The obese uremic patient: a newcomer in the nephrology clinic?

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This issue of the journal contains a description of three cases of impaired renal function, associated with the use of the anti-obesity drug Xenical® (orlistat) [1]. This drug has been used for more than two decades and the safety profile of orlistat, which is only absorbed to about 1%, is very well established. However, as the authors point out, this is the reason to suspect that, in some rare cases, orlistat may be the underlying reason for the development of impaired renal function and, as also suggested by the authors, there are also plausible mechanisms to explain this unfortunate development. The problem is not new and has been addressed elsewhere [2, 3].

The association of a drug used for the treatment of obesity with the development of impaired renal function, opens for an inevitable discussion about the imminent arrival of the obese subject with uremia on the clinical stage. During recent years, obesity has emerged as an upcoming risk factor associated with chronic kidney disease. In the past, patients with end-stage renal disease would generally be in a catabolic situation with chronic kidney disease. In the past, patients with end-stage renal disease would generally be in a catabolic situation and weight problems were not an issue. However, with the exploding obesity epidemic all over the world, there is a well-documented increase in the prevalence of type 2 diabetes, and in a subgroup of obese patients with type 2 diabetes, the associated cardiovascular complications will lead to not only myocardial infarction and stroke, but also to impairment of the renal function, eventually leading to uremia, dialysis and transplantation [4, 5].

This is a new clinical situation which nephrologists have to face and address. Over recent years, treatment of obesity in patients with chronic kidney disease has become an issue, which doctors have never been used to in the past. Just like other clinicians trying to develop strategies to fight obesity in general, nephrologists will be confronted, since it is well known that weight loss has marked positive effects on type 2 diabetes and may even cause reversal of the disease.

However, the treatment modalities for obesity are unfortunately not well developed. The classical treatment programmes consisting of diet, exercise and behaviour modification have been tried and do work under certain conditions. Generally, the short-term effects are quite acceptable in the hands of capable therapists, but the long-term results are not too promising. Very low calorie diets (VLCD) have been tried in general populations and seem to offer an interesting alternative. In a recent programme in an outpatient setting, the weight loss after 1 year was quite impressive as was weight loss maintenance [6]. Clearly, there is a role for VLCD programmes in obese individuals and such individuals also with type 2 diabetes, and this opportunity has not been fully utilised in the primary health care sector. The VLCD programmes fill a void of treatment strategies between the standard diet exercise and behaviour modification programme and the most advanced form of obesity therapy, which is bariatric surgery.

It is now well established that bariatric surgery will reduce mortality in severely obese patients and improve several of the associated risk factors [7]. The first impressive results were generally associated with the improvement in glycaemic control, which was maintained for several years after bariatric surgery. Weight loss after surgery would also result in blood pressure reduction and improved lipid control, but these risk factors would begin to reappear again a few years after surgery.

Summarising the results after up to 18 years of follow-up, it can be said that bariatric surgery has reduced overall mortality and reduced the cancer mortality but only in certain groups. The costs to society have not been much reduced, but the quality of life has definitely improved.

In this situation, it is obvious that there is a need for a treatment opportunity to fill the gap between diet, exercise and behavioural modification and bariatric surgery. This is where anti-obesity drugs would have a role to fill [8]. However, the story of anti-obesity drugs has been filled by mishappenings (Table 1). Several of the products used in the second part of the previous century were short-lived because of complications. Hence, it was with great expectations that the three new compounds developed and marketed during the end of the last century were introduced. Orlistat (Xenical®), a lipase inhibitor, was the first compound on the market and has been extremely well documented over some 20 years. Orlistat resulted in modest weight loss which however was reasonably sustained when patients continued to take the drugs. Orlistat is only absorbed to about 1% which meant that systemic effects were unlikely to occur. Both physicians and patients...
often complained about the so-called side-effects, which in fact was the result of a misunderstanding: diarrhoea was the anticipated effect of non-compliance with a diet that was described to be low in fat. If such a diet would have been adhered to, the fat content in the stools would have been so low that side-effects would not have appeared. Patients who complained about loose stools in fact only demonstrated that they had not adhered to a low fat diet—hopefully prescribed. Clearly, however, this was sometimes the fault of the prescribing physician, who had not been careful enough to explain the mode of action of the drug. In the XENDOS trial, orlistat was shown to reduce the incidence of type 2 diabetes by about 37% over a 4-year period, which in fact for a selected group made it an interesting and valuable tool [9].

Sibutramine (Reductil® or Meridia®) was launched a few years later and had quite a different mode of action affecting appetite through combined adrenergic mechanisms [10]. As a small increase in pulse rate was anticipated and in a few patients also a blood pressure increase, sibutramine was launched with strict instructions for the prescribing physician to control these factors. Weight loss was quite impressive, and so the reduced adrenergic tone that followed weight reduction would in many cases lead to a reduction both in pulse rate and blood pressure. Only a small fraction of patients had to be withdrawn because of these side-effects. However, the licencing health authorities requested a trial demonstrating the potential of sibutramine in high-risk patients, which was never the target when the drug was launched. When the so-called SCOUT trial was eventually published [11], the study demonstrated a small significant increase in non-fatal myocardial infarct incidence, which was seen to be unacceptable and hence the drug was withdrawn.

Rimonabant (Acomplia®) worked as a cannabinoid receptor inhibitor and had again a quite different mode of action [12]. Of the three drugs, rimonabant was probably the most effective with a weight loss close to about 10%. Side-effects were very modest but already from the beginning there was an awareness about the risk that depression might occur. This could be controlled reasonably well by check lists which were developed to identify suicidal ideation. However, a few suicides occurred during treatment and eventually rimonabant was also withdrawn.

Hence, at present, bariatric surgery is the only reasonably effective treatment method, which however is costly and restricted to severely obese subjects. At the end of the day, the main benefits of surgery are a considerable increase in the quality of life, whereas risk factors have reappeared over time and the procedure has not been found to be very cost-effective.

This means that, at present, we are in a situation where there is very little pharmaco-therapy to offer any obese patient [13]. Unfortunately, the future does not look too promising. Lorcaserin, liraglutide and the combination of topiramate/phenthermine are in the pipeline. Topiramate/phenthermine has been licenced in the USA in 2012, but surprisingly enough this drug was not accepted by the European authorities in spite of the fact that the producing company provided all the information needed and requested for an approval.

It is intellectually disturbing that scientific bodies on both sides of the Atlantic using the same scientific material come to opposite conclusions. Topiramate/phenthermine at present is licenced in the USA but unlikely to be accepted in Europe. On the other hand, the opposite happened with rimonabant, which was approved in Europe but not in the USA, again based on the same scientific background.

This means that nephrologists at present have little to offer the new type of upcoming obese type 2 diabetic uremic patients. All studies forecasting the development of type 2 diabetes have underestimated the rapid progress of the disease. It is only obvious that, with the explosion of type 2 diabetes, there will be a new type of uremic patients with weight problems, which need to be taken care of in a way that previous generations of nephrologists have never had to face. Insufficient data exist on the effects of intentional weight loss in chronic kidney patients [14]. Many of these patients have a diet with a high protein content, and weight loss may be harmful.

However, it would be interesting to develop a treatment programme where weight loss could be induced in chronic kidney failure patients with VLCD under such strict control that the protein energy component of these products does not comprise a clinical problem during weight loss. All clinical results in other patient groups underscore the fact that the weight loss induced by these tools have been beneficial and led to many other metabolic, mechanical and psycho-social improvements above that from weight loss in itself. The improved mode and increased self-esteem after successful weight loss should not be underestimated as an important beneficial outcome of successful treatment.

**Table 1. Previous history of antiobesity drug treatment.**

<table>
<thead>
<tr>
<th>Date</th>
<th>Drug</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1893</td>
<td>Thyroid hormone</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>1933</td>
<td>Dinitrophenol</td>
<td>Nerve toxicity, neuropathy</td>
</tr>
<tr>
<td>1937</td>
<td>Amphetamine</td>
<td>Drug dependence</td>
</tr>
<tr>
<td>1967</td>
<td>‘Rainbow pills’</td>
<td>Death</td>
</tr>
<tr>
<td>1971</td>
<td>Aminorex</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>1975</td>
<td>‘Last chance diet-VLCD’</td>
<td>Cardiac death</td>
</tr>
<tr>
<td>1997</td>
<td>Fenfluramine</td>
<td>Valvular heart disease</td>
</tr>
</tbody>
</table>

+ DEXfenfluramine (‘fen-fen-frenzy’) | -+- |

## Diagnosis of obesity in chronic kidney disease: BMI or body fat?

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Excess of body fat is a major global public concern that is associated with both mortality and comorbidities such as diabetes, cardiovascular disease, some types of cancer and chronic kidney disease (CKD) [1–4]. In most epidemiological studies and clinical trials, excess fatness has been defined on the basis of body mass index (BMI; in kg/m²). According to the 1997 report of the World Health Organization Consultation on Obesity, BMI cutoffs of $\geq 25$ and $<30$ kg/m² and $\geq 30$ kg/m² are defined as overweight and obesity, respectively [5]. In the general population, BMI $>30$ kg/m² is associated with higher rates of mortality when compared with ‘normal’ BMI ($\geq 18.5$ and $<25$ kg/m²) which has been recently confirmed in a systematic review and meta-analysis on a sample of more than 2.88 million individuals [6]. Although objective and simple methods to identify obesity such as BMI are greatly convenient, its use in clinical settings has created a number of problems. The mortality J-shaped relationship with BMI found in the general population is not seen in patients with severe chronic diseases including advanced CKD [7]. In contrast, higher BMI, in the range of obesity, has been consistently associated with decreased mortality in this population of patients, a phenomenon named obesity paradox or reverse epidemiology of obesity. This finding has raised concerns over the suitability of BMI as a marker of adiposity under such clinical conditions.

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