a mean arterial pH at 7.31 ± 0.02 and plasma bicarbonate at 20.5 ± 1.0 mmol/l.

Patients received dobutamine (10–20 μg/kg/min) in order to correct their haemodynamic disorders without changing other simultaneously given treatments, namely trinitrin and furosemide received at mean doses of, respectively, 3 ± 1 mg/h and 250 ± 125 mg/day. Myoclonia appeared on the second or third day after starting dobutamine treatment, persisted throughout treatment and disappeared 2 days after treatment arrest. This neurological sign has been attributed to dobutamine after having excluded all other potential causes of myoclonia. The close relationship between the occurrence of myoclonia and its disappearance in association with dobutamine treatment was a strong clinical argument in favour of a causal link, in the absence of other clinical or biological changes.

To explain this side effect, we propose a more marked dobutamine uptake by the central nervous system, induced by two cumulative mechanisms secondary to renal failure: a decrease of dobutamine biotransformation and an increase of blood–brain barrier (BBB) permeability caused by *P*-glycoprotein (Pgp) inhibition. The principal dobutamine metabolic pathway is *O*-methylation by catechol-*O*-methyltransferase (COMT). An association between renal failure and impaired hepatic drug metabolism has been reported [2]. In uraemic patients, *O*-methylation could be altered by non-competitive erythrocyte COMT inhibition due to larger amounts of endogenous methyl acceptors in uraemic plasma than in normal plasma [3]. This mechanism could prolong dobutamine half-life.

Pgp activity has been shown to be reduced in rats with acute renal failure [4], together with a suppression of its brain function [5]. Pgp inhibition could be enhanced by furosemide [6], which was part of patients' treatment. It is admitted at present that Pgp, which is expressed at the site of the blood–brain barrier, limits the entry of xenobiotics and prevents them from reaching toxicological concentrations. Therefore, Pgp inhibition could increase brain delivery of dobutamine.

Our hypothesis would explain a longer dobutamine half-life and a more marked penetration of the drug into the nervous system, ultimately responsible for myoclonia. As for other α_1 adrenergic drug-like tricyclic antidepressants, stimulation of α_1 post-synaptic adrenergic receptors leads in turn to an activation of serotoninergic neurons. This could induce myoclonia, when occurring at the cortical level. To our knowledge, dobutamine-induced myoclonia has not been reported before, despite the wide utilization of this drug, considering the well-known prevalence of congestive heart failure. Severe renal failure appears to be an obligatory associated condition to induce myoclonia. It is possible that in such patients the described side effect of dobutamine is likely to be underestimated or neglected because of other major signs and symptoms caused by severe cardiac failure.

Conflict of interest statement. None declared.

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The impact of visceral fat on multiple risk factors and carotid atherosclerosis in chronic haemodialysis patients

Sir,

We read with much interest the original article by Yamauchi *et al*. [1] reporting the importance of visceral fat (VF) in carotid atherosclerosis, lipid abnormalities and hyperinsulinaemia in maintenance haemodialysis patients. In their study, the patients were separated into three groups according to VF content, and three groups were compared for well known atherosclerotic risk factors such as age, blood pressure, lipid levels, duration of haemodialysis, haemaodialysis efficiency (Kt/V_{urea}), fasting plasma glucose and insulin levels. They evaluated systemic atherosclerosis with carotid intima media thickness (CIMT), plaque score (PS) and stiffness parameter (SP) by high-resolution B-mode ultrasonography. All three methods shows that patients with higher VFA had greater carotid atherosclerotic changes. In this study, although VFA was not correlated with CIMT, it was correlated with PS and SP. Using multivariate regression analysis, they found that VFA was the strongest predictor of PS, but not SP and CIMT.

When looking at the relationship between VFA and lipid abnormalities and hyperinsulinaemia, it was clear that VF was a good predictor of metabolic disorder as it was shown in non-dialysis subjects. However, as stated in the Discussion (para 3), it seems to be difficult to conclude that VF had an additional risk for atherosclerotic disease and contributed to the accelerated atherosclerosis. As shown, VFA was highly correlated with well-known risk factors such as low high-density lipoprotein (HDL), high triglyceride and high plasma insulin levels. If there were a correlation analysis between these factors (HDL, plasma insulin, fasting glucose and triglyceride) and systemic atherosclerosis (CIMT, PS and SP), one would expect the existence of a correlation between metabolic factors and systemic atherosclerosis. In addition, the multivariate regression models including body mass index (BMI), SFA and VFA (independent variables) were performed to clarify which was the most strongly related to carotid atherosclerosis (PS, SP and CIMT taken as dependent variables). They found that only PS seems to

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be related to VFA and there was a very good correlation between blood lipids (HDL and triglyceride) and VFA.

In the same issue of the journal, London *et al*. showed that arterial intimal calcification (AIC) was much more correlated with classical atherosclerosis risk factors in comparison with patients with arterial media calcification (AMC). Whilst, CIMT, PS and SP were highest in the AIC group, age, duration of dialysis and lipids were the independent factors for AIC [2]. Therefore, as shown in this study of Yamauchi *et al*., in addition to these independent parameters (BMI, SFA and VFA), blood lipids and age should have been included in the multivariate model because of their possible effect on carotid atherosclerosis. Without including them in the analysis, it cannot be concluded reliably whether VFA have any independent significant impact on carotid atherosclerosis.

In a previous study, we showed the significant correlations between CIMT and age, left ventricular mass index, blood pressure and the ACE D allele. In multiple regression analysis, the risk factors for increased CIMT in haemodialysis patients were pre-dialysis systolic blood pressure and the ACE D allele in the additive model [3]. In the study of Yamauchi *et al*., whilst no significant difference in the three groups (according to VF) was noticed, there was a tendency that the high VF group was the oldest group. Since age is a well known risk factor for atherosclerosis, it would be interesting to see whether there was any correlation between systemic atherosclerosis measures (CIMT, SP and PS) and age in this study.

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Regression of uraemic pruritus by cyclosporin treatment in a haemodialysis patient

Sir,

Recent studies suggest that low dose (2.5–3.0 mg/kg daily) cyclosporin treatment is an effective, safe and well-tolerated treatment for atopic dermatitis which is refractory to conventional treatment modalities. This treatment can also lead to long-term remission of the disease in some patients [1].

Uraemic pruritus is a distressing disease that is difficult to treat. Its prevalence is high in the dialysis population. An effective treatment of severe uraemic pruritus is needed, as its consequences can be devastating for the patients. We describe the case of a 78-year-old woman who, at the end of 1999, 2 years after the beginning of haemodialysis, developed intense and generalized pruritus. Secondary hyperparathyroidism, dry skin, hyperphosphataemia, anaemia, peripheral neuropathy, high aluminium levels and hypervitaminosis A were all excluded. Although Kt/V was already satisfactory at 1.5, duration of dialysis was increased to 240 min, a more biocompatible membrane (polymethylmethacrylate) was used and swine heparin was changed with an EDTA-purified preparation. Other causes of pruritus (metabolic and endocrine diseases, biliary obstruction, myeloproliferative diseases, polycytaemia vera, iron deficient anaemia and cancer) were excluded.

Symptomatic treatment with antihistamines, steroids and ultraviolet B (UVB) light were ineffective. Rather, the intensity of pruritus worsened, determining a deterioration of the quality of life to the point of an attempted suicide. Therefore, in November 2000, immunosuppressive treatment with cyclosporin was attempted. Starting doses of 200 mg/day were tapered to reach and maintain a therapeutic range between 130 and 160 ng/ml. Serum levels of the drug were monitored weekly at the beginning of treatment and every other week in the maintenance phase. By December 2000, symptoms improved and eventually regressed. In March 2001, cyclosporin was reduced and stopped, but severe pruritus quickly recurred. The patient again expressed suicidal thoughts. Therefore, at the beginning of 2002, a new course of cyclosporin treatment was started. Again, symptoms markedly improved, but in April 2002 treatment was stopped because of cholestatic jaundice due to two biliary stones in the choledocus. Interestingly, jaundice developed in the absence of pruritus, which recurred immediately after the interruption of cyclosporin treatment. Endoscopic papillectomy resolved this complication and in June 2002 treatment with cyclosporin (associated with ursodesossicolic acid, 300 mg/day) was resumed. Since then, our patient has remained in good clinical and psychological conditions. Cyclosporin demonstrated a good safety profile during long-term treatment and was, generally, tolerated well.

Several different therapies have been proposed for uraemic pruritus: antihistamines, opiate antagonists and even placebo have been reported to be effective in previous reports, but many patients, including ours, do not respond to any treatment. Recently, Mettang *et al*. [2] pointed out that research on the pathogenesis of uraemic pruritus is concentrating in two areas: the 'opioid hypothesis' and the 'immuno-hypothesis'. The former is controversial and is based on the finding that several μ-receptor-agonistic drugs can induce pruritus and is supported by the observation that administration of opiate antagonists was successful in the treatment of cholestatic pruritus. Indeed, in a preliminary study of uraemic patients, Peer *et al*. [3] demonstrated that naltrexone, an oral μ-receptor antagonist, was effective in relieving symptoms in all of the treated patients. However, Pauli-Magnus *et al*. [4] could not reproduce these results in a larger cohort treated for a longer time (4 weeks).

The immuno-hypothesis is the base of the therapeutic approach we chose for our patient. According to this hypothesis, uraemic pruritus is a systemic disease due to a derangement of the immune system with a pro-inflammatory pattern [2]. In support of this hypothesis, uraemic pruritus is extremely rare in transplanted patients with renal failure, as long as cyclosporin treatment is maintained [2]. The IL-2-suppressing effect of cyclosporin might correct the immunological disturbances causing some of the most severe forms of

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