Changes of protein kinetics in nephrotic patients

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Nephrotic patients show various abnormalities in protein kinetics. Plasma albumin levels and the total plasma albumin pool are reduced. The rate of hepatic absolute and fractional albumin synthesis are increased. Trasferrin synthesis is also increased. Fibrinogen levels are elevated in nephrotic syndrome because of an increase in the hepatic synthesis. Regulation of albumin and fibrinogen synthesis seems to be coordinated. A low protein diet has been proposed as a therapeutic tool in nephrotic patients – clinical studies have shown that such a diet reduces proteinuria and increases renal survival. Nephrotic patients can adapt to moderate protein restriction with no sign of malnutrition and maintenance of a neutral nitrogen balance. Albumin and fibrinogen synthesis are ameliorated by dietary protein restriction and these changes are correlated with the beneficial effect of the diet on proteinuria. Curr Opin Clin Nutr Metab Care 5:51–54. © 2002 Lippincott Williams & Wilkins.

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Introduction

Nephrotic syndrome is characterized by complex and interrelated changes of electrolyte, protein and lipid metabolism. Principal features of the syndrome include heavy proteinuria, generalized edema and hypoalbuminemia [1]. The alterations in protein metabolism induced by the nephrotic syndrome are not limited to the decline in albumin levels but affect the circulating levels of various other proteins such as antitrombin III, transferrin, and erithropoietin. In contrast, fibrinogen, which is not readily filtered by the diseased glomerulus, tends to be increased. The rates of whole body protein synthesis, degradation and oxidation are also affected by nephrotic syndrome. In addition, both whole body protein metabolism and the turnover rate of specific plasma proteins are greatly affected by the dietary protein and calorie intake as well as by the degree of daily proteinuria.

For many years the appropriate level of dietary protein intake in patients with nephrotic proteinuria has been a matter of discussion. In order to compensate for urinary protein losses and avoid the risk of protein malnutrition, it was initially suggested to maintain nephrotic patients on an elevated dietary protein intake (1.1 g of protein per kilogram of body weight or more) plus 1.5 g of protein per gram of proteinuria [2]. In later years, clinical studies showed that high protein intake fails to significantly increase serum albumin levels and its use is associated with an increased rate of proteinuria and an accelerated progression of renal insufficiency [1].

In contrast, the use of low protein diets showed a beneficial effect on proteinuria and progression of renal insufficiency. The demonstration by Maroni *et al.* [3] of the mechanisms of adaptation to proteinuria and to dietary protein restriction mitigated the concern for malnutrition and provided further support for the use of a low protein diet in nephrotic patients.

Whole body protein turnover and nitrogen balance

Whole body protein turnover as determined by the analysis of 13 1-C and 14 1-C labelled valine or leucine is the stochastic result of all the various processes that determine the rate of individual protein synthesis and degradation. It can be described by the formula

$$F = D + I = S + OX$$

where *D* represents protein degradation, *I* is the protein or amino acid intake (either intravenous or oral), *S* represents protein synthesis and *OX* protein oxidation.

In response to protein feeding the rate of protein degradation is inhibited and both the rates of protein synthesis and oxidation are stimulated. The absolute rate of protein synthesis becomes greater than the rate of protein degradation and this determines a net anabolic response [4]. In contrast, during a low protein diet basal post absorptive protein degradation and amino acid oxidation are reduced and the rise in amino acid oxidation induced by protein feeding is also blunted. These mechanisms of adaptation determine a 'protein sparring effect' which allows the maintenance of a neutral nitrogen balance. Various studies evaluated nitrogen balance and the rate of whole body protein metabolism in nephrotic patients [3,5,6•]. Under comparable conditions of protein intake, whole body protein metabolism and oxidation are similar in nephrotic patients and controls. Amino acid oxidation is correlated with nitrogen excretion. Maroni *et al.* [3] evaluated the metabolic response to a diet providing either 0.8 or 1.6 g of protein per kilogram of body weight plus 1 g of protein per gram of proteinuria and 35 kcal per kilogram of body weight in adult patients with nephrotic syndrome. Whole body protein metabolism was independently assessed with nitrogen balance and stochastic analysis of 13 C labelled leucine infusion. Nitrogen balance remained positive during the two dietary regimens in both control and nephrotic patients. During a low protein diet, endogenous protein degradation and amino acid oxidation declined in both groups. A similar protein sparring effect was reported by our group in nephrotic patients consuming either 1.1 or 0.6 g of protein per kilogram of body weight plus 1 g of protein per gram of proteinuria. With the use of the continuous indirect calorimetry we showed a complex metabolic adaptation to a low protein diet with a lower rate of protein oxidation and compensatory changes of lipid and carbohydrate utilization, which tended to increase [7••]. An additional compensatory response to a protein restricted diet is a lower rate of amino acid oxidation in response to protein feeding which allowed a more efficient utilization of ingested protein. Of interest in nephrotic patients, basal protein oxidation correlates with nitrogen excretion. Furthermore, the rise in protein oxidation induced by protein feeding correlates inversely with daily urinary protein excretion [3,5].

An even more pronounced decline in protein oxidation occurs in rats with experimental nephrosis maintained on a very low protein diet with no additional dietary protein supplementation to compensate urinary protein losses [8].

Thus, in nephrotic patients a dietary protein intake of 0.8/0.6 g of protein per kilogram of body weight plus 1 g of protein per gram of proteinuria is safe and allows the achievement of a neutral nitrogen balance. In contrast, the maintenance of a neutral nitrogen balance with protein intake lower than 0.6 g of protein per kilogram of body weight remains to be tested. Similarly, further data are need on the effect of protein restricted diets in patients with nephrotic syndrome secondary to inflammatory disorders or metabolic diseases, such as poorly controlled diabetes mellitus which can independently affect protein homeostasis [9].

Liver derived protein metabolism

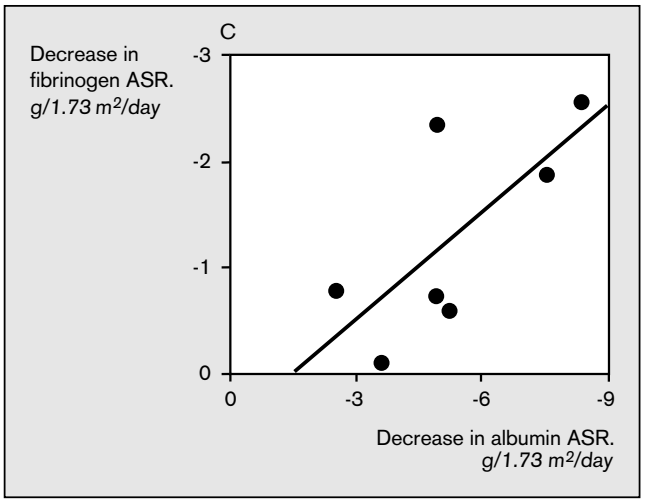
Visceral protein metabolism is profoundly altered in patients with nephrotic syndrome. The first and more evident effect of massive proteinuria is a marked reduction in circulating albumin levels [1]. These levels are reduced both in children and in adults and represent the metabolic hallmark of the nephrotic patients. Data on changes in circulating plasma volume are less consistent. In children with minimal change disease the volume of distribution of albumin and the total albumin pool are always reduced, with clinical signs of marked hypovolemia and activation of the renin angiotensin aldosterone system [10•,11]. In adults, the decline in plasma volume and albumin distribution volume are reported less consistently and are limited to the early phases of the development of the nephrotic syndrome. Later in the course of the disease body water tends to equilibrate between plasma, extracellular and intracellular compartments. We employed the Evans Blue Dye dilution method to evaluate plasma volume in adult patients with nephrotic syndrome [7••]. Plasma volume (as expressed per kilogram of body weight and lean body mass) was not reduced in comparison with controls. Due to the concomitant hypoalbuminemia, however, the total plasma albumin pool was significantly reduced. These changes were associated with an increase in both the absolute and the fractional synthetic rate of albumin [7••]. Various studies have reported a correlation between the degree of proteinuria and the rate of hepatic albumin synthesis [7••,12••]. In order to allow an elevated rate of hepatic albumin synthesis it was proposed to maintain nephrotic patients on a high protein intake [2]. It has been demonstrated, however, that the latter induces a rise in urinary protein excretion and has no beneficial effects on circulating total protein and albumin levels [1]. In contrast, it has been shown that in nephrotic patients the institution of a protein restricted diet determines an increase in serum albumin levels and total albumin pool [2]. Giordano *et al.* [7••] demonstrated that after a low protein diet the decrease in proteinuria and the decrease in absolute albumin synthesis are directly correlated. Zanetti *et al.* [12••] demonstrated an inverse correlation between plasma

oncotic pressure and the absolute synthesis of albumin. Taken together these data suggest that in the presence of hypoalbuminemia the rate of hepatic albumin synthesis is regulated by its catabolic rate via changes in plasma oncotic pressure. If the latter is ameliorated, the rate of albumin synthesis is reduced. Kinetic data on albumin metabolism also provide an alternative methodological approach to evaluate the antiproteinuric effect of low protein diet regimens. The amelioration of the albumin catabolic rate is consistent with an improvement in the glomerular sieving coefficient. In fact if the effect of a low protein diet were mediated by an increased rate of tubular reabsorption with no change in the glomerular filtration of protein, this would ameliorate proteinuria but not the rate of albumin catabolism. In turn, the reduced glomerular filtration of protein ameliorates the concentration of several plasma proteins and plasma oncotic pressure. As a result, the rise in hepatic albumin synthesis is mitigated. It should be pointed out, however, that the available data do not allow one to exclude that the lower rate of albumin synthesis may be dependent upon a limitation of substrate availability induced by the low protein diet. An estimate of the effect on albumin synthesis of a non-dietary therapeutic intervention, such as the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockade, may contribute to a better understanding of the relationship between protein intake, urinary losses of albumin and the rate of hepatic protein synthesis.

In nephrotic patients, plasma transferrin levels are often reduced. Hypotransferrinemia may lead to iron deficiency anaemia. Prinsen *et al.* [13••] showed a direct correlation between urinary excretion of transferrin and albumin. Hepatic albumin and transferrin synthesis are correlated as a part of the general response of hepatic protein synthesis to urinary protein losses. This rise, however, is not sufficient to normalize circulating transferrin levels. In addition, no correlation was found between the rise in hepatic transferrin synthesis and the decline in circulating iron concentrations.

Various studies have reported elevated fibrinogen levels in nephrotic patients secondary to an increase in hepatic synthesis. Fibrinogen is a high molecular weight protein that, because of its size, is not filtered by the diseased glomerulus of the nephrotic patient. The elevated rate of synthesis determines an increase in its circulating levels and total intravascular pool. High fibrinogen levels are a risk factor for ischemic cardiovascular diseases since they contribute to hypercoagulability, hyperviscosity and increased platelet aggregation. Preliminary reports suggest that high fibrinogen levels may also accelerate the progression of renal diseases. De Sein Van der Velden *et al.* [14] showed a positive correlation between the absolute synthesis rate of albumin and fibrinogen in nephrotic patients. Zanetti *et al.* [12••] reported an increased rate of fibrinogen synthesis in patients with a moderate degree of proteinuria. Kang *et al.* [15] reported that in an animal model of nephrotic syndrome the intracellular levels of messenger RNA for both albumin and fibrinogen were upregulated, suggesting that they are harmoniously controlled. This is at variance to what has been observed in other metabolic diseases such as uncontrolled diabetes mellitus or acute inflammatory state. In the latter condition, negative acute phase inflammatory protein, such as albumin, and positive acute phase inflammatory protein, such as fibrinogen, are inversely regulated [9]. Giordano *et al.* [7••] demonstrated a reduction in fibrinogen synthesis rate following dietary protein restriction in nephrotic patients. It was also demonstrated that the individual decrease in albumin synthesis induced by the low protein diet was directly correlated with the decline in fibrinogen synthesis (Fig. 1). These findings represent the first experimental evidence of coordinated changes of fibrinogen and albumin metabolism in nephrotic patients, which can be advantageously modulated by therapeutic intervention.

Figure 1. Relationship between the decreases obtained after 4 weeks of a protein restricted diet in the daily albumin absolute synthesis rate versus daily fibrinogen absolute synthesis rate in nephrotic patients ($r = 0.719$, $P < 0.05$)



Data taken from Giordano *et al.* [7••].

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- • of special interest
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