Discussion

The discussion of the Molecular Topics in Dialysis meeting focused on two questions provided by the audience during the meeting, a synopsis of which is provided.

Question 1
What is the clinical significance of the neo-angiogenesis in the peritoneum membrane and how much can diabetes teach us about the role of glucose in this context. Can therapeutic options used in diabetes be of use in the context of PD?

Theoretically, an increase of the vasculature can increase the transport of all solutes and thereby reduce ultrafiltration [1]. It may therefore be of clinical significance. In the long term, it is going to be important to understand the linkage between neo-angiogenesis and the development of peritoneal fibrosis [2]. Diabetes is an interesting model and the anatomic and pathological features are similar to those in peritoneal dialysis, but we need more data to substantiate the link between them, although, given that glycation appears to be important in both conditions, this might provide some therapeutic rationale [3,4]. It was pointed out, however, that linking diabetes mellitus and the situation in PD directly might be problematic given that diabetes is a systemic disease and that in the peritoneal cavity we have a local alteration of the peritoneal structure with other contributing factors (solution components other than glucose, chronic inflammation) [5]. Vascular degeneration and neo-angiogenesis both also happen in diabetes. There is a theory that advanced glycation end-products are also important in the atherosclerotic process; however, the sorbitol/polyol pathway may be more important in the process of neo-angiogenesis [6].

In animal models at least, there is a direct correlation between the loss of ultrafiltration and neo-angiogenesis [7,8]. Once these data are substantiated in humans, in the future blocking angiogenesis with, for example, a VEGF antagonist (or other angiostatins) may be a therapeutic possibility given that there are data in the literature suggesting the potential importance of VEGF in driving vascular alterations [7,9].

The potential link between neo-angiogenesis and the fibrotic process is worthy of further investigation, given that there is a statistical link between them; it is, however, important to understand which is chicken and which is egg? [2]. There is the danger of oversimplification; the data suggest that there is neo-angiogenesis and there is no doubt that there are elevated VEGF levels driving the process in the peritoneum [10–12]. There is, however, a third factor (identified by the Biopsy Registry) and that is the process of vascular degeneration (or vasculopathy) [2]. We need to understand the temporal relationship between these two events as well as their overall clinical significance. Are changes in membrane function all related to neo-angiogenesis or does the fibrotic and sclerotic element play a role in the process of ultrafiltration or solute clearance? Equally, it is important to understand the nature of the new vessels; are they fully functional? Endothelial cell permeability is important as well, contributing to the behaviour of both degenerating vessels and the newer ones, which develop. We do not know anything about that aspect.

A link is often made between the changes we see in the peritoneum and the changes seen in diabetic retinopathy. Experience, however, suggests that in the legs (for example), we lack neo-angiogenesis. This suggests that there are differences in different organs; the peritoneum may be a good example of neo-angiogenesis as is the eye, but it does not necessarily reflect what is going on in other parts of the microcirculation. It is possible that what occurs in the leg is an atherosclerotic kind of vascular disease, i.e. one of the larger vessels different from the micro-angiopathy defined in organs, such as the retina and the kidney. Studying diabetes has certainly developed our understanding of the mechanisms that seem to be important in peritoneal membrane changes; for example our knowledge that VEGF is important in the development of diabetic retinopathy has driven peritoneal VEGF research in the peritoneum. There are also, however, local factors in the situation of peritoneal dialysis other than the glucose alone; diabetes might help us in understanding the processes by which the alterations happen and of potential treatments that might be used. There are therefore potentially many interesting strategies that might retard peritoneal alterations.

Question 2
Should the measurement of leptin with its association with malnutrition become a standard marker that we measure in all of our dialysis patients?

We do need accurate markers to evaluate malnutrition and inflammation. More clinical trials are required to answer whether it is useful as a routine clinical measurement. The general consensus was that at the moment we do not have enough information about the potential role of measuring leptin levels.
If you lack leptin, you eat like a horse and you become obese. If you give such patients leptin, they normalize their food intake. In PD patients, a significant number of them have elevated leptin levels [13–15]. It turns out that leptin is not really removed by the dialysis process and thereby creates the problem. The production of leptin in the fat cells is actually reduced, as the body tries to shut down its production of leptin. High levels of circulating leptin are maintained in dialysis patients [14].

Once there is a leptin antagonist on the market, then the impact of reducing its effects can be properly investigated; to date there is no way of reducing it otherwise. If there is an ongoing inflammatory process, then leptin levels will be modulated since leptin is regulated by cytokines [16]. So in a group of PD patients you can really see a difference in leptin levels compared with controls, and even higher levels if you look at someone on PD with an inflammatory process going on as evidenced by an elevated CRP for example.

Leptin production comes mainly from the subcutaneous fat, but there is production in omentum. It is not known whether leptin mRNA is down-regulated in the omentum during PD. There is a good correlation between the amount of fat cells you have and the leptin levels that are circulating in the body. But that does not exclude, and certainly does not change, the fact that in states of pathology, leptin really does seem to matter. For example, in those that have a mutated leptin production, and cannot regulate their hypothalamus, they are going to be 250 kilo human beings invariably; all the families known become hugely obese and, also, it seems that if you increase leptin levels in a normal, non-obese, individual, which would be exactly what is happening in PD, because it is not filtrated out, because it stays in the circulation, the mRNA goes down but the levels are still high in the circulation. The body is trying to compensate but it cannot. This is equivalent to administrating leptin into a normal weighted individual.

If you look at treatment paradigms both in humans and in rats, 1 month of leptin treatment reduces the body fat from a norm of 14% in the rats to less than 1% body fat in 1 month. So this is a very powerful molecule in terms of body fat. In PD, you get higher circulating leptin levels, because you are not removing leptin during dialysis [17,18]. One answer is to change dialysis strategy so that you can remove leptin.

There is a clear difference in handling of leptin if you use haemodiafiltration vs haemodialysis [19]. However, it is not clearly known if these differences are due to the use of the high-flux membranes rather than to the filtration process or even to the use of the more pure substitution and dialysis fluid you use in haemodiafiltration. So there is a difference anyway but it is not quite clear what is the clinical relevance of that difference.

References