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FROM THE EDITORS

The ISPD Cardiovascular and Metabolic Guideline for Adults Treated with Peritoneal Dialysis

In this issue of *Peritoneal Dialysis International* we publish the International Society for Peritoneal Dialysis (ISPD) guideline relating to cardiovascular and metabolic complications of peritoneal dialysis (PD) in adults. The guideline is published in 2 parts, with the first paper (Wang AY *et al.* this issue) covering the assessment and management of cardiovascular risk factors, and the second (Wang AY *et al.* this issue) confined to the management of cardiovascular complications. The print versions present each guideline with a brief rationale, and the detailed supporting evidence is presented in the online supplements. The guideline working group of 12 authors, chaired by Angela Yee-Moon Wang, represents expertise from across our specialty and is to be congratulated on delivering a rigorous and detailed piece of work that will be of considerable value to clinical teams in their goal of providing optimal patient care. The introduction to the documents describes the process of study selection and acknowledges the problem that clinical evidence in our specialty is often not robust, or is lacking. The question then was whether to extrapolate evidence from chronic kidney disease or hemodialysis—and although there are concerns about taking that approach, it provides the only pragmatic solution. Thus for dyslipidemia or anemia, the recommendation is to use existing KDIGO guidance. Evidence was assimilated using the modified GRADE system that classifies both the strength of the recommendation (the balance of desirable and undesirable consequences, quality of evidence, economic considerations) and the level of evidence upon which it is based.

These guidelines have a broad prospectus since cardiac risk factors in PD patients go beyond the traditional to include residual renal function, volume control, inflammation, nutritional status and dialysate glucose exposure. Synthesizing the evidence to develop a recommendation was often challenging, for example when defining a blood pressure target. In this area, a registry study demonstrated differential risk associated with hypertension according to whether the patient was transplant listed or not (1); and an intervention study provided a mechanism of blood pressure control through salt and water restriction but at the expense of residual renal function (2). Volume management is couched in concerns regarding the overuse of the stronger dialysate glucose concentrations while being clearly conscious of the dangers of overhydration. The message relating to the impact of obesity on outcome in patients on PD is not consistent.

The articles conclude with research recommendations—and in this area there is much to do. Powering studies adequately is a challenge that many would regard as almost insurmountable, and our specialty is unlikely ever to compete with cardiology or diabetes for study size and evidence evolution. Our patient populations are heterogeneous, coming from a range of disease backgrounds, carrying a significant burden of co-morbidity, and even if the start of therapy is used as study entry, it does not present a level baseline. Furthermore, high dropout rates due to kidney transplantation or PD technique failure pose additional difficulties in conducting clinical trials that examine hard outcomes. Advancing the knowledge base requires strong collaboration and a detailed understanding of research methodology as well as a committed and motivated clinical community. As far as these latter points are concerned, we have considerable grounds for encouragement.

Martin Wilkie
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Staphylococcus aureus Infections: Adipocytes Join the Fight

Despite improvements in connection technology and prophylactic measures, peritonitis remains a major complication of peritoneal dialysis (PD), causing technique failure and increased morbidity and mortality (1). Because it is a common cause of skin infection, *Staphylococcus aureus* (*S. aureus*) is one of the most frequent etiological agents of catheter-related peritonitis in PD patients. Moreover, the frequency of methicillin-resistant *S. aureus* (MRSA) is increasing, associated with lower primary response rates and worse outcomes (2). Reducing the frequency and severity of peritonitis in patients treated by PD and understanding the basis of virulence and infection control remain high priorities and major challenges for researchers.

In a recent study published in *Science*, R. Gallo and colleagues describe elegant experiments demonstrating, for the first time, that skin adipocytes are involved in the protection against *S. aureus* infections (3). Using a mouse model of subcutaneous injection of MRSA in the dermis, these investigators noted that the pathogens caused a marked expansion of the dermal fat layer caused by the hypertrophy and proliferation of adipocytes. The adipogenesis due to *S. aureus* infection was driven by specific transcription factors (called zinc finger protein 423, ZFP423; and peroxisome proliferator-activated receptor γ, PPAR-γ). Next, they showed that adipocyte activation was important for host defense against *S. aureus*, by using mouse models defective in ZPF423 or by treating normal mice with pharmacological inhibitors of PPAR-γ. In both cases, impaired adipogenesis resulted in increased susceptibility to *S. aureus* skin infection.

In order to find out how adipocytes might protect against *S. aureus* infection, the authors compared the expression of antimicrobial peptide genes in a well-established model of undifferentiated vs mature, differentiated mouse (3T3-L1) adipocytes. They discovered that the mouse antimicrobial peptide cathelicidin was strongly and specifically induced during differentiation of the adipocytes. Cathelicidin was also produced by human adipocytes and detected in human and mouse subcutaneous adipose tissue, and its production by adipocytes was significantly enhanced during *S. aureus* infection *in vitro* and *in vivo*. Furthermore, conditioned medium containing secreted cathelicidin inhibited the growth of *S. aureus*, whereas mice knocked out for the *Camp* gene, which codes for cathelicidin, were more susceptible to infection. Also, adipocytes from the *Camp* KO mice lost the capacity to inhibit bacterial growth.

Taken together, these findings show that adipocytes produce an antimicrobial peptide which is important for protection against *S. aureus* infection. Adipocytes are thus joining other resident cell types and recruited leukocytes in the host defense against microbial infections. If verified for other types of adipocytes, including those located in the visceral peritoneum, the role of adipocytes in innate immunity could open a new avenue into the control of invading pathogens and of the infectious complications in PD.

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