Dear Sir,
We thank Smulders et al. for their comments. In our study the albumin excretion rate was more important than serum creatinine in determining plasma homocysteine concentrations [1]. However, this could vary in different diabetic groups depending on the proportion of patients with nephropathy and the distribution of its different stages. The actual existence of a link between albumin excretion rate and plasma homocysteine has been greatly reinforced, and extended, by the contemporaneous publication of three reports [2–4] with similar results to that of ours [1]. Especially relevant is one [3] reporting the study of a random sample (n =680) of Caucasians aged between 50 to 75 years in which a consistent link between microalbuminuria and plasma homocysteine concentrations was found in people with isolated microalbuminuria, in patients with hypertension and, especially, in patients with diabetes mellitus. Both Smulders et al., as well as the authors of the abovementioned study [3], favour the possibility that hyperhomocysteinaemia causes microalbuminurie rather than the other way around as suggested by us. In our study [1], introducing the albumin excretion rate as the dependent variable, and age, time of evolution of the diabetes, plasma glucose concentration, HBA_{1C} and homocysteine as independent variables in the multivariate analysis results in a significant ($p < 0.01$) β of 0.34 for homocysteine. Therefore, statistical relations exist in both directions and it is not possible, with this analysis, to establish a definitive cause-effect relation between them. Although our data cannot exclude hyperhomocysteinaemia causing microalbuminuria through dysfunction of the vascular endothelium, there is biological evidence inconsistent with this idea. We know of no report suggesting that severe hyperhomocysteinaemia (such as that of classical homocystinuria and folate or vitamin B12 deficiency), which is characterized by plasma homocysteine concentration two- to tenfold that of control subjects, causes microalbuminuria or any other kind of nephropathy [5]. A synergistic relation between diabetes mellitus (and, perhaps, other pathological conditions such hypertension, insulin resistance, etc.) and hyperhomocysteinaemia so as to cause vascular damage could, however, exist [2]. In our opinion, the increase of homocysteine caused by the diabetic nephropathy could promote, rather than provoke, the progression of the nephropathy similarly to what has been described for diabetic hyperlipidaemia. More studies – including prospective ones – are needed to confirm and extend the associations reported and to clearly establish cause vs effect, especially considering that hyperhomocysteinaemia in particular could increase the risk of cardiovascular disease in Type II diabetic patients [6].

Yours sincerely,
A. Chico, A. Pérez, A. Córdoba, R. Arcelús, G. Carreras, A. de Leiva, F. González Sastre, F. Blanco-Vaca

Corresponding author: Dr. F. Blanco-Vaca, Hospital de la Santa Creu i Sant Pau, Servei de Bioquímica, Antoni M. Claret 167, E-08025 Barcelona, Spain

References

1. Chico A, Pérez A, Córdoba A et al. (1998) Plasma homocysteine is related to albumin excretion rate in patients with diabetes mellitus: a new link between diabetic nephropathy and cardiovascular disease. Diabetologia 41: 684–693
2. Hofman MA, Khol B, Zumbach MS et al. (1998) Hyperhomocysteinemia and endothelial dysfunction in IDDM. Diabetes Care 21: 841–848 (an earlier version of this paper published in Diabetes Care (1997) 20: 1880–1887 was withdrawn).
3. Hoogeveen EK, Kostense PJ, Jager A et al. (1998) Serum homocysteine level and protein intake are related to risk of microalbuminuria: the Hoorn study. Kidney Int 54: 203–209
4. Lanfredini M, Fiorina P, Deca MG et al. (1998) Fasting and post-methionine load homocyst(e)ine are correlated with microalbuminuria and could contribute to worsening vascular damage in non-insulin dependent diabetes mellitus patients. Metabolism 47: 915–921
5. Mudd SH, Levy HL, Skovby F (1995) Disorders of transsulfuration. In: Scriver CR, Beaudet AL, Sly WS, Valle D (eds) The metabolic and molecular basis of inherited disease, 7th edn. McGraw-Hill, New York, pp 1279–1327
6. Hoogeven EK, Kostense PJ, Beks PJ et al. (1998) Hyperhomocysteinemia is associated with an increased risk of cardiovascular disease, especially in non-insulin-dependent diabetes mellitus. Arterioscler Thromb Vasc Biol 18: 133–138

Scant evidence of periodic starvation among hunter-gatherers

Dear Sir,
In the April issue of Diabetologia Reaven [1] proffered an alternative hypothesis to Neel's thrifty genotype hypothesis [2]. His proposal, called the 'not-so-thrifty' genotype hypothesis, argues that the gene was not one which conferred exceptionally efficient storage of food energy but instead conserved muscle protein during periods of starvation by reducing gluconeogenesis from amino acids. In our opinion the basis of both hypotheses – periods of food scarcity in pre-agricultural populations – is not supported by the scientific literature.

Corresponding author: Professor L. Cordain, Department of Exercise and Sports Science, Colorado State University, Fort Collins, CO 80523 USA

Implicit in both Neel's and Reaven's hypotheses is the assumption that pre-agricultural people must have gone through regular, periodic episodes of starvation that had a negative impact on reproductive potential and hence resulted in the selection of a gene or genes which would have survival value during the fluctuations between 'feast and famine'. This concept is frequently invoked to explain the high incidence of diseases of insulin resistance [Type II (non-insulin-dependent) diabetes mellitus, hypertension, obesity and coronary artery disease] among recently acculturated populations.

Although Neel's hypothesis has become 'one of the orienting concepts of nutritional and biomedical anthropology', it is founded upon an assumption which cannot be corroborated by the available ethnographic data derived from living hunter gatherer populations nor by the fossil record. Indeed, periodic starvation became more frequent and nutritional status declined when hunter gatherer populations made the transition to agriculture less than 10 000 years ago [3, 4]. Starvation among early agriculturists was quite common because of the