Letters to the editor

Endothelial dysfunction and diabetic angiopathy

Dear Sir,

In a recent paper [1] Dr. Tesfaye and co-workers describe morphological and functional alterations of nutritional blood vessels of sural nerve in patients with diabetic neuropathy, detected by novel techniques. Their findings strongly support the hypothesis that diabetic neuropathy [2–4] is based on diabetic angiopathy within the “vasa nervorum” with subsequent tissue hypoxia. Even if diabetic neuropathy is undoubtedly accompanied by or based on morphological vascular abnormalities, some points concerning the data on nerve fluorescein angiography should be further discussed.

On one hand, the authors show significantly reduced fluorescence intensity in patients with diabetic neuropathy compared to healthy control subjects or non-neuropathic diabetic patients. On the other hand, they observe a non-significant increase in fluorescence intensity in non-neuropathic patients compared to control subjects. Mean differences in fluorescence intensity, calculated from Table 3, between control subjects and neuropathic patients (1.10 after 372 s and 1.26 after 576 s) and between control subjects and non-neuropathic patients (1.15 after 372 s and 1.18 after 576 s) are very similar. Therefore, this non-significance seems to be based on a very small number of observations and a heterogeneity of the non-neuropathic group rather than on a lack of real difference. This directly leads to the main problem of the results: the authors discuss increased fluorescence as comparable to increased blood flow seen in early uncomplicated diabetes in retina [5], kidney [6] or skin [7]. But both increased blood flow and vascular leakage have been shown by Tilton et al. and Corbett et al. [8, 9] and our group [10] to be a result of hyperglycaemia (i.e. glucotoxicity) itself and to be related to an increased endothelial formation of nitric oxide. Such functional alterations are found in morphologically intact vessels before the occurrence of morphological changes and can be termed “endothelial dysfunction” [11]. Therefore, in our opinion, two points may be criticized. First, in the non-neuropathic group only one patient

was free from retinopathy. On the other hand it has been clearly demonstrated that increased blood flow decreases with the onset of vascular complications such as retinopathy [7] and becomes pseudo-normal before being impaired. Second, the same patient had the highest fluorescence intensity by far, suggesting a high blood flow at a lower rate of vascular leakage than in the other patients of this group since HbA_{1c} was the lowest of all. Thus, excluding patients with overt diabetic angiopathy (i.e. retinopathy) would probably have resulted in a more homogeneous group with even higher fluorescence intensity (flow). Furthermore, glycaemic control should be matched whenever comparing parameters of blood flow to exclude differences in nitric oxide formation or vascular leakage.

Despite these precautions the results perfectly match the hypothesis of early increases of blood flow in tissues preferentially affected by diabetic complications. As a result of this increased flow, resistance-work might be shifted downstream towards smaller vessels thus facilitating the occurrence of angiopathy by local, microvascular hypertension.

In conclusion, the techniques described in this paper provide a new, powerful tool to study the effects of early intervention with drugs such as aminoguanidine [12], antioxidants [13], or aldose reductase inhibitors [14] in patients free from overt vascular alterations. This might be of particular importance for the evaluation of preventive strategies before the onset of diabetic complications at the stage of early endothelial dysfunction.

Yours sincerely,
T. C. Wascher, H. Toplak

References

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Response from the authors

Dear Sir,

We are grateful to Drs. Wascher and Toplak for their comments about our work involving photography of sural nerve vessels and fluorescein angiography. We accept their comment that there is a need to make similar observations in non-neuropathic diabetic patients who do not obviously have microvascular complications, but as the procedure involved was significantly invasive, although with no long-term complications, the number of non-neuropathic subjects volunteering to undergo the procedure during the study period was rather limited. This was in contrast to the number of neuropathic patients who were often very willing to volunteer for the procedure. We are now in the process of developing techniques for measuring nerve blood flow including fluorescein angiography through a

much reduced incision as the technique of light-guide spectrophotometry and laser Doppler has been developed and miniaturised.

The other point raised by Drs. Wascher and Toplak was the need to match glycaemic control when comparing indices of blood flow. There was no significant difference in either mean HbA_{1c} or mean ambient blood glucose between both the diabetic groups, nor was there any correlation between the intensity of fluorescence and HbA_{1c}, although admittedly the numbers could have been too small for a decent correlation.

We accept there is a great need to investigate the effect of various therapeutic agents on nerve blood flow (gamma lipoic acid, angiotensin converting enzyme inhibitors) and we hope that our miniaturised technique will allow such studies.

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Yours sincerely,
S.Tesfaye, J.D.Ward

Autonomic neuropathy: comparison of two screening procedures

Dear Sir,

The EURODIAB IDDM Complications Study Group reported on the frequency of microvascular and acute complications in patients with insulin-dependent diabetes mellitus [1]. We would like to reflect on autonomic test results. Two tests were applied in the above-mentioned study: changes in heart rate (30/15 ratio) and in systolic blood pressure on standing. In 19.3 % of patients the 30/15 ratio was abnormal, while postural hypotension was observed in only 5.9 % of patients. Corresponding data in the Hungarian cohort were 37.1 % and 7.9 %, respectively.

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The aim of the present study was to compare the efficacy of two different screening procedures: those of the EURODIAB IDDM Complications Study with those of our self-developed protocol.

We examined 206 IDDM patients (mean age: 32.2; range: 14–57 years, mean duration of diabetes: 11.2; range: 0–43 years). Heart rate responses induced by deep breathing, Valsalva manoeuvre and standing up (35/15 ratio) and changes in blood pressure induced by standing and sustained hand-grip were evaluated [2]. Eighty-three patients (40 %) had normal results in all five tests. Thirty-five patients (17 %) had one abnormal reflex test and 88 patients (43 %) had more than one abnormal reflex test. Abnormal heart rate response to deep breathing (in 84 patients) as well as abnormal 30/15 ratio (in 80 patients) were found significantly more often than an