulin secretion is variously described as "immature", "poor", "abnormal", "failed" (to release) and to have "impaired coupling". Similar terms are used in relation to metabolism in fetal islets.

There is abundant evidence that insulin production and action in the fetus is of critical importance for normal fetal growth and development [2]. Thus, fetal insulin secretion must be judged to be entirely normal, mature, appropriate and properly coupled for the roles it fulfils in fetal physiology. My purpose in making what might otherwise be thought to be a rather pedantic point is to suggest that research on fetal insulin secretion is in danger of focusing on how "odd" it is rather than on the more interesting questions of how and why it is established with such a different regulation from that in the adult.

Yours faithfully,
C. N. Hales

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