Water and Sodium Balance: A Nutritional Goal

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Introduction

Back in the 5th century BC, Empedocles suggested that the biosphere was composed of four elements: earth, wind, fire and water. These four components of life are currently known under names different from those dear to the early philosophers. ‘Earth’ contains the nutritional substrates including vitamins and trace elements. ‘Wind’ refers to the respiratory gases supporting cell life or produced as byproducts of metabolic processes occurring within the cell. ‘Fire’ is the energy resulting from substrate oxidation. ‘Water’ is the only element that is still called by its original name owing to it being the original ‘milieu’ in which life was made possible.

In this chapter we will review some basic aspects of water and electrolyte metabolism emphasizing those that bear a relation to major areas of clinical nutrition such as body composition, undernutrition, nutrition assessment and refeeding.

Body Water and Its Fellow Sodium

The original watery broth from which life emerged contained a similar concentration of sodium and electrolytes other than that of the extracellular fluid of mammals [1]. In fact, the autonomous life of mammals was made possible only after a complex evolutive process led to the internalization of this original sea thanks to the development of a sophisticated system to preserve water and sodium allowing survival in a dry environment. As a result of this process, water represents the most abundant component of the human body and mammals. Water- and sodium-retaining mechanisms are more powerful than those
designed for water and electrolyte excretion, and this is one of the reasons why sodium excretion constitutes a major metabolic problem in undernutrition and stress.

**Distribution of Water in the Body**

Total body water (TBW) is divided into two main compartments: the intracellular (ICW) and extracellular water (ECW) compartments. The ICW is the site of all the metabolic processes and contains approximately two thirds of the TBW (40% of the body weight). The ECW (20% of the body weight) provides a constant external environment in which the cells live and through which they exchange nutrients and byproducts of metabolism. For practical purposes, we shall consider the ECW subdivided into the plasma water and interstitial water compartments (fig. 1).

**Distribution and Exchangeable Fractions of Body Electrolytes**

The concentrations of the major electrolytes found in the ECW and ICW are summarized in table 1. The ionic composition of the two subcompartments of the ECW (interstitial and plasma water) is almost identical; the most significant difference among them being that plasma water contains significantly more protein. In contrast to the ECW, the concentration of Na$^+$ in the ICW is low, and K$^+$ is the predominant cation in this compartment. The uneven distribution of Na$^+$ and K$^+$ across the cell membrane is maintained by

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**Fig. 1.** The body water compartments. Figures are percentages of body weight in the average individual.
the much energy-consuming Na\(^+\)-K\(^+\)-ATPase that continuously pumps Na\(^+\) out of the cell in exchange for K\(^+\).

The exchangeable fraction of a given electrolyte is the percent of its total body content that can freely move between the ECW and ICW compartments, and between the ECW compartment and the external environment. The non-exchangeable fraction is that fraction combined with other substances (i.e., bone or collagen). Only 70% of the total body sodium (about 60 mEq/kg body weight) is readily exchangeable. The average normal adult has a total body potassium of 53 mEq/kg body weight, with an exchangeable fraction of 92%, and it is distributed within the cells. Only 2–3% of exchangeable potassium is located outside the cells and this is the reason why measurements of plasma potassium concentrations do not reflect the body potassium pool. Nevertheless, the extracellular potassium concentration is extremely important for the acid base balance and for the membrane polarization/depolarization processes.

### Extracellular Water, Sodium and Albumin

ECW is of critical importance for organ perfusion, nutrient supply to the cells, and in making intercellular communication possible by supporting humoral signals (hormones, cytokines, neurotransmitters). For this reason severe circulatory and/or respiratory distress makes substrate uptake and oxidation by cells impossible. The intimate relationship between cardiorespiratory homeostasis and substrate oxidation were masterfully delineated by Siegel et al. [2].
The Interstitial Space and Edema Formation

Interstitial water behaves as a buffer space for changes occurring in the plasma volume. As opposed to the systemic regulatory mechanisms controlling plasma volume, the regulation of interstitial volume is largely local, depending on Starling’s law [3]. Lymph drainage of the interstitium is of paramount importance to prevent edema formation. If water shifts towards the interstitium, it overcomes the lymphatic drainage (which can increase up to 30 times) and edema ensues. This occurs typically in aggressive fluid administration, heart failure or a combination of both. In severe chronic malnutrition, extreme hypoalbuminemia (serum albumin <25 g/l), often associated with water retention and infection, results in low colloid osmotic capillary pressure and interstitial edema, the so-called ‘famine edema’.

Albumin in ECW

There is a constant transcapillary flux of proteins across the capillary wall, its magnitude depending on their molecular weight and electric charge, capillary hydrostatic pressure and the type of capillary bed. Albumin is the most important plasma protein in terms of both concentration and transfer across the capillary membrane: the physiological transcapillary flux of albumin may amount to 150 g/day, half of its total mass. 60% of the albumin pool is situated in the interstitial space while the remaining 40% is in the intravascular compartment. This ratio, however, may change when alterations in the interstitial matrix occur.

The normal interstitial matrix is composed of a hyaluronan glycosaminoglycan gel embedded in collagen fibers. The physical space occupied by this interstitial matrix is partially excluded for macromolecule and plasma protein distribution. Nevertheless, the available interstitial space for albumin and other macromolecules may change when variations in matrix hydration occur: the more hydrated the interstitial matrix, the more space there is for protein distribution [4]. This explains why an expansion of the ECW volume is paralleled by a decrease in the albumin plasma concentration (fig. 2).

Regulation of Body Water Compartments

The volume and osmolarity of body water are tightly regulated by systemic mechanisms through two major physiological actions: (1) water and electrolyte balance, and (2) body water distribution. Both major physiological mechanisms have the same target: to regulate within narrow limits both the osmolarity of body fluids and the extracellular fluid volume that is effectively perfusing the tissues (effective circulating volume).

Control of ECW Osmolarity

Osmolarity is maintained through control of water balance in the range of 285–295 mosm/l. In normal conditions, thirst is the major signal to increase
water intake. The kidneys are responsible for adjusting the water balance by diluting or concentrating urine. Vasopressin (ADH) is the major endocrine mediator between changes in plasma osmolarity and the renal response. A decrease in blood volume or arterial pressure also stimulates ADH secretion. This effect is less sensitive than that of osmoreceptors. Thus, a decrease of 5–10% in blood volume or arterial pressure is required to stimulate ADH secretion.

**Control of the Effective Circulating Volume**

Sodium balance closely regulates the ECW fraction that perfuses the body tissues, the so-called effective circulating volume. Alterations in osmolarity due to changes in sodium balance are rapidly counteracted by ADH. Thus, addition of sodium to ECW is similar to adding an isosmotic solution. Conversely, a negative sodium balance results in a decrease in the ECW volume. Under normal conditions the kidneys share responsibility for keeping the ECW volume constant by adjusting sodium excretion through activation of renin secretion.

**Thirst Regulation through Water Balance**

The motivation to drink water is provoked when the hypothalamic osmoreceptors detect an increase in ECW osmolarity. These specialized sensors send signals to the nearby neuroendocrine cells located within the supraoptic and paraventricular nuclei of the hypothalamus that synthesize and release ADH to the bloodstream from the posterior lobe of the pituitary gland. Thirst is also stimulated by a reduced effective circulatory volume. Hypovolemia stimulates
the juxtaglomerular apparatus inducing the synthesis and release of renin which results in a subsequent increase in angiotensin II, the most powerful dipsogenic substance known. The subfornical organ appears to be the preferred site of action of angiotensin II. It is connected to the endocrine cells in the supraoptic and paraventricular nuclei secreting ADH [5].

Metabolic Links: Glucose, Water and Sodium

Transport of glucose across the intestinal epithelium and the proximal renal tubules is closely linked to the transport of sodium and water. The first hint on the anti-natriuretic effect of glucose was derived from the physiological information gained from studies by Gamble [6] carried out during World War II. The basic aims of Gamble's work were both to determine the minimal water requirement in the state of fasting and whether this minimum requirement changed according to the quantity and quality of food intake. He showed that glucose intake has a sodium-sparing effect by diminishing the renal excretion of this cation. Briefly, he found that the administration of 100 g glucose/day induced a sparing effect on sodium balance that even surpassed the effect of a daily intake of 4.5 g NaCl. When sodium and glucose were given together, this sodium-sparing effect was potentiated (fig. 3). Other authors [7–9] later confirmed the sodium-sparing effect of glucose. These studies set up the basis for our current standards of intravenous fluid therapy during short periods of fasting. They also laid the foundations for further exploring the relationship between carbohydrate intake and water and sodium retention in apparently different settings such as kwashiorkor and intravenous refeeding, which bear some metabolic resemblances as far as water and sodium metabolism is concerned.

Body Water in Starvation and Stressful Conditions

Starvation, severe trauma or sepsis are linked to alterations in the size of the body water compartments and exchangeable electrolytes, particularly sodium. Malnutrition and severe disease are associated with an expansion of ECW. In fact, in the early 1980s, Tellado et al. [10] went so far as to suggest that a Na_e/K_o of >1.22 was diagnostic of malnutrition.

Prolonged reduced intake of protein and calories results in subtle alterations in water and electrolyte metabolism. The most well-known phases of these changes are the early diuretic and natriuretic phases, the relative expansion of ECW as depletion progresses, and the final phase of a kwashiorkor or kwashiorkor-like picture dominated by an absolute expansion of ECW, edema and hypoalbuminemia.

Starvation: Early Natriuretic Phase and Late ECW Expansion

Shortly after a drastic reduction in food intake occurs, there is an early diuretic and natriuretic renal response probably mediated by the low-insulin plasma concentrations. Excretion of sodium salts of ketones during early
ketonuria has also been implicated in sodium losses. Some degree of ECW depletion may occur during this phase. This renal response is, however, short lasting and may not be present if fasting is not complete. From the nutritional point of view it is not particularly relevant since partial starvation is far more common than complete fasting both in the clinic and in countries were food shortage is endemic.

Prolonged partial starvation results in a complex and only partially understood renal response characterized by sodium retention or, at least, by an abnormal renal handling of sodium and a tendency towards positive sodium balance [11]. In fact, despite severe weight loss occurring after a reduction in food intake, the ECW compartment does not diminish. Keys et al. [12] found that, in semi-starving volunteers, the ECW volume remained constant despite a 30% weight loss. Thus, it is now well established that protein-energy malnutrition results in an ECW expansion, which is relative or absolute to the weight of the patient [13].

**Edematous vs. Marasmic Malnutrition**

Chronic undernutrition results in ‘dry’ (marasmus) or in ‘wet’ cachexia (kwashiorkor). In both cases, a severe depletion (25–35%) of protein and fat

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**Fig. 3.** The effect of salt and glucose intakes on water and sodium balance in fasting normal volunteers. Adapted from Gamble [6].
stores are present but they differ from each other mostly on water and sodium handling. Marasmus is characterized by a maintained ECW, which is only expanded in relationship to body weight, and normal or normal-low serum albumin concentrations (i.e., anorexia nervosa, food shortage). By mechanisms not completely understood, some individuals with protein-calorie malnutrition develop edema and hypoalbuminemia. In these cases, the ECW expands well above its normal volume.

Observations made in concentration camps during the early 1940s drew attention to the fact that malnutrition edema was only seen in subjects with a low-protein but normal or high-carbohydrate intake [14] or in malnourished individuals when sodium intake was increased [15]. Elevated plasma insulin can be found in kwashiorkor at variance with the low values observed in marasmus [16]. This would favor the hypothesis that carbohydrate intake may be essential for the development of absolute ECW expansion perhaps through sodium retention.

Chronic anemia may also facilitate water and sodium retention. Anand et al. [17] found that patients with severe chronic anemia exhibited retention of salt and water with 32% expansion of their ECW associated with activation of the salt-retaining hormones. Finally, a kwashiorkor-like picture can result when patients with marasmus suffer from an acute disease process such as trauma or infection. In these cases, the association of fluid infusion and the antidiuretic drive of stress lead to further sodium retention and absolute ECW expansion resulting in edema and distributional hypoalbuminemia.

**Impact of Acute Pathological Conditions on ICW**

In protein-energy malnutrition as well as in certain acute conditions (trauma, sepsis, major surgery), the cells become energy-deficient, the high energy-consuming membrane ATPase activity is reduced, and water, sodium and chloride tend to accumulate within the cell causing a spurious potassium-poor ICW expansion [18, 19].

This phenomenon has relevant clinical implications. Almond et al. [20] found significant potassium depletion in the ICW of surgical patients with malnutrition due to inflammatory bowel disease. They also noted that intracellular potassium depletion and repletion, during catabolism and refeeding, may be more rapid that changes in cell protein synthesis or degradation. This finding may explain the early positive clinical response to nutritional repletion in malnourished individuals even prior to any measurable change of the body protein [21].

**ECW Derangements in Acute Stress**

ECW expansion is the hallmark of acute disease and is usually the result of a multifactorial process involving the physiologic response to disease, the
underlying nutritional status and the infusion of intravenous fluids, sodium and nutrients.

The mechanisms that have been implicated in the expansion of the ECW in acute illness are shown in table 2.

**Volume Expansion and Hypoalbuminemia**

The pioneering work of Moore [22] characterized the antidiuretic renal response observed after hemorrhage, surgery and trauma. Activation of the sympathetic and the renin-angiotensin systems occur in acute illness, particularly in severe sepsis and hypovolemia. A reduction in effective plasma volume due to a massive shift of fluid and albumin to the interstitium may also contribute to a reduction in the glomerular filtration rate, oliguria and further activation of sodium-retaining mechanisms.

In critically ill patients, the expansion of the ECW occurs in absolute terms reaching up to 50% of the usual body weight. After resuscitation from hypovolemic shock, Böck et al. [23] found a 55% increase in ECW, mainly affecting the interstitial compartment. Massive ECW expansion is almost the rule after resuscitation from severe sepsis [24].

ECW expansion has undesirable consequences [25–27]: interstitial edema impairs gas exchange, hypervolemia may precipitate heart failure, excess subcutaneous water may impair wound healing, and alterations in the pharmacokinetics of drugs. All these may explain why ECW expansion closely correlates with clinical outcome. When the normal ECW is doubled, the risk of death approaches 80% [10].

Hypoalbuminemia is a multifactorial phenomenon associated with a poor outcome in many clinical conditions [28, 29]. In acute injury and in some chronic conditions, the transcapillary escape rate of albumin is increased up to fourfold [30]. The mechanisms underlying this albumin shift to the interstitium are not completely understood. Two major hypotheses have been advanced: (1) increased available space in the interstitial compartment due to matrix degradation, and (2) increased capillary permeability to macromolecules (fig. 4). Degradation of the interstitial matrix occurs because hyaluronan, an essential component of the glycosaminoglycan, is washed out of the

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**Table 2. Pathogenesis of ECW expansion in acute disease**

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<td>Activation of water and sodium retaining mechanisms by hypovolemia and pain</td>
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<td>Increased capillary permeability and ‘albumin leak’ to the interstitium</td>
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<td>Aggressive fluid therapy during resuscitation</td>
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<td>Excessive administration of water and sodium during the flow phase</td>
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<td>Reduction of effective plasma volume</td>
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<td>Administration of vasoactive adrenergic drugs</td>
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<td>High-glucose low-protein diets</td>
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Fig. 4. Schematic representation of the two major hypotheses explaining distributional hypoalbuminemia in acute illness. *a* Interstitial illness. *b* Capillary leak syndrome.
interstitial space. This can occur by a simple clearing mechanism related to increased interstitial hydrostatic pressure due to overhydration, or may be induced by mediators or sepsis [31, 32].

On the other hand, it has been postulated that in acute injury, inflammatory mediators would increase the permeability of the endothelial capillary lining. Brett et al. [33] found that tumor necrosis factor increased capillary permeability.

In this clinical context, hypoalbuminemia is an epiphenomenon of disease and is not related to any primary nutritional derangement. For this reason, therapeutic efforts should be directed to treat the underlying illness rather than focusing on the management of low-plasma albumin concentrations. Therapeutically, there seems to be little role for exogenous human albumin administration [29, 34]. In fact, exogenous albumin may worsen the situation by increasing the interstitial colloid osmotic pressure thus facilitating the immobilization of water in the interstitial space. When possible, usually after the underlying process has improved, diuretics may be given to promote a negative water and sodium balance, which will be paralleled by an increase in the serum albumin concentration. At this non-stressed stage, Lobo et al. [35] have recommended low doses of human albumin to mobilize fluid excess and facilitate diuresis.

Water and Electrolyte Metabolism during Refeeding

Refeeding of the malnourished non-stressed patient should lead to repletion of fat and protein stores, improved muscular strength, diuresis of any ECW excess and restoration of subjective well-being. In severely depleted individuals, however, aggressive refeeding may lead to complications through two major metabolic responses: acute intracellular cation shift and water and sodium intolerance.

Early works on refeeding, reported inappropriate physiological responses consisting mainly in disturbances affecting the ECW and the cardiovascular system: hemodilution, congestive heart failure, edema, and excessive weight gain. After the Stalingrad Siege, refeeding of the population led to an epidemic of hypertension and congestive heart failure [36]. Heymsfield et al. [37] reported cardiac decompensation when glucose-based total parenteral nutrition (TPN) was given to undernourished patients and Viart [38] reported an increase in the blood volume and hemodilution during oral refeeding of malnourished children. Briefly, water and electrolyte metabolism appears to be an important determinant of an appropriate response to refeeding.

The Anabolic Response: Intracellular Cation Shift

Not only is intracellular protein lost during malnutrition but also potassium and other intracellular cations such as phosphate and magnesium. Thus, during refeeding, two anabolic phenomena occur: a positive nitrogen balance,
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$5a$

$5b$

$5c$
and a correction of the reduced intracellular ion concentration [39]. Both result in increased demands of electrolytes and may lead to hypokalemia, hypophosphatemia or hypomagnesemia if supply is inappropriate. Dyselectrolytemia has been noted to occur if hypercaloric glucose-based parenteral nutrition is administered to cachectic patients. Hyperinsulinemia forces nutrients and electrolytes into the cells and this may result in life-threatening hypophosphatemia, hypokalemia, rhabdomyolysis and seizures [40].

**Water and Sodium Retention and Hypoalbuminemia**

Rudman et al. [41] demonstrated that between 35 and 50% of the weight gain observed shortly after parenteral refeeding was accounted for by ECW. Withdrawal of sodium from the TPN formula stopped weight gain and induced negative sodium, weight and ECW balances. Heymsfield et al. [37] reported a rapid expansion of intracardiac volume early after starting oral plus parenteral refeeding. In other studies [42, 43], surgical patients who were refed preoperatively with TPN and showed an expansion of ECW developed more postoperative complications. MacFie et al. [44] demonstrated that glucose-based parenteral nutrition regimens result in more water retention and fat gain than those including fat as a source of 60% of the nonprotein calories.

Thus, administration of high-glucose and sodium loads during TPN can now be definitely implicated as a cause of ECW expansion. To help elucidate the role of parenteral nutrition formulas in inducing ECW expansion, we investigated the response to refeeding with low-sodium low-water TPN regimens. Animals refed with high-glucose regimens and larger sodium loads exhibited a more positive weight balance largely due to ECW expansion secondary to diminished natriuresis [9, 45]. Furthermore, rabbits receiving high-glucose regimens had higher urinary metanephrine excretion, pointing towards increased sympathetic activity as a result of the high-glucose intake.

In a randomized trial we compared a 10-day course of two different preoperative TPN regimens in depleted cancer patients [46]. One group received a water and salt-poor diet while the other group was refed with a standard protocol. There was a correlation between water and sodium balances but almost exclusively dependent on the response of the patients given high-water and sodium formulas (fig. 5). Patients in the standard group showed positive sodium and water balances, weight gain and decreased serum albumin concentration levels. The modified diet group exhibited the opposite response (table 3). The restriction of water and sodium seemed to act synergistically with carbohydrate reduction to prevent ECW expansion.

**Fig. 5.** Correlations between weight balance and water balance in severely malnourished patients receiving preoperative TPN for 10 days. **a** The whole population study is included. **b** The correlation found in patients receiving high-glucose-Na TPN contrasting with the lack of correlation (**c**) observed in patients receiving a lipid-based low-Na formula. From Gil et al. [46].
Lobo et al. [35] also found a relationship between weight decrease and increases in serum albumin concentrations during refeeding of malnourished patients, and their study further emphasizes the relevance of adjusting the water and sodium contents of the refeeding diets.

These concepts may also apply to patients with ongoing infection receiving TPN. Experimental data have shown that the septic animal with an intra-abdominal abscess is also susceptible to suffering a further expansion of the ECW by high-volume and high-glucose TPN and that, in sepsis, ECW expansion is favored by the hypoalbuminemia already present at the start of intravenous feeding [47].

It is interesting to note that the 3 human studies investigating water and sodium metabolism during preoperative TPN [42, 43, 46] have shown that only between 50 and 60% of patients refed with large glucose loads did in fact exhibit an inappropriate expansive response. The same was true for the only animal study [9]. The reasons for this are unclear. A hypothesis can be put forward implicating genetic differences in the ability to handle glucose loads and, specifically, differences in the ability of glucose to retain sodium via an increase in plasma insulin and/or catecholamines.

References


Discussion

Dr. James: I was delighted to see such an analysis elegant. Could I just put in a bit of ancient history. When we looked at this whole relationship of albumin metabolism and sodium balance in the classic children with kwashiorkor and marasmus in Jamaica in the 1960s, we managed, exactly as you described, to drop the mortality from about 40 to 4% by virtue of knowing that the total body sodium was very high and looking at the relationship between total body potassium and lean tissue, and therefore what was true potassium deficiency, and we were able to drop it. The sensitivity of that whole issue, you are talking about Western hospitals, but you still find astonishing death rates in many parts of the world because of the inappropriate provision of not only sodium but quite high calorie loads in the first few days. We had quite a lot of problems because colleagues from Uganda had death rates of 40%, and characteristically these babies just dropped dead. In fact we showed that it was acute heart failure that they were dying of, which is quite intriguing. That is historically well recognized. You talked about the Starling growth seizure, and I had the privilege of looking after many of the Auschwitz adults in my first medical training in London. They used to describe very vividly that the survivors were very proud of the fact that as the Western troops came...
in and gave huge amounts of food, they observed that the people were dying very rap-
idly, and these young people restricted their sisters and brothers from eating for 3 or 4 days and gradually had the same practical monitoring of intake which they believed was critical to their survival. So I think that the application of your sophisticated analy-
sis to the sort of primitive acute coping in many of these crisis problems in Africa and elsewhere is still quite a big issue.

Dr. Sitges-Serra: I want to show my deep respect for what you and Dr. Waterlow did in the early ages of kwashiorkor. This literature has been very stimulating for many of us to do research in this field, and these historical observations are in a certain sense very stimulating for increasing our knowledge on this difficult topic, but because this is still not a very attractive field, there is not much research. If you look at the past years on the pathophysiology of kwashiorkor involving fluid and sodium, you find very little indeed. So it is this kind of research stop in this still very common condition which I think we should review.

Dr. Allison: Both your and Dr. James’ remarks emphasized that, in looking at any nutritional program, salt and water should be considered in the same category as calo-
ries and grams of protein as equally important, although they are much neglected. Both your remarks suggested rather that the Veterans Administration trial [1] results on perioperative parenteral nutrition could be clearly and entirely explained by dif-
fferences in salt and water balance and have nothing to do with the nutrients given at all, or the route by which they were given, because as we know the amount of salt and water you can give by the enteral route is restricted by gastrointestinal tolerance whereas the amount of fluid you can give through a central line or even a peripheral line is virtually unlimited. Have you thought that a lot of these data comparing enteral and parenteral nutrition or parenteral with nothing in fact may just be related to the fluid problems and not with the nutritional problems?

Dr. Sitges-Serra: Absolutely, in fact I was amazed to see not only the difference but, if you look back at the studies on total parenteral nutrition (TPN) refeeding before surgery, there are at least 3 or 4 trials but none of them has assessed the response to TPN refeeding [1, 2], so you won’t find any data on albumin changes or weight changes or extracellular water (ECW) expansion or whatever physiological mechanism you like to see. The effect of TPN, it is just giving TPN and then doing sur-
gery, but in none of the studies is the effect of TPN assessed so that is very difficult then to understand what is going to happen afterwards if you don’t have a fair idea of what is refed in these patients. So again I emphasize that in all future trials the response to whatever means of nutrition is used must be explained so we can have a good idea of how much these patients really gain.

Dr. Allison: All future intervention studies should control for the fluid salt and water balance, as well as for the nutritional balance.

Dr. Biolo: I would like to comment on the potential role of insulin on the refeeding syndrome. Do you think that is the major player in this game because insulin can retain sodium, can decrease potassium concentration and also may directly activate the symp-
thetic system?

Dr. Sitges-Serra: My bias would be that increased carbohydrate or regular carbo-
hydrate intake would cause continuous insulin secretion which in fact would lead both to sympathetic activation and fluid and sodium retention, so maybe the whole clue of the refeeding syndrome as far as sodium and carbohydrate is related may be insulin secretion, although I must say we don’t have data on refeeding and insulin as such. But the pathophysiology thinking would lead us to think insulin is one of the major issues in causing this refeeding syndrome, I agree with you. In fact in some of our studies we measured catecholamines, and catecholamine secretion is higher when you refeed animals with carbohydrate than without carbohydrate, and that has also been done by Nordenström et al. [3] showing that refeeding with high-glucose loads may also
activate the sympathetic system, so probably insulin and catecholamines are involved in this retention phenomenon.

Mr. Lobo: You did mention the role of glucose in inducing sodium retention in both the work of Gamble [4] and your own work. But we have conducted some studies in volunteers who were not in a stressful situation, so they are perfectly healthy, and we haven’t been able to demonstrate that glucose actually produces sodium retention. So maybe it is a prerequisite that you need to be in a stressful situation like prolonged fasting or being septic postoperatively for glucose to induce this, and so it may be a result of other endocrine responses rather than insulin alone. I would like your comments on this.

Dr. Sitges-Serra: We used malnourished rabbits without stress, and in this circumstance glucose was able to show some degree of sodium retention. I don’t know either the characteristics of your study, the dosage of sodium or the dosage of glucose and the time schedule, there may be some methodological differences explaining these experimental settings.

Mr. Lobo: We gave the same dose of glucose as Gamble, that is 50 g of glucose and an overload of 300 nmol of sodium. Again Gamble’s volunteers, to whom we gave the life raft ration, a prolonged starvation, and your animals were malnourished, so maybe that has got another confounding variable in it.

Dr. Kopelman: Can I come back to the insulin story. In my own experience of refeeding patients with chronic anorexia nervosa, their insulin levels remain quite low for about 72 h as refeeding starts. The problems faced with these patients tend to occur very early on, and we always assumed that they were related to fluid rather than simply insulin, although I am sure insulin contributes at a later stage.

Dr. Sitges-Serra: The problem is that refeeding may be different if the patient has marasmus and ECW is normal or slightly increased, or if patients who start nutrition are edematous, hypoalbuminemic and have a very expanded ECW. So refeeding under these two circumstances may perhaps be different because the compliance of the cardiovascular system may be different. Certainly in both cases it is now accepted that refeeding has to be progressive, slow and with low volumes of water and sodium. Whether insulin would under these circumstances increase to the level of being able to interfere with sodium and water retention, I don’t know. Perhaps very high insulin levels are needed to show a renal effect. Certainly in our experiment we were infusing hypertonic glucose, and really stressing the insulin axis in certain way by giving patients or animals 70% of calories as glucose, which means that probably our insulin levels were in the high range. So probably here the insulin concentration may have some kind of effect, but that remains to be investigated.

Dr. Shenkin: I wonder if I could put a combined question to you and Mr. Lobo about the redistribution of albumin in sickness? This is a question of trying to distinguish between situations in which you have increased transcapillary escape of albumin as opposed to the expansion of interstitial fluid. If we understood more about the mechanism, if it is due to some kind of cytokine effect on the width of the capillary spaces or whatever it is, so that one could actually know the point at which albumin transcapillary escape is greatest and is starting to return to normal. If we could find a way to distinguish between how much transcapillary escape has gone up and has been able to settle as opposed to the redistribution of the expansion of the overall interstitial space, then we might know how to treat by restricting fluids as opposed to controlling inflammation.

Dr. Sitges-Serra: The pathophysiology of hypoalbuminemia, whether it is convective or there is inflammation of the capillary endothelium, may play a secondary role in management because in the end what you are going to do is to treat the fundamental illness, whether sepsis or trauma, and then restrict fluids if the hemodynamics of the patients allow it because sometimes in these patients you need huge amounts of
volume to maintain their hemodynamics and diuresis. So at the point that patients start to tolerate fluid restriction and diuretics, that is a way to go. The final mechanism is still a matter of debate and I said that my personal bias is that with Starling's law principles you can understand why albumin is escaping through the capillary, but we shouldn't use the word 'escaping' as a signal for the capillary bed being sick or diseased. You can purely explain that on the basis of hydrostatic pressures and hydration of the interstitial matrix. Increased permeability exists on a local basis; whether it also exists on a systemic basis is another cup of tea, but in the end I think we all would agree that we should treat the fundamental disease and then promote a negative fluid balance. It is amazing to see how albumin will increase and patients lose weight and fluid, and this is why we would be very cautious to give serum albumin under these circumstances, because if there still are some problems in the capillary bed or excess of fluid then albumin would go throughout the body fluids and lose the desired oncotic effect. So I would stress: to treat disease, put the patient on a negative water balance, nutrition support if necessary, and then use serum albumin under very selected circumstances.

Dr. Allison: The point about those selected circumstances: unfortunately the Cochrane review was written by people who knew a lot of statistics but have no experience of the underlying problem. I would agree with their conclusion and yours that the treatment of hypoalbuminemia is not giving albumin, it is treating the cause of the hypoalbuminemia as you have emphasized. But there are certain patients who perhaps have had complications of surgery or sepsis and have continuing leakage as you emphasized, protein from the gut, protein-losing enteropathy for some reason. These people end up with edema and expanded interstitial space but a low plasma volume. Now they will never start excreting salt and water with a low renal plasma flow, and until you correct perfusion of the kidney you will not get any diuresis. Now what are you going to do to correct that volume? You have a patient who is already overloaded by 15 liters in the interstitial space, so if you give any sodium-containing fluids of any sort you are going to make the situation worse. My experience of these patients is where there is a volume problem in a post-acute stage that is where albumin infusion produces a dramatic improvement, and I agree with you that albumin infusion should be restricted to that very narrow group of patients in whom you wish to treat the intravascular volume in the presence of a total ECW overload.

Dr. Sitges-Serra: The best evidence-based paradigm of what Dr. Allison was saying is the treatment of ascites. Now it is well accepted that if you do a massive evacuation of ascites and a rapid infusion of albumin improving renal function, you will have a cure of the ascites and you will have good renal function. Apart from that we need more evidence in selected clinical circumstances because not only the Cochrane but also a review in the Annals of Surgery by Vincent et al. [5] again opened several questions on what the precise settings are which could profit from albumin infusions. I am sure that you have enormous experience on that and you would probably select the right patient to give serum albumin, but that is difficult to extrapolate to other institutions.

Dr. Allison: What I say for the students, if everything else fails let’s examine the patients. If you put the patients at 45° and look at the jugular venous pressure, if it is elevated you give them a diuretic. If you can’t see it you lower them down and if you still can’t see it when they are lying flat then probably the intravascular, the plasma volume is diminished, and giving these patients concentrated salt or albumin is what people call a coconut every time. But you must monitor. The idea that you can give a fixed dose of physiological treatment is ridiculous unless it was one of the Cochrane errors. You can’t just randomize to units of albumin against none; you have got to titrate it against the cardiovascular response, but if you do that in a sensible way it is a coconut every time.

Dr. Wongkietkachorn: Let’s come back to the clinical setting, talking about the impact of hypoalbuminemia. If a patient has hypoalbuminemia after surgery and he is
still receiving suboptimum caloric intake, albumin will drop and albumin can also leak, extracellular leakage. Can you give some practical aspects, the mechanism of hypoalbuminemia? How can you differentiate catabolic excess and catabolism from leakage?

Dr. Sitges-Serra: When you look at the cause of hypoalbuminemia, and of course there are several, one is distributional or convective and then there are others. In malnutrition you can see patients with a body mass index below 15 but with normal serum albumin, so it has no clear-cut relationship with caloric intake in the long run. Of course marasmus at the end can develop into kwashiorkor and then you have hypoalbuminemia. But for malnutrition per se to have an impact on serum albumin, it must be very severe as a single factor. Usually what you see is malnutrition plus leakage through gastrointestinal cancer plus some degree of inflammation and maybe downregulation in the liver. So that is the context in which clinical hypoalbuminemia develops. There are multifactorial issues and probably in our Western societies the problem of chronic suboptimal intake is not that relevant to understanding hypoalbuminemia as it may be in other circumstances.

Dr. Allison: We produced some data on this some years ago in fractured female patients where we showed that infective injury and perioperative fluid administration, as you described, were the cause of a fall in serum albumin in all patients whatever their nutritional status, but the well-nourished patients recovered their serum albumin within 7 days. The very malnourished patients, very thin patients, had a delayed recovery beyond that, so if you look at the serum albumin in a serial and dynamic sense you can then start to differentiate between the nutritional groups. Furthermore that delay in serum albumin was corrected back to the well-nourished return when you gave nutrition. So nutrition does play a part in the recovery of serum albumin but only if all other things are equal like the fluid balance, the inflammatory state, and so on. So I think there is a nutritional component but in most patients we see, as Dr. Sitges-Serra has described, the main problem is distributional and perhaps dilutional.

Dr. Biolo: I would like to mention a study performed giving stable isotopes and measuring albumin synthesis rate in different situations. According to this study albumin synthesis is not decreased in an acute situation like sepsis, actually it increased the albumin synthesis rate as in the nephrotic syndrome. The lesson that we can draw from these studies is that the main regulator of liver albumin synthesis should be the plasma concentration of albumin, then in the situation where the albumin concentration is decreased, the fraction of synthesis rate is increased. According to these observations, nutrition should not play a major role and I agree perfectly with you.

Mr. Lobo: I have a comment and response to Dr. Shenkin's question. It is extremely labor intensive to measure the transcapillary escape rate (TER) of albumin because blood has to be drawn every 3 min for an hour, and then there are a lot of problems with dilution. However, our own work has suggested that there is quite a close correlation between the TER of albumin and the C-reactive protein concentration, so it is a good salivary marker of capillary escape, and Tisi et al. [6] from Birmingham recommend that you look for microalbumin in the urine and if there is microalbumin present in the urine that suggests the patient has got an increased TER of albumin, if the microalbumin is 0 then the patient's TER has returned to normal.

References

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