

Pathophysiological and clinical aspects of malnutrition in chronic renal failure

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Kidney diseases are the ninth leading cause of death in the USA. In these patients cardiovascular mortality is greater than in the general population. This observation, not completely explained by the so-called 'traditional' cardiovascular risk factors, lead the authors to postulate other 'emerging' ones found in chronic renal failure patients. Among these new findings, nutritional status, considered as the balance existing between nutrient requirements and intakes, plays an important role for the development of cardiovascular diseases. In fact several nutritional parameters are widely known as pathophysiological determinants of cardiovascular disturbances, which are based on accelerated atherosclerosis, due especially to enhanced oxidative stress and endothelial dysfunction. Chronic renal failure is a clinical condition that from many points of view seems to be a chronic inflammatory state, and many studies confirm this observation. This influences nutritional status especially in dialysis patients. Malnutrition is related in turn to accelerated atherosclerosis thus leading to a postulated 'malnutrition, inflammation, atherosclerosis' (MIA) syndrome in which malnutrition, inflammation and atherosclerosis contribute to an elevated cardiovascular mortality rate. The present review explores this issue, first by describing epidemiological aspects of malnutrition in chronic renal failure patients and then by analysing the specific biochemical and metabolic features of these patients.

Chronic renal failure: Kidney disease: Atherosclerosis: Malnutrition

Malnutrition in chronic renal failure: general aspects, epidemiology and clinical effects

It is estimated that every year 80 000 new diagnoses of chronic renal failure (CRF) are made (Collins *et al.* 2003). Kidney disease is the ninth leading cause of death in the USA (Arias *et al.* 2003).

In the complex variety of CRF syndrome, malnutrition deserves particular attention. In the last two decades it has become one of the most important causes of increasing morbidity and mortality during CRF. This observation is partly explained by an increase in the mean age of patients because an older age, along with diabetes mellitus and cardiovascular diseases (Qureshi *et al.* 2002) are important risk factors for the onset of malnutrition in a clinical setting (Johannsson & Ahlmen, 2003). Although oral supplementation and parenteral (even intradialytic) nutrition are common therapeutic tools in clinical practice, the prevalence of malnutrition in CRF patients is not influenced by the choice of therapeutic intervention (Norton, 2002; Guarnieri *et al.* 2003). During conservative treatment the incidence and severity of malnutrition increase in

association with the degree of renal function loss and exhibit a predictive value for 1-year mortality (Cano, 2000).

In haemodialysis (HD) patients, the prevalence of malnutrition increases from 18 to 75 %, although this value depends on the criteria used to define malnutrition. A widely accepted indicator of optimal dialysis dose is the Kt:V ratio (where K is system clearance, t is dialysis time, and V is the distribution volume of urea). Malnutrition in these patients is associated with a Kt:V ratio less than 1.1 (Cano, 2000). Also in peritoneal dialysis (PD) the prevalence of malnutrition is extremely variable (10–50 %; Flanigan *et al.* 2001).

In Europe, signs of malnutrition were found in 20–35 % of HD patients (Chazot *et al.* 2001). In northern Italy, among subjects aged over 65 years, more than 32 % of deaths are reported to be closely related with malnutrition; this rate rises to 41 % in patients older than 75 years (Manno *et al.* 2001). In southern Italy the prevalence of malnutrition is about 9.6 %; this value increases in older males (Querques *et al.* 2002).

Such a pronounced variability in the prevalence of reported malnutrition might be due to the absence of

Abbreviations: AGEp, advanced glycation endproducts; CRF, chronic renal failure; CRP, C-reactive protein; GFR, glomerular filtration rate; HD, haemodialysis; IGF, insulin-like growth factor; nPNA, normalised protein N appearance; PD, peritoneal dialysis.

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malnutrition among the causes of death listed in dialysis registers; even where it is listed it is rarely considered, so the phenomenon is really underestimated (Manno *et al.* 2001). Another causal factor is the absence of a decisional standardised flow chart.

The term 'malnutrition' is usually taken to indicate a shortfall of intake relative to requirements (Allison, 2000). In the early stages malnutrition is often described in terms of biochemical measures of nutrient adequacy; if the deficiency persists the clinical features of malnutrition become evident, such as reduction in body weight, subcutaneous adipose tissue and muscle mass.

In CRF patients, two principal patterns of malnutrition are present (Manno *et al.* 2001). The first is due to a reduced energy intake and it is frequently present in uraemic syndrome. The second is subsequent to a systemic chronic inflammation. It is associated with diseases accompanying CRF and its complications such as infections, heart failure, and membrane bioincompatibility. In subjects who participated in the Hemodialysis (HEMO) Study, markers of malnutrition were strongly associated with a poor quality of life (Chumlea *et al.* 2003), partly through their relationship with a reduction of physical and mental activity (Allen *et al.* 2002).

Evaluation of nutritional status in chronic renal failure

The assessment of nutritional status in CRF patients, according to the National Kidney Foundation/Dialysis Outcome Quality Initiative Guidelines (National Kidney Foundation, 2002), should be made by integrating clinical, biochemical and anthropometric measurements. Among the anthropometric measurements, mid-arm muscle circumference, skinfold thickness and hand-grip strength are frequently performed (Stenvinkel *et al.* 2000). Through a combination of all these data, we obtain the Subjective Global Nutritional Assessment (Detsky *et al.* 1984).

Among the biochemical biomarkers, serum albumin and prealbumin have been proved to be useful indicators of morbidity (Lowrie & Lew, 1990). Several factors, such as altered protein synthesis, overhydration, reduced protein intake, bowel malabsorption and protein losses (as during nephrotic syndrome) influence plasma albumin concentration, a lowering of which is usually considered a late marker of undernutrition. A fall in prealbumin is an earlier indicator that correlates with body weight, mean arm circumference, creatinine and albumin concentration (Cano, 2000) but it is not totally reliable for it is commonly excreted by the kidney (Manno *et al.* 2001).

Transferrin, with a half-life of 7–8 d, is very sensitive to various dietary and non-dietary factors. Serum transferrin rises in Fe deficiency, whilst its decrease indicates Fe overload or inflammation (Memoli *et al.* 2002).

In HD patients, hypoalbuminaemia, a reduced Kt:V ratio, an increased percentual variation of body weight and a low BMI should not be considered as reliable nutritional markers in undernourished patients (Mancini *et al.* 2003). Retinol-binding protein (half-life 12 h) is generally considered to be a useful marker of energy and protein restriction. However, due to its low molecular weight, it

increases in CRF patients, so its value is limited in these subjects (Golden, 1982).

Carbamoylation index, obtained from the carbamoylated and free amino acid ratio, reflects, for each essential amino acid, its free quota reduction. The measurement of α and ϵ carbamoylation could be a more sensitive index than protein intake and measures of catabolism, thus helping the nephrologist to decide when to start replacement therapy (Kraus & Kraus, 2001).

In dialysed patients the daily protein intake is expressed as the normalised protein N appearance (nPNA), also defined as protein catabolic rate. Kt:V and nPNA are related to each other and both of them are correlated with clinical outcome. In the same patients nPNA and albumin concentrations have a predictive value for hospitalisation and mortality when Kt:V is greater than 1.2 (Kalantar-Zadeh *et al.* 2003). As far as is known, this value is the minimum level of dialytic dose which is required to improve the survival of haemodialysed patients (Salahudeen *et al.* 2003). Protein intake might influence clinical response when the dialysis dose is adequate or even elevated (Kalantar-Zadeh *et al.* 2003). A more reliable and sensitive estimate requires a muscle biopsy, as muscles are the major amino acid storage site. After the biopsy has been performed, alkali-soluble proteins, RNA:DNA ratio and cathepsin D are measured; but considering its invasiveness, this method is employed in strictly selected patients (Guarnieri *et al.* 1983).

As immune function is impaired in CRF, several immune parameters are frequently evaluated to support conventional measures of nutritional status. These include the circulating IgG concentration; all the complementary factors (with the exception of C4) and the lymphocyte count, which is considered an index of mortality in PD patients (Carvounis *et al.* 2000). A lymphocyte count less than 1500/mm³ has been related with a poor nutritional status but it is worthy of mentioning that this parameter is influenced by different factors among which the volume overload plays an important role (Ates *et al.* 2004).

Body composition can be estimated using various approaches such as bioimpedance analysis, or, in experimental settings, whole body K measurement, *in vivo* neutron activation, IR reactance, computerised tomography and nuclear magnetic resonance.

Chronic renal failure: causes of malnutrition

Malnutrition in CRF has a complex aetiology, including a reduced nutrient intake, increased oxidative stress, chronic inflammation, and metabolic and endocrine alterations.

Reduced nutrient intake

In CRF patients a decreased food intake can be due to many factors, such as: uraemic dysgeusia; inadequate compliance to dietary restrictions; psychosocial factors; drugs; chronic inflammation; gastrointestinal alterations (delayed gastric emptying, abdominal distension due to dialysis fluid, impairment of gastric myoelectric activity) (Mak, 2000); anorectic effect of dialytic fluid (Manno *et al.* 2001). Prolonged glucose infusion beyond the peritoneum reduces

food intake and induces endocrine alterations that further reduce nutrient ingestion (Mak, 2000).

Food intake is regulated by short-term (gastric distension, amino acids, glucagon, serotonin, middle molecules) and long-term (leptin, insulin) mechanisms. These different signals are further integrated in the central nervous system. From the metabolic point of view, uraemic anorexia is associated with increased cerebral and plasma levels of short- and long-term satiety factors (Bergstrom, 1999).

Particular attention has been devoted to leptin, a 17 kDa protein secreted by adipocytes; as it is released in blood, it crosses the haematoencephalic barrier, activates the histaminergic system and inhibits neuropeptide Y production (Zoccali *et al.* 2003). These effects are amplified by CRF; in fact the reduced renal clearance of leptin is the *primum movens* of the increased leptin blood levels in CRF patients as shown by the inverse correlation present between creatinine clearance and leptin concentrations (Zoccali *et al.* 2002). Recent work shows an independent association between plasma leptin levels and C-reactive protein (CRP) (Shamsuzzaman *et al.* 2004). This is more interesting if we consider, as discussed later, that CRF is considered a chronic inflammatory condition in which malnutrition and inflammation coexist, thus worsening the clinical outcome of CRF patients. Additional investigations (Pecoits-Filho *et al.* 2002) reported that in patients with end-stage renal disease, although elevated serum leptin levels are present, a similar alteration in its receptors was not found, thus underlining the role of free bioactive leptin in uraemic anorexia and accelerated atherosclerosis.

Insulin and glucocorticoids stimulate leptin production, whilst it is reduced when food intake and/or body weight decrease. TNF- α stimulates preformed leptin release from adipocytes while a direct relationship between leptin levels, BMI, total body fat content, insulinaemia and TNF- α concentration has been widely demonstrated. Plasma leptin is inversely related to glomerular filtration rate (GFR) in patients with different levels of renal disease, thus suggesting that its removal is impaired from the early stages of CRF. In dialysed patients, as GFR decreases to 10.5 ml/min, leptin removal is not sufficient to effectively counterbalance its production, especially in women (Cano, 2000).

Although there are no conclusive data about the relationship between leptin and malnutrition, this might be mediated by chronic inflammation. Moreover, leptin seems to act as an acute-phase protein, thus suggesting that it could be, along with IL-6, the physiological link between the adipose tissue (which is actually considered a source of inflammatory cytokines) and the immune system (Zoccali *et al.* 2003). Also CRP is strongly related to leptin and nutritional status. Finally IL-1, IL-6 and TNF- α reduce food intake in animals, thus suggesting that they might greatly reduce appetite.

The role of insulin is very important; in fact leptin and insulin, in healthy subjects, are directly related to each other. In CRF patients, hyperinsulinaemia and insulin resistance stimulate leptin synthesis. Increased plasma leptin concentration (as is observed in CRF) inhibits insulin production, thus favouring protein catabolism and leading to a worsening nutritional status (Stenvinkel *et al.* 1997).

Many efforts have been made to reduce hyperleptinaemia by correcting insulin resistance using very-low-protein diets supplemented with amino acids and ketoanalogues, but the results obtained are not encouraging (De Precigout *et al.* 2000). On the contrary, the administration of a recombinant analogue of growth hormone is associated with a better nutritional status and a significant reduction of leptin levels. It is possible that this effect is due to insulin-like growth factor (IGF)-1 which could inhibit leptin synthesis (Norton, 2002).

Renal transplantation, dialysis with biocompatible membranes and correction of anaemia may also induce leptin reduction (Cano, 2000).

Oxidative stress and chronic inflammation: the malnutrition, inflammation, atherosclerosis syndrome

In CRF, oxidative stress, defined as an imbalance between reactive oxygen species and antioxidant systems, increases for many reasons (Massy & Nguyen-Khoa, 2002). These include: neutrophils and complement activation (Ceballos-Picot *et al.* 1996); Fe overload; increase of advanced glycation endproducts (AGEP) (Miyata *et al.* 1997); removal, during dialysis, of antioxidant hydrosoluble factors (Morena *et al.* 2000); increased homocysteine levels (Chauveau *et al.* 2000; Apeland *et al.* 2002); stimulation of NO synthesis with subsequent peroxynitrite formation; malnutrition (Stenvinkel & Alvestrand, 2002). In CRF, oxidation of lipoproteins (Galle & Wanner, 1999) and plasma proteins can occur. Albumin oxidation is associated with a loss of antioxidant properties, which exacerbates oxidative stress. Oxidative stress also targets muscle lipids and proteins, thus contributing to the skeletal muscle disease observed in these patients (Dalle-Donne *et al.* 2003).

Oxidative stress is involved in atherogenesis and it is related with endothelial dysfunction (Annuk *et al.* 2003), which is widely described in different clinical conditions (Channon & Guzik, 2002) and present in CRF patients. NO is inactivated by O_2^- which reacts with it to form peroxynitrites. The latter, which are stable compounds, are in dynamic equilibrium with their corresponding acid forms which dissociate into nitrates and the hydroxyl radical, a highly reactive radical. The endothelium is affected by this series of reactions in two different ways: firstly, NO scavenging impairs its vasodilating action with subsequent alteration of organ perfusion; on the other hand, the hydroxyl radical provokes cell damage and contributes to the inflammatory condition. Oxidative stress is thought not to be simply an epiphenomenon but to be involved in the early stages of atherogenesis (Galle & Wanner, 1997). The pivotal role of endothelial dysfunction is confirmed by the identification of asymmetrical dimethylarginine, an endogenous NO inhibitor (Vallance *et al.* 1992) and a cardiovascular risk factor in patients with CRF. It is present in increased concentrations in the plasma from patients in the early stages of renal diseases and it is associated with endothelial dysfunction (Zoccali *et al.* 2002).

The relationship between malnutrition and endothelial dysfunction could be mediated by inflammation; in fact, TNF- α induces both endothelial dysfunction and insulin resistance (Stenvinkel & Alvestrand, 2002). Inflammation

and oxidative mechanisms are related to each other; a positive correlation between CRP levels and lipid peroxidation has been demonstrated (Nguyen-Khoa *et al.* 2001). The same authors found a negative correlation between CRP and α -tocopherol, thus further suggesting that inflammation induces antioxidant depletion.

Inflammation is a common finding in CRF patients (Galle *et al.* 2003) and it could accelerate atherogenesis through the stimulation of adhesion molecule synthesis, such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 whose levels in CRF patients who undergo a conservative treatment are correlated with inflammation markers, malnutrition and cardiovascular risk (Stenvinkel *et al.* 2000).

Markers of malnutrition are also strongly correlated with inflammation mediators (serum cytokines and acute-phase proteins), indicating that the inflammatory markers may be a consequence of inflammation present in CRF (Kaysen & Kumar, 2003). IL-1, IL-6 and TNF- α seem to be involved in the mechanism through which inflammation leads to malnutrition by means of their influence on hunger, muscle catabolism and synthesis of albumin, prealbumin and transferrin (Memoli *et al.* 2002). IL-6 regulates CRP synthesis and its receptor is included in the gp120 family of receptors, the structure of which resembles the extended form of the leptin receptor. Leptin and CRP have been recently shown to be independently associated and adipocytes could be the basis for this association as they produce leptin and pro-inflammatory cytokines (IL-6, IL-1, TNF- α) that influence the CRP synthesis in the liver. Moreover, all these cytokines can induce leptin secretion in adipocytes (Shamsuzzaman *et al.* 2004).

Both inflammation and malnutrition cause a reduction of serum albumin levels. In the participants of the HEMO Study (Kaysen *et al.* 2002) it was observed that the reduction in plasma albumin during chronic inflammation depends on the breakdown in albumin homeostasis. Nutritional status influences protein synthesis and both these variables are associated with energy and protein balance so that Kaysen *et al.* (2002) suggest that several mechanisms mediate the interaction between BMI and nPNA.

These relationships are interesting if we consider that inflammation is a determinant of the increased cardiovascular risk observed in these patients (Locatelli *et al.* 2003; Stenvinkel, 2003). CRP and IL-6 showed a predictive value for cardiovascular mortality and accelerated atherosclerosis in CRF patients.

Stenvinkel & Alvestrand (2002) described the malnutrition, inflammation, atherosclerosis (MIA) syndrome, in which these three determinants, connected to each other by a vicious cycle, were the key determinants of the reduced survival observed in these subjects. The same authors also demonstrated that lipoprotein (a) is correlated with CRP levels, thus suggesting further that inflammation contributes to lipoprotein (a) increase, which represents a cardiovascular risk.

The complex interaction between inflammation, malnutrition, oxidative stress and accelerated atherosclerosis needs additional research but it is important that they are seen from a unifying point of view (Himmelfarb *et al.* 2002).

Alterations of protein metabolism

In healthy subjects the minimal recommended daily intake of protein is about 0.6 g/kg and this value applies equally well to CRF patients. During CRF an increased muscle protein mobilisation occurs, probably to support gluconeogenesis (as demonstrated by enhanced alanine uptake) (Garibotto, 1999; Garibotto *et al.* 2001).

In the plasma of CRF patients a reduced concentration of essential amino acids is evident. Generally the valine:glycine, tyrosine:phenylalanine and essential:non-essential amino acid ratios are decreased. A reduction in serine, threonine, valine, lysine, histidine and the increase of citrulline and aspartate are often reported. These alterations are a result of enzyme defects that especially affect the synthesis and the conversion of amino acids.

In CRF, protein metabolism is altered for several reasons, including impairment of renal participation in amino acid metabolism, abnormal hepato-splanchnic use of proteins, alterations in muscular protein catabolism induced by metabolic acidosis, chronic inflammation, replacement therapy and carbamoylation.

Impairment of renal participation in amino acid metabolism. During CRF, amino acid metabolism in the kidney is altered, leading to a significant reduction of total amino acid concentrations. Moreover, the lack of glutamine uptake and the impaired production and urinary excretion of ammonia contribute to metabolic acidosis, which stimulates protein catabolism (Cano, 2000). Amino acid plasma levels, with the possible exception of the branched-chain amino acids, seem to be weak predictors of nutritional status in HD subjects (Qureshi *et al.* 1998).

Abnormal hepato-splanchnic use of proteins. In healthy subjects, when the postprandial stage is finished, many amino acids are taken into the hepato-splanchnic area along with NH_4^+ , while citrulline, glutamate and urea are synthesised. In CRF all these processes are altered. The reduced hepato-splanchnic use of proteins is associated with a decreased protein and urea synthesis; the latter increases after the correction of metabolic acidosis (Cano, 2000).

Role of metabolic acidosis in muscular protein catabolism. Both an enhanced protein synthesis and catabolism with no variation in net proteolysis have been reported in CRF. The proteolysis:proteosynthesis ratio is directly related to cortisol levels and inversely related to bicarbonate concentration. Factors which worsen metabolic acidosis, such as an increased secretion of cortisol or a reduced protein intake, stimulate muscle protein breakdown (Cano, 2000). In fact, in the presence of glucocorticoids, acidosis stimulates proteolysis by activating the muscular ubiquitin-proteasome system which is the most important proteolytic system (Szeto & Lai, 1998). Similarly, in CRF insulin resistance and several cytokines (such as TNF- α) might contribute to the activation of this tissue-specific metabolic pathway (Mitch *et al.* 1999).

Metabolic acidosis is also responsible for anorexia, weakness, bone lesions, cardiovascular and gastrointestinal alterations, endocrine defects, insulin resistance, hyperkalaemia, impairment of triacylglycerol metabolism and

neoglucogenesis, and accelerated progression of CRF (Goodship 1998; Szeto & Lai, 1998; Kovacic *et al.* 2003).

Protein intake is a decisive factor for acid–base balance. Consequently, it is possible that a persisting acidosis might be due to an acid overload caused by an increased protein intake, which is able to counteract the catabolic effects of acidosis (Chauveau *et al.* 2000) such as the protein loss from the muscles. The proteolysis-derived amino acids are directly recycled by means of oxidation; alternatively they will support hepatic gluconeogenesis. Correction of acidosis improves N and K balance in CRF patients by reducing proteolysis and amino acid oxidation (Johannsson & Ahlmen, 2003).

Chronic inflammation. Several inflammatory cytokines, such as IL-1, IL-6 and TNF- α , might induce glucocorticoid-mediated protein catabolism. Another possible mechanism might be mediated by IGF-binding protein-1, that inhibits IGF-1-stimulated protein synthesis (Garibotto *et al.* 2001).

Replacement therapy. In dialysed patients the protein requirement is almost doubled. During an HD session, a variable amount (the average value is 6–12 g) of proteins is removed and this value increases when non-biocompatible membranes are used, as they activate the complement and stimulate the production of inflammatory mediators (IL-1 and TNF- α). The quantity of amino acids removed by HD is similar or higher than 5–6 g but the postdialytical plasma levels of amino acids are only reduced by 20–50 % or even increased, suggesting that some organ might counterbalance protein loss by increasing the amino acid release. The amount of the lost amino acids increases in nourished patients and it is compensated for by an increased amino acid mobilisation from skeletal muscles and splanchnic area (Garibotto, 1999; Garibotto *et al.* 2001).

PD provokes a daily protein loss of about 10 g but this value is markedly influenced by the peritoneal membrane permeability; in fact the risk of malnutrition is elevated in patients with a high permeability. However, PD could inhibit the activity of the branched-chain α -ketoacid dehydrogenase, by improving acid–base balance (Szeto & Lai, 1998).

Among the lost amino acids, about 30 % are essential amino acids. There are no conclusive data regarding the correction of catabolic status after, respectively, nutritional and/or dialysis treatment (Johannsson & Ahlmen, 2003). In HD patients, a moderate insulin increase causes an anabolic response. The same effects are not present in PD patients, probably because of a reduced availability of some amino acids that could prevent the action of insulin; thus it was suggested that, in these subjects, protein metabolism is qualitatively and quantitatively impaired (Sofia *et al.* 2002).

Carbamoylation. With the progression of renal damage, urea-derived cyanate increases. Its active form, by acting as a potential toxin, causes the carbamoylation of amino acids, proteins and other molecules whose structure, and consequently charge and function, are altered. The most frequently changed amino acids are tyrosine, serine, threonine and cysteine. *In vivo* these reactions modify the action of enzymes, cofactors, hormones, lipoproteins,

antibodies, receptors and transporters, thus contributing to malnutrition. Carbamoylated proteins were found in kidneys of CRF patients, but not in renal transplant recipients. Carbamoylated proteins might influence the destiny of uncarbamoylated proteins, because of their ability to block several metabolic pathways. During HD sessions a variable amount (from 5 to 65 %) could be removed (Kraus & Kraus, 2001).

Alterations of glucose metabolism

In CRF patients an abnormal glucose metabolism is well documented. Non-diabetic patients with CRF often show a rapid hyperglycaemia onset and an impaired glucose tolerance. On the contrary, other patients have normal glycaemia in spite of hyperinsulinaemia. Spontaneous hyperglycaemia has been found in CRF apart from the presence of diabetes mellitus (Mak, 2000).

Low glycaemic levels are a very common finding in CRF (Haviv *et al.* 2000). Several mechanisms are thought to contribute: reduced clearance of insulin; β -blockers; alcohol; sepsis; gastroparesis; liver diseases; heart failure. Spontaneous hypoglycaemia in CRF might be due to the deficiency of neoglucogenetic factors (such as alanine), and to the altered and reduced levels of counterbalancing hormones. Postdialytic hypoglycaemia depends on hyperinsulinaemia caused by the high glucose levels in the dialysate. Another possible reason is the loss of 15–25 g glucose if a glucose-free dialysate is used (Kopple, 1999).

In non-diabetic CRF patients the abnormal metabolism of glucose is involved in the development of hyperlipidaemia, probably by influencing lipoprotein lipase. These alterations might contribute to the increased cardiovascular risk of these patients. In diabetic CRF patients on HD, a poor glycaemic control is a predictor of peripheral vascular calcifications (Ishimura *et al.* 2002). As a consequence, the correct monitoring of glycaemia is essential for the evaluation of CRF patients, even for the non-diabetic ones (Mak, 2000).

In physiological conditions, the kidney contributes to the maintenance of normal glycaemic levels for several reasons, such as gluconeogenesis, breakdown of counterregulating factors and glucose excretion. The kidney's role in maintaining glucose homeostasis is essential, so that the loss of these functions contributes to the glycaemic disorders present in these patients (Cano, 2000).

In CRF the most important factors in the altered glycaemic control are reduction of insulin clearance, insulin resistance, impairment of insulin secretion and alterations of somatostatin production (Mak, 2000).

Insulin clearance. An alteration in insulin clearance is present when GFR is below 40 ml/min. With the progression of renal disease, insulin peritubular uptake increases to ensure the insulin clearance until GFR is 15–20 ml/min. The reduced peripheral degradation of insulin (liver, muscle) contributes to the prolonged half-life of this hormone. During CRF, insulin clearance is decreased but it can be normalised by HD. Also, uraemic toxins might inhibit insulin degradation, especially in the liver, which physiologically removes about 50 % of the insulin taken in the portal circulation (Mak, 2000).

Insulin resistance. Insulin resistance is a common finding in patients with CRF, as demonstrated by the reduced hypoglycaemic response after insulin administration (Mak, 2000). Diabetes onset is less frequent (Cano, 2000). The muscular system is the most frequent site at which insulin resistance is observed and the defect is post-receptorial. Skeletal biopsies showed that receptor binding, β subunit phosphorylation and glucose transporter expression are normal.

Insulin resistance in CRF could be due to different factors: reduced renal catabolism of regulating proteins; metabolic acidosis; uraemic toxins (as pseudouridine); protein catabolism products; reduced physical activity; anaemia; chronic inflammation (Stenvinkel & Alvestrand, 2002); malnutrition.

Recently the homeostatic model assessment index (HOMA), a simple method to estimate insulin resistance, has been developed and accepted as an independent predictor of cardiovascular mortality in end-stage renal disease (Shinohara *et al.* 2002).

In non-diabetic CRF patients under conservative treatment, the sensitivity to insulin might be reduced. Dialysis improves this condition. Moreover, for these patients, HD is also an energy source in so far as the glucose transferring from the dialysate is able both to counteract the energy loss and to reduce the intradialytic amino acid loss, probably by stimulating insulin secretion.

In CRF subjects with type 1 diabetes mellitus, intraperitoneal insulin administration during PD markedly improved the glycaemic control and the sensitivity to insulin, thus contributing to better nutritional status (Nevalainen *et al.* 1997).

Recently, venous L-carnitine administration after HD was found to increase the peripheral effectiveness of insulin, simultaneously improving the β -cell response (Vazellov *et al.* 2003).

In CRF a prolonged half-time, a loss of insulin oscillations and a hypersynchronisation between insulin oscillations and variations in glycaemic homeostasis have been well demonstrated. All these defects are more evident in the postprandial period but they also persist during the fasting stage. A common dysfunction might explain the insulin resistance in peripheral tissues, the relative insulin hyposecretion and the impaired modulation of insulin oscillations (Feneberg *et al.* 2002).

Insulin secretion. Aside from insulin resistance, only 50% of CRF subjects are affected by impaired glucose tolerance and hyperglycaemia, due to the different response in insulin excretion during hyperglycaemia. In fact, when the secretion rate is normal, CRF subjects may have normal blood glucose levels due to hyperinsulinaemia. Abnormal Ca metabolism contributes to these alterations. Hyperparathyroidism and/or vitamin D deficiency might cause an altered insulin secretion while a correction of both normalises glycaemic levels and increases insulin secretion (Mak, 2000).

Another reason for the abnormal insulin secretion is the reduced intracellular K concentration found in these subjects (Cano, 2000).

Altered release of somatostatin. In CRF patients a reduced release of somatostatin might precede the alterations of glucose metabolism and insulin secretion. It is known that this hormone inhibits glucose absorption and pancreatic secretion of insulin and glucagon. CRF patients show a reduced secretory response of D cells after an oral glucose load (Franceschini *et al.* 1998).

Alterations of lipid metabolism

In CRF patients a reduction of HDL-cholesterol and an increase of triacylglycerol and VLDL levels occur. The total VLDL and intermediate-density lipoprotein mass increases when HDL decreases. All these alterations are more evident in HD patients and the increased triacylglycerol concentration is the most frequent (Cano, 2000).

There are several explanations for these observations including reduced degradation of lipoproteins, increased lipoprotein (a) concentration (Stenvinkel *et al.* 1998), reduced activity of lipoprotein lipase, decreased apo C2:apo C3 ratio, structural variations of lipoproteins and altered recognition by receptors, increased synthesis of triacylglycerols and essential fatty acid deficiency (Peck, 1997).

Both LDL and HDL frequently undergo oxidation (Tsumura *et al.* 2001), glycation (Galle & Wanner, 1999) and carbamoylation. LDL and lipoprotein (a) oxidation contribute to atherosclerotic lesion development and endothelial dysfunction (Galle & Wanner, 1999).

Growth hormone and insulin-like growth factor-1 alterations

In CRF subjects, both in conservative and in replacement therapy, a resistance to the action of growth hormone has been found (Johannsson & Ahlmen, 2003). In paediatric subjects such an alteration causes severe growth defects. This resistance is attributed both to the reduced hepatic synthesis of IGF-1 (due to the decreased receptorial expression) and to the increase of IGF-binding proteins (Tonshoff *et al.* 1995).

In CRF adult subjects both a resistance to IGF-1 and an impaired response to the administration of IGF-1 recombinant analogue have been documented. These alterations, especially due to a reduced receptorial activity, contribute to the malnutrition onset, by negatively influencing azotised balance. However, all the forms of resistance are favourably affected by hormonal substitute therapy. In dialysed subjects growth hormone administration causes significant anabolic effects, thus increasing muscular mass (Johannsson & Ahlmen, 2003). IGF-1 recombinant analogue administration, besides positively influencing intrarenal haemodynamics, also improves protein metabolism and oxygen consumption (Garibotto *et al.* 2001). IGF-1 induces arteriolar vasodilation and increase of GFR probably through NO action (Feld & Hirschberg, 1996).

Uraemic toxins

The uraemic syndrome has been attributed to the retention of many different compounds that are physiologically excreted by the kidney (Vanholder *et al.* 2003). Many of

these so-called uraemic toxins contribute to uraemic symptoms and signs and it has been demonstrated that dialytic outcome is better when the clearance of uraemic toxins with a molecular weight between 1000 and 5000 Da (defined as middle molecules) is strengthened (Leypoldt *et al.* 1999). Many of these molecules are protein-bound and their concentrations vary as the lowest has been found for middle-sized molecules (Vanholder *et al.* 2003). Urea is involved in determining anorexia, nausea and vomiting. Creatinine interferes with different metabolic reactions. AGEP are the most important uraemic toxins. They derive from non-enzymic reactions between protein side chains and glucose (or its degradation products). After binding specific surface receptors they induce alterations of cell functions, often causing cell death (Kasper & Funk, 2001). They are also bidirectionally related with oxidative stress (Henle, 2003).

Among AGEP, pentosidine is significantly associated with both inflammation and malnutrition. Its levels increase with the decrease of residual renal function but it is actually not a predictor of the clinical response to dialysis (Suliman *et al.* 2003). AGEP also give flavour and taste to food (Henle, 2003) but the dietary restriction of these foods in CRF subjects is inevitable (Uribarri *et al.* 2003).

Conclusions

From all these considerations, malnutrition emerges as an important topic for those who are involved in treating CRF. In fact, a better nutritional status, achieved through an intensive diet programme, could contribute not only to the delay of the start of replacement therapy but also to a more positive prognosis in these patients.

In our opinion, a deeper understanding of the molecular mechanisms involved in malnutrition onset will help physicians to realise a complete approach to the CRF patient.

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