The long forgotten salt factor and the benefits of using a 5-g-salt-restricted diet in all ESRD patients

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Writing about older concepts of therapy in medicine often provoke an automatic negative response based on assumptions that they are dinosaurian and empirical and consequently unlikely to impact upon modern therapeutic paradigms unless supported by randomized controlled studies. However, occasionally, new ideas resuscitate these forgotten paradigms and allow one to make progress from observational studies without the benefit of evidence-based medicine [1].

Such is the case with the long abandoned use of a salt-restricted diet in the routine management of patients with end-stage renal disease (ESRD). The reason for this change of attitude is best exemplified by examining two recent learned proclamations. The first published in 2004 and entitled Dialysis Outcomes Quality Initiatives Guidelines on the problem of cardiovascular disease in ESRD patients (K/DOQI) devoted a miniscule paragraph in the lifestyle changes section to salt restriction, unconvincingly recommended in the very early stages of chronic kidney disease and positively contraindicated in later stages [1]. The second document, published 2 years later by the same learned body [2], devotes eight pages and over 60 references to the use of a salt-restricted diet in the treatment of ESRD patients on haemodialysis.

The reason for this significant change of policy may be traced to a potentially plausible and acceptable scientific explanation of a hitherto empirical observation that we published over 40 years ago [3]. When we described our initial dramatic results obtained with a 5-g-salt-restricted diet in severely hypertensive ESRD patients maintained on


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Intermittent HD and Body Weight, Blood Pressure and Exchangeable Sodium


Fig. 1. The delayed reduction in mean arterial pressure occurred several months after the exchangeable sodium and body weight had stabilized.

haemodialysis, we observed that it took several months to achieve ultimate drug-free blood pressure control. This late (lag) phenomenon was independent of the initial reduction in blood pressure associated with reducing extracellular volume and reaching an arbitrarily defined dry body weight. In addition, serial exchangeable sodium measurements showed no further reduction with the appearance of the ‘lag’ phenomenon (Figure 1). The lag phenomenon, now recognized by many authors, has been shown to be due to a reduction in peripheral resistance [4]. The possible explanation may be linked to the reduction of non-osmotically active sodium, first described 40 years ago [5] which is potentially bound in the interstitial matrix lining the intimal surface of blood vessels containing proteoglycans and glycosaminoglycans [6]; this sodium store takes months to normalize on a 5-g salt intake [7,8]. The concept depends upon observations in vitro that the gene responsible for inducing the inflammatory cytokine cycle, MAPK38 (mitogen-activated protein kinase), stimulated by a local high sodium concentration and resulting in an ADMA (asymmetric dimethyl arginine)-induced increase in peripheral resistance by reduction in nitric oxide synthesis will be reversed by a low-salt dietary intake, as will the production of inflammatory cytokines.

Thus, the lesson to be learned from the almost unique experiences of Tassin [9] and Izmir [10] is that the most important determinant of improved survival in ESRD patients on haemodialysis is less related to the technical aspects of therapy, than to the insistence on a 5-g daily salt intake. Reinforcement of this concept has been provided by a 25% reduction in cardiovascular morbidity and mortality in a low-salt group (5 g per diem) compared to a normal unrestricted salt intake recently reported by Nancy Cook and colleagues in a randomized controlled study of ‘prehypertensive’ normals between ages of 35 and 55 years followed up for 10 years with compliance estimated by monthly 24-h urinary sodium determinations [11].

The tragedy of this conclusion is that the tendency to increase the salt intake of the world’s population by the spread of processed food and instant cooking makes the problem of adherence to such a diet more difficult to achieve.

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(See related article by D. A. McCarron. Dietary sodium and cardiovascular and renal disease risk factors: dark horse or phantom entry? Nephrol Dial Transplant 2008; 23: 2133–2137.)


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**Water and solute transport in peritoneal dialysis: models and clinical applications**

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**Keywords:** aquaporin; distributed model; glycocalyx; peritoneal transport; three-pore model

**Introduction**

The physiology of water and solute transport across the peritoneal membrane during peritoneal dialysis (PD) has been widely studied during the last 30 years. The peritoneum can be viewed as a semi-permeable, heterogeneous membrane containing three major components: a monolayer of mesothelial cells; an interstitial tissue containing fibroblasts, macrophages and a conjunctival matrix; and a network of capillaries. It is now commonly accepted that the endothelium lining the peritoneal capillaries represents the main barrier to water and solute transport during PD [1].

**Diffusion** is the main mode of transport for small solutes (e.g. urea, creatinine, etc. from blood to the dialysate and glucose in the opposite direction) whereas higher molecular weight solutes (e.g. albumin, immunoglobulins, etc.) are transported by **convection** and water flow is driven by osmosis [1]. Only the perfused membrane in contact with the dialysate participates in solute and fluid transport. Therefore, the effective peritoneal surface area available for transport depends on the number of capillaries that have been recruited or dilated by the dialysis procedure itself. Determination of transport properties and loss of ultrafiltration (UF) are the main reasons for technical failure in PD, explaining the necessity for models aiming at a better understanding of the transport mechanisms across the peritoneal membrane.

In this issue, Michael Flessner [2] and Bengt Rippe [3] debate the nature of and utility of the models used to predict water and solute transport across the peritoneum as well as the potential importance of the endothelial glycocalyx in these processes. The debate is completed by an original study from the group of Raymond Krediet [4], which details the determinants of water transport during PD in relation with the evolution of the osmotic gradient during the dwell.

**The three-pore model**

The most widely used model for the transport of water and solutes across the peritoneal membrane is the ‘three-pore model’ (TPM) based on computer simulations [5]. This model postulates that the major transport barrier of the peritoneum is the capillary endothelium, which contains three distinct types of pores. The ‘small pores’ (radius 40–50 Å) correspond to the clefts, or gaps, located between endothelial cells. They account for ∼95% of the hydraulic...