Module 15.2

Nutrition Support in Chronic Kidney Disease (CKD)

Pr Denis Fouque
Renal Dept,
Centre Hospitalier Lyon Sud,
France

Learning Objectives

- To understand the metabolic abnormalities in patients with CKD;
- To know the determinants of nutritional state and the causes of protein energy wasting (PEW) in CKD;
- To learn how to evaluate nutritional status in CKD;
- To know the nutritional requirements in CKD;
- To be aware of the aims of nutritional support and the type and composition of diets in CKD;
- To learn how to manage PN and EN in CKD.

Contents

Key Messages

- Adequate nutritional screening and monitoring can influence long-term prognosis in CKD;
- Insufficient nutritional care and metabolic disturbances mainly due to metabolic acidosis, hormonal disturbances, chronic inflammation and partially from loss of nutrients in heavy proteinuria, are considered as main causes of PEW;
- Other contributory reasons for PEW could be low social status and poverty, altered dentition and malabsorption;
- Protein-energy wasting (PEW) leads to loss of body weight and decrease of body mass index below 23 kg/m^2, major loss of muscle mass, and decrease of serum albumin and transferrin, which together influence morbidity and mortality in CKD;
- PEW, chronic inflammation and metabolic disturbances (mainly lipid, carbohydrate and mineral bone disease) can accelerate atherosclerotic processes;
- In patients with mild PEW linked to insufficient spontaneous intake, dietary counselling and nutritional supplements are worthwhile;
- In patients exhibiting severe PEW, enteral nutrition is highly recommended in addition to dietary counselling;
- In patients exhibiting severe PEW with spontaneous intake less than 20 kcal/ kg/day or in stress conditions (eg. severe infection, surgery) daily nutritional support is necessary. Whenever possible, enteral nutrition should be preferred to parenteral nutrition.

1. Introduction

Nutritional derangement and nutritionally related metabolic modifications in patients with renal failure have been the object of in-depth studies for years.
Uraemic patients are especially sensitive to the effects of PEW and of nutrition therapy, both of which can determine modifications in the natural course of the disease affecting quality of life, morbidity, mortality and the rate of progression of the disease.
In clinical nutrition, kidney diseases are unique among other clinical conditions in that diet therapy for renal patients allows control of most of the metabolic disturbances and has therefore the same clinical relevance as other types of available medical therapy.
The uraemic syndrome leads to PEW. The causes are summarized in **Fig.1**:

Causes of PEW in CKD
- reduced oral intake
- restrictive diet
- metabolic acidosis
- microinflammation
- hormonal derangements
(insulin, PTH, erythropoietin, leptin, etc)
- gastrointestinal disease

Fig 1. Causes of PEW in CKD

The strategy for nutritional intervention in CKD patients is determined by specific metabolic alterations:
- Insulin resistance
- Abnormal plasma lipid clearance
- Metabolic acidosis
- Hypocalcaemia and hyperphosphataemia
- Secondary hyperparathyroidism, uraemic bone disease
- Vitamin D3 deficiency
- Hypercalcaemia
- Renal anaemia
- Chronic inflammation
- Activation of protein catabolism due to intercurrent acute illness, acidosis and inflammation.

2. The Aim of Nutrition in CKD

The main aims of nutritional interventions can be summarized as follows:
1) Avoid PEW; 2) reduce metabolic disorders; 3) delay renal disease progression.
An exhaustive overview and complete guidelines on nutrition in renal disease are made somewhat complicated by the fact that the term "renal disease" embraces a number of clinical conditions whose common features are a decrease in glomerular filtrate, or a condition of uraemic toxicity products, or some derangement of kidney physiology.
Moreover the cut-off point between early and advanced renal failure, as well as the time to start dialysis treatment are not exactly defined.

3. Evaluation of Nutritional State in CKD

It has been shown recently that the much feared complication of protein-energy wasting (PEW) in dialysis patients may be partially caused by inadequate nutritional management and protein and/or energy deficiency in the predialytic phase, causing the patients to enter dialysis in a malnourished state (1-7).
For these reasons, nutritional status must be carefully monitored in all CKD stages. Nutritional deficiencies should be detected and accurately identified before they become clinically relevant. No single parameter providing reliable information on the overall nutritional status is available. Moreover, nutritional assessment should thoroughly investigate all body compartments and functions. Combined evaluations of dietary intake and compliance, as well as of anthropometric measurements, biochemical determinations, serum and cell-mediated immune responses, and more in-depth assessment of body compartment status are recommended. Subjective global assessment (8,9) or other combined nutritional indexes (10,11), if appropriately used, can be useful tools for the nutritional assessment of uraemic patients.

3.1. Assessment of Dietary Intake and Compliance

This step is of crucial importance in all uraemic patients. Direct investigation by a skilled dietitian (dietary interviews and three day recalls, or by food diaries) is recommended (12-14), since no simple ways of determining total energy intake and distribution of energy sources (lipids or CHO) are available. Objective methods for measuring protein and phosphorus intake are, on the contrary, well established. Urea nitrogen appearance, "protein catabolic rate", urea nitrogen urinary excretion and blood urea levels are directly related to protein intake in stable uraemic patients. Phosphaturia is also related to dietary intake of phosphorus, but the correlation is less close, depending on P absorption, use of oral binders, and degree of Vitamin D deficiency and hyperparathyroidism (11,15,16,).

3.2. Anthropometry

These measurements may be influenced by a number of factors not related to nutrition.

3.2.1. Body weight: severe biases hamper its validity as a nutritional index: i.e. a) lack of national or regional standards; b) dependence on the total body water content. However the knowledge of body weight and its time-related modifications are mandatory and often useful.

3.2.2. Skinfold thickness and arm muscle circumference: If oedema or important body water changes are not present, skinfold thickness is related to total body fat (13, 18-21). Reproducible information is best given by measurements from multiple locations. Arm muscle circumference is a reliable index of total body protein and lean body mass. Only gross changes can be distinguished and results are influenced by overhydration.

3.3. Plasma Proteins

Plasma proteins are indices of protein synthesis, mainly by the liver. Serum albumin levels have been recently identified as prognostic indices (1, 22-25) in chronic uraemia. However, albumin concentration in plasma is also influenced by extracorporeal losses, fluid retention, vascular permeability and hypercatabolism ("negative acute phase

protein"). Serum transferrin: due to its short half-life (9 days), this protein is a sensitive marker of PEW; iron status, infections and the influence of inflammation, however its levels are independent of nutritional status. Short half-life proteins (retinol-binding protein, prealbumin/transthyretin) should be useful to monitor short-term nutritional changes: unfortunately, because of their low molecular weight, they are normally filtered by the kidney, and therefore they are of little value in non-dialyzed renal insufficiency (26-29).

3.4. Other Biochemical Determinations

Plasma creatinine is related to muscle mass. The value of creatinine/height index is however diminished in stable uraemic patients also by tubular and gut excretion. Plasma urea, potassium and phosphate levels are indices of dietary intake and/or actual protein status. Low serum cholesterol (<150 mg/dl; <4mmol/L) is a sign of protein energy wasting. Urinary 3-methylhistidine (3-MH) correlates with muscle mass and protein catabolic rate (some authors have found a different 3-MH turnover for different proteins). In uraemia, its usefulness is limited by reduced excretion rates.

3.5. Immune Function

The immune system is often deranged in renal failure but the relative importance of toxicity, drugs, PEW, or other deficiencies is not known. Levels of C3, C3a, Clq are reduced in uraemic patients, and the total lymphocyte count is often low. PMN metabolism and function are also impaired.

3.6. Nitrogen Balance

Nitrogen balance (including nitrogen output in faeces) studies are traditionally used to assess the adequacy of protein intake, but nitrogen balance is sensitive also to the amount of other nutrients (e.g. energy (8)). If properly performed, nitrogen balance studies can be very accurate and precise, but they do not give any information on the mechanisms of nitrogen depletion or gain. In addition, it must be pointed out that, in malnourished populations like uraemic patients, nitrogen balance can be achieved with less protein or at the expense of a reduced body protein pool and therefore may not be a reliable criterion for nutritional adequacy (18,30-35).

3.7. Amino Acids

The fasting plasma amino acid concentrations in patients with renal failure show characteristic abnormalities that can be dependent on uraemia itself or on nutritional abnormalities and deficiencies. Such abnormalities can be partially corrected by modified amino acid formulas.

3.8. Body Composition

The increasing complexity of available technologies allows greater accuracy in measuring body composition. Body impedance analysis for total body water, intracellular water and lean body mass or dual-energy X-ray absorptiometry for bone or soft tissue assessment are widely used. Other more sophisticated instruments to determine total body potassium or nitrogen or other elements might give the best information for

measurement of body composition and for the evaluation of the efficacy of nutritional interventions, but are seldom available.

Two levels of methodology for assessing nutritional status can be proposed:
1) A simple level, for clinical purposes, with the following items:
• Dietary history, estimation of protein intake (from Urea Nitrogen Appearance, Protein Catabolic Rate, etc.);
• Anthropometry: weight (BMI, Ideal BW, Relative BW, Usual BW, Dry BW), skinfold thickness (multiple locations), arm muscle circumferences and fat areas;
• Visceral proteins: in relation to their half life (albumin, transferrin); small molecular weight proteins are of little value;
• Creatinine, urea, potassium, phosphate, cholesterol in serum. Urea, creatinine and phosphate urinary excretion;
• Lymphocyte count, complement protein concentration.

2) A more complex level, for scientific work, with the following items:
• Nitrogen balance studies, if properly designed, are among the most precise methods for investigating N needs and equilibrium;
• BIA gives easy, accurate and reproducible measurements of total water, fat mass and fat-free mass. DEXA gives measurements of bone and fat mass and lean body mass;
• Neutron activation analysis gives the most reliable measurement of subtle modifications of body composition at the molecular level (36-42);
• The best insights into intracellular metabolic events can be gained by directly approaching single tissues (e.g. muscle biopsy) (31), by NMR studies, by isotopes (radioactive or stable) examining total body or organ/tissue protein and amino acid synthesis, degradation and oxidation, or by studies of the metabolism of other substrates;
• Immunological and muscle function.

4. Prevalence of PEW in Chronic Kidney Disease (CKD)

Evidence for wasting and PEW is also found also in CDK receiving conservative treatment (43-46). Several years ago, Bajardi (47) found a 40% prevalence of PEW in kidney patients with advanced renal disease at the beginning of their HD treatment. Because of the high percentages of uncontrolled patients with CKD (up to 30%) the prevalence of PEW is still high. Observed signs of PEW are found in 10-70% at the beginning of HD treatment and 18-51% in CAPD (48-53).
Severe derangements of protein metabolism have been found in the skeletal muscle of CKD patients, who seemed clinically well nourished (11, 16). But unfortunately, there was no direct link between measured nutritional parameters and muscle mass (41, 42, 54, 55).
The characteristics of PEW in uraemic patients are variable, and large differences in the involvement of different body compartments have been described (18), body fat stores and visceral proteins being most frequently compromised. On the other hand, even obese CKD patients may be wasted, partly from chronic inflammation (2, 56-60).
More sophisticated methods are often required for early diagnosis of PEW. In the early phase of chronic renal failure subclinical modifications of nutritional status were found only at the cellular level (19). Measurement of body cell mass by determination of total body potassium has revealed a mean 10% reduction in patients starting HD and 6% in those starting CAPD (34, 53, 55, 61).

5. Effects of PEW on Morbidity, Mortality and Quality of Life

5.1. Effects of PEW on Morbidity and Mortality

PEW in chronic kidney disease is associated with poor clinical outcome and mortality. Unfortunately, the mechanisms behind PEW are multifactorial and it is difficult to extrapolate a definite nutrition-related cause for morbidity or mortality. For instance, patients with a low serum albumin from either low nutritional intakes or chronic inflammation will have a lower survival than those with a higher albumin (1).
However, this correlation does not indicate a causal relationship, because hypoalbuminaemia can be an effect of illness unrelated to nutrition. Albumin levels <30 g/L are associated with the worst prognosis. Besides albumin, other nutritional variables also show relationships with to mortality (anthropometry, body weight, transferrin, lymphocyte count, plasma amino acids, serum creatinine, etc.)(1, 22, 27, 29, 32).
The most obvious way for PEW to induce worsening of morbidity and mortality rates is immunodeficiency, which increases infectious complications by lowering both serum and cellular immune responses.

5.2. Effects of PEW on Renal Function

Besides metabolic effects and the influence on outcome, PEW itself has some negative effects on renal functions (frequently associated with metabolic acidosis): it impairs the kidney's ability to eliminate an acid and a salt load, and it reduces the renal plasma flow, the GFR and the urine concentrating capacity.

6. Mechanisms Responsible for PEW

6.1. Two Types of PEW in CKD

The pathogenesis of PEW in patients with kidney failure is multifactorial. The principal causes are poor dietary intake (due to anorexia, nausea, dysgeusia, protein, salt or water intolerance or excessive dietary intake), abnormal lipid and carbohydrate metabolism, amino acid imbalance, abnormal hormonal response, loss of nutrients, and metabolic acidosis (PEW type1 according to Stenvinkel).
In many complicated CKD patients, the main reason for PEW is chronic inflammation (PEW type 2). The therapeutic options should focus on restricting or even on elimination of inflammation. In CKD there are patients with chronic inflammatory processes as components of underlying systemic illness, and patients with severe forms of nephrotic syndrome. It has been repeatedly confirmed, that the most devastating processes are those linked to severity of metabolic acidosis (7, 44, 45, 46, 61, 62).

6.2. PEW from Inadequate Nutrient Intake

CKD patients may develop an imbalance between nutritional requirements and intake. A low energy intake is particularly involved: despite adequate nutritional recommendation (35 kcal/kg/day), a large percentage of patients in most studies eat less energy than is prescribed (i.e. between 25 and 30 kcal/kg/day) (11, 22, 23). Compliance with the low protein prescription and generally altered composition of the diet is also often inadequate. A spontaneous reduction in protein intake is usually associated with the pre-

uraemic state and severe metabolic disorders (mainly metabolic acidosis and renal anaemia) and steps to avoid this should be taken (18, 23, 33, 54, 63, 64).
A key role for metabolic acidosis (MA) has been clearly demonstrated in determining PEW: MA is a mediator of protein breakdown and amino acid oxidation (25) and proteolysis is related to its severity. Cortisol increases in MA, as well as BCKA dehydrogenase activity. Intracellular valine is directly related to blood pH. Acidosis stimulates ubiquitin mediated proteolysis and the m-RNA for ubiquitin and proteasome (26). MA impairs insulin activity and glucose utilization, and its correction improves nitrogen balance and lowers the urinary 3-MH/creatinine ratio (34, 61, 64, 65).

7. Management of Nutritional Care in CKD

For decades protein restriction has been the mainstay of the non-dialytic conservative treatment of CKD. It was the only treatment for irreversible uraemia until chronic dialysis became available. These principles remain essentially unchanged. Accumulation of urea, other nitrogen waste products, phosphates, and potassium, and metabolic acidosis, are diminished by lowering protein intake; uraemic symptoms like fatigue, anorexia and itching are better controlled. However, protein intake should not be too low since this can lead to PEW. Most of the time, there is also an energy deficient state, which increases the risk of PEW. Therefore regular dietary interviews are needed to avoid this situation.
An additional comment on the nutritional treatment of patients with CKD derives from the fact that, PEW is a multifactorial complication of advanced CKD (stages 4-5) and, alongside control of nutrient intake, it is very important to treat other causes of PEW, such as acidosis and hyperparathyroidism in the best possible way and to improve dialytic dose (based on Kt/V urea).
In uraemic patients the best nutritional treatment aims at maintaining optimal body composition for the best possible rehabilitation and quality of life (Subjective Global Assessment-SGA).

8. Conservative Nutritional Treatment in CKD Patients (CKD 3-5)

8.1. Low Protein Diets

8.1.1 Conventional Low-protein Diet

An amount of 0.6-0.8 g protein/kg ideal body weight/day is the minimum protein requirement for CKD patients without proteinuria exceeding 1.5 g/day. This intake equals the requirement of normal healthy individuals. If proteinuria exceeds 1.5 g/day, an equal amount of protein should be added to the dietary limit (35, 66-70).
All CKD patients treated with 0.6-0.8g/kg IBW/day should be carefully monitored and the nutritional status regularly assessed. This amount of protein is considered safe in normal stable clinical conditions: nitrogen balance and body composition can be maintained. Serum urea levels can be easily maintained below 25 mmol/l (70mg/dl).
The amount of protein intake must be calculated according to ideal body weight. 50-75% of dietary proteins must be of high biological value such as meat or fish to ensure adequate intake of essential amino acids. Meticulous attention to acidosis and fluid and electrolyte disturbances is required.

With this amount of protein, the amount of dietary phosphate can also be easily cut down to 800mg/day. When serum albumin is below 35 g/l nutritional supplements are necessary. In some cases administration of keto amino acids could be helpful (71-74).

8.1.2. Supplemented Very Low-protein (VLPD) Diet

In more advanced CKD (CKD stages 4-5) VLPD supplemented with keto amino acids (KA) could be prescribed: 0.30 g protein/kg/day + KA according to the ESPEN Consensus, or 0.3-0.4 g/kg/d + KA according to the National Kidney Foundation (3).
Such a diet has the following advantages:
1) The sum of protein and amino acid intake does not exceed 0.7 g/kg/day, which is sufficient for nitrogen balance in steady state patients. Thanks to the administration of keto and hydroxy forms of essential amino acids, serum urea levels decrease;
2) It usually improves compliance, by increasing the variety of foods;
3) Neutral nitrogen balance and a good nutritional status can usually be maintained provided that an adequate energy intake is maintained.

Keto or hydroxy acids, analogues of leucine, isoleucine, valine, methionine and phenylalanine plus tyrosine, threonine, lysine and histidine can be added to VLPD. They can be provided as calcium salts or salts of ornithine, lysine or histidine. Beside better control of urea production and nitrogen balance, improvements in hyperphosphataemia, hypocalcaemia, metabolic acidosis and glucose metabolism have been reported (14, 75, 76, 77).

8.2. Energy Requirements

A crucial role in determining nutritional adequacy of LPD and VLPD in CKD patients on conservative treatment is linked to the appropriate energy intake.
Indeed, also in physiological conditions the optimal use of minimal quantities of protein requires a good energy supply (30). It was clearly demonstrated that higher energy intakes - in the range of 35-45 kcal/kg/day - are associated with better nitrogen balance in predialysis patients on LPD (0.6g/kg/day), with gain in body weight and improved body composition. On the other hand, the energy requirements of CKD are not reduced. For these reasons the low energy intake often described in CKD patients is probably one of the main reasons for abnormal body composition and PEW. The energy needs of these patients are the same as for normal populations. 35kcal/kg BW/day is recommended with adaptation (±20%) to individual needs (severe PEW or overweight/obesity) (33,69,78–81).
Recommendations for the general population are also valid for patients with CKD: 30% or less of energy as fat, with saturated fats <10% of total calories, cholesterol <300 mg/day, and simple sugars <10%, is a reasonable goal for all uraemic patients. If an overt dyslipidaemia is present further modifications are recommended, but because of the need for appropriate energy intake, the dietary treatment of uraemic dyslipidaemia can be difficult.

8.3. The Role of the Dietitian

As a general rule, successful dietary treatment requires close cooperation between a trained physician and a skilled dietitian. It also requires thorough education of the patients and their families. It is important to recognize the limitations of dietary

treatments, which are, on one hand, the development of nutritional deficiencies and, on the other, the frequent sudden occurrence of terminal uraemic symptoms, which require immediate start of dialysis.

Conclusions

1) Closely supervised low protein diets provide a safe and cheap treatment for the early stages of uraemia in renal failure. The treatment should maintain nutritional status and if the nutritional status is threatened and supportive measures are ineffective, dialysis should be contemplated without delay.

2) Close measurement of nutritional status and monitoring of nutrient intake are strictly required.

9. Positive Effect of Nutritional Therapy on Progression of Renal Insufficiency

Nutritional adequacy and efficacy in managing some uraemic metabolic disturbances of LPD or supplemented VLPD are well established. On the contrary, it has not yet been definitively established whether protein (and phosphate) restriction in CKD patients during conservative treatment is able to slow down the progression of renal failure. The reasons are multiple: heterogeneous populations, different kidney diseases, low dietary compliance, difficulties in measuring progression and nutritional adequacy, different end-points, co-existence of other factors responsible for progression, different diet composition (quality of protein, type of energy supply, etc.).

It remains less clear if patients with GFR >60ml/min and progressive renal failure benefit from protein restriction.

According to some experimental studies, a low protein diet is effective in reducing microalbuminuria and proteinuria in diabetic nephropathy. This beneficial effect is much more evident in patients with early renal insufficiency than in patients with more advanced renal failure.

In diabetic patients with more severe renal damage (heavy proteinuria, more advanced renal failure) the results are less equivocal (65, 77, 82–85), but other factors are involved in the control of progression of nephropathy, mainly:

- hypertension
- proteinuria
- hyperlipoproteinaemia
- hyperglycaemia
- calcium and phosphorus metabolic disorders

The role of dietary phosphate could be independent from that of proteins, and could be mediated by abnormal intracellular calcium metabolism. A low daily phosphorus intake is generally achieved in patients compliant with VLPD + KA, and this allows an improvement in divalent ion metabolism, PTH function and hyperparathyroidism. Hyperparathyroidism might be responsible for a state of cellular calcium toxicity (86-91).

Conclusions

Some evidence strongly suggests that protein restriction may have beneficial effects on the decline of renal function. The time at which to start LPD is difficult to establish. Worsening of nutritional status in the late phases of CKD can be a reason for beginning dialysis treatment.

Many other factors responsible for progression are likely to be important. A predominant role is attributed to proteinuria, to the type of nephropathy, to hypertension and to its genetic determinants.

10. Guidelines for Nutritional Treatment of CKD in Patients on Conservative Treatment

10.1. Proteins and Energy Intake

Table 1
eGFR, Considered Daily Protein Supply, Keto/Amino Acids

Stage	eGFR (mL/minute/1.73 m^2)	Considered Daily Protein Supply	Keto/Amino Acids
1	≥ 90	Normal protein intake (RDA: 0.8 g protein/kg body weight/day)	Not required
2	60 - 89	Normal protein intake (RDA: 0.8 g protein/kg body weight/day)	Not required
3	30 - 59		
	a. 45-59 (with increasing serum creatinine)	Normal protein intake (RDA: 0.8 g protein/kg body weight/day)	Not required
	b. 30-44 (with increasing serum creatinine)	Protein restriction 0.6/0.7 g protein/kg body weight/day)	Optional: 1 tablet/5 kg body weight/day (depending on the biological value of dietary protein)
4	15-29 (with increasing serum creatinine)	Protein restriction 1. 0.6 g protein/kg body weight/day	1. Optional: 1 tablet/5 kg body weight/day (depending on the biological value of dietary protein)
		2. 0.3-0.4 g protein/kg body weight/day	2. 1 tablet/5 kg body weight/day
5	< 10-15 (not on dialysis)	Protein restriction 1. 0.6 g protein/kg body weight/day	1. Optional: 1 tablet/5 kg body weight/day (depending on the biological value of dietary protein)
		2. 0.3-0.4 g protein/kg body weight/day	2. 1 tablet/5 kg body weight/day

eGFR, estimated glomerular filtration rate; RDA, recommended daily allowance.

Energy intake: up to 35 kcal/kg; in obese patients energy restriction to 25-30 kcal/kg iBW/day
From Aparicio et al. Journal of Renal Nutrition, Vol 22, No 2S (March), 2012: pp S22-S24

10.1.1. Meticulous Nutritional Supervision is Mandatory for Groups 3 to 5

Animal proteins are necessary to increase the biological value of LPD; in VLPD with KA, the biological value, because of KA supplements, is less important, and more vegetable proteins can be allowed. The long-term nutritional adequacy of vegetarian LPD is not proven.

Most active patients, with body weight in the range ±10% IBW, need 35kcal/day. Overweight (>120% of ideal) or malnourished patients might need adjustment of daily energy intake. The normal percentage distribution between lipid and carbohydrate (30% and 55-60% respectively) is suggested, with emphasis on fibre, complex carbohydrates and unsaturated fatty acids. If hypertriglyceridaemia is present, avoid simple sugars and ethanol. If hypercholesterolaemia is present: dietary cholesterol <300 or 200 mg/day, saturated fatty acids <10%, monounsaturated fatty acids > 10%.
In malnourished patients, if anorexia inhibits a higher energy intake, supplements can be given.

10.2. Phosphate

A lower intake of phosphate can be achieved by more or less severe exclusion of phosphate rich foods of animal origin (dairy products, egg yolks, meat). Also vegetable foods can be chosen according to their phosphate content. The foods (meat, fish, and vegetables) can be boiled in large amounts of water so as to discard or eliminate as much phosphate as possible. By following this recommendation a phosphate intake between 5 and 10 mg/kg/day can be reached (70, 74, 92). Careful attention should be given to phosphate additives recently increased in many processed foods and beverages.

10.3. Calcium

Low-protein, low-phosphate diets are low in calcium because of a low intake of dairy products. Vegetarian diets pose even more risk of calcium deficiency, because of the poor calcium bioavailability in vegetarian foods, due to poorer intestinal absorption. Calcium supplementation, to reach a total calcium intake of 1.5-2.0 g/day is recommended: this is efficient in preventing secondary hyperparathyroidism and its metabolic and clinical consequences (66, 92).
Calcium carbonate has a higher calcium content than other salts, and it is also efficient as a therapeutic measure to control acidosis. Supplements of calcium salts of the keto-analogues of essential amino acids supply proportionally large amounts of calcium. These calcium supplements are indeed sometimes responsible for hypercalcaemia.

10.4. Vitamins

10.4.1. Water Soluble Vitamins

LPD or VLPD present, in the long term, a risk of water-soluble vitamin deficiencies. Low levels of riboflavin (B2) and to a minor extent of thiamine (Bl) were found after 6 months of a diet giving 0.6 g/kg/day of protein. Functional tests indicate an even greater deficiency of pyridoxine, regardless of treatment, that increases with time. Therefore supplements of 5 mg/day of pyridoxine in predialysis patients are recommended. Cyanocobalamin (B12) levels are normal in CKD, and supplements are required neither for this vitamin nor for folic acid, unless specific reasons for deficiency are present. Ascorbic acid is often low in CKD patients in conservative or dialytic treatment and a supplement of 100 mg is generally suggested in all uraemic patients. Higher amounts are not recommended because of the risk of secondary oxalosis (93-96).
As a general rule, patients treated with VLPD plus supplements of KA+EAA must be systematically supplemented with water soluble vitamins. Patients treated with long term vegetarian diets (e.g. nephrotic patients) are also at risk of developing water-soluble vitamin deficiency.

10.4.2. Fat Soluble Vitamins

The plasma levels of Vitamin A are directly related to serum creatinine and therefore they are frequently high in CKD, but the signs of hypervitaminosis are generally not evident, possibly because of high levels of carrier proteins. Supplements of the fat soluble vitamins A, E and K are not recommended. Deficiency of Vitamin D active metabolites develop progressively with the lowering of GFR, and symptoms of hyperparathyroidism and osteodystrophy appear. Therefore long term oral supplements of 1-25$(OH)_2$ D3 are recommended. An initial dose of 0.25 µg/day can be increased to 1 µg/day, until optimal correction of hypocalcaemia has been obtained. Plasma calcium levels must be monitored to avoid hypercalcaemia, especially in the case of calcium carbonate supplementation (93, 97).

10.5. Iron

Iron needs might be better assessed by the plasma concentration of ferritin, than by the iron and transferrin values (9). In predialysis patients, iron deficiency is rare but supplementation might be necessary in patients on VLPD supplemented with KA and/or EEA and in patients on a long-term vegetarian diet. In dialysis the prevalence of iron deficiency is higher, because of the larger blood losses.
The phosphate binders reduce iron absorption and consequently they must be taken separately. During EPO therapy, iron supplements can be necessary to obtain better erythropoietin efficacy. On the other hand, blood transfusions and reduced erythrocyte life span may cause iron overload.

10.6. Trace Elements

If the macronutrient intake and the dietary adequacy are suboptimal, there is the risk that some deficiency of trace elements may develop. However, the continuous supplementation of trace elements is not recommended in CKD patients (68).
Zinc deficiency can worsen some uraemic symptoms (18) such as dysgeusia, impaired olfactory acuity; anorexia, delayed wound healing, sexual dysfunction, and impaired PMN leukotaxis. Zinc deficiency in renal failure patients can be caused by decreased intestinal absorption, deranged tubular transport, and urinary loss with heavy proteinuria or diminished carrier proteins.
Selenium: its role is strongly associated with the activity of glutathione peroxidase that protects cells against oxidative damage. Low selenium levels have been found in CKD patients with cardiovascular complications. Both zinc and selenium deficiencies may be due to chronically low protein intake or to diminished plasma carrier proteins, and can be corrected by enhancing protein intake or correcting low levels of such transport proteins.
Copper: Hypercupraemia occurs in CKD, but no clinical symptoms of the uraemic patient have been attributed to high copper levels (95, 98, 99, 100).

Current practices: They are uneven among different centres and countries, related to cultural reasons, nutritional habits, dialysis facilities, and the economic background. Some centres use dietary restrictions from a very early stage, while others limit the use of LPD and VLPD to advanced renal failure, in patients with uraemic symptoms. Similarly the decision to begin dialysis is in some centres earlier and in others later.

11. CKD Patients and the Need for Parenteral Nutrition (PN) and Enteral Nutrition (EN)

Conservatively treated patients with CKD seldom need PN. Potential indications for PN in CKD patients are similar to the indications for PN in non-renal patients. Malnourished CKD patients requiring nutritional support should only be considered for PN when ONS and EN are impossible or fail to reach nutritional goals. Special attention should be given to CKD patients requiring PN during perioperative periods.

When nutritional requirements cannot be met by dietary intake (with or without ONS) in combination with EN or by the enteral route alone, the goals of PN in CKD patients are: a) prevention and treatment of undernutrition leading to cachexia: b) ensuring the provision of optimal levels of energy, essential nutrients and trace elements; and c) attenuation of disease (CKD) progression through protein or phosphate restriction.

In nutrition of non-dialyzed CKD patients there is a fragile balance between the induction of toxic effects by providing an excess of nitrogen-bearing compounds and pro-oxidants and the induction of undernutrition by providing too little energy and/or protein. In this regard, low protein diets should be associated with a strict monitoring of energy intake and of nutritional status.

Because no data are available on specific PN formulae, if PN is indicated standard PN admixtures should be used. In patients receiving PN without any oral or enteral supply, vitamins and trace elements should be administered intravenously. If the patient continues PN for a period exceeding two weeks, the risk of accumulation of vitamin A and trace elements should be considered.

The use of PN could be implemented as an initial complementary short-term nutritional strategy in patients with inadequate oral intake. Also, PN is a desired choice in conservatively treated CKD patients who cannot achieve adequate nutritional status through normal dietary intake or enteral feeding, or whose enteral route is compromised by severe gastro-intestinal complications. A suggested decision tree for nutritional support in conservatively treated CKD patients with signs of PEW might be:

Is the gastrointestinal tract functioning normally?

- If the answer is yes:

1) Increase dietary intake by augmenting energy and protein. The use of oral supplements is recommended;

2) If the patient's nutritional status keeps worsening, start tube feeding. Oral intake can be maintained in combination with oral supplements;

3) If the patient's nutritional status keeps worsening start PN.

- If the answer is no:

1) Start with PN. The PN can be:

a) Peripheral PN: in cases of short-term therapy, with or without fluid restriction depending on concomitant complications and with the purpose of supplementing immediate needs;

b) Central PN: in cases of long-term therapy, with fluid restriction.

2) When the gastrointestinal tract is working again, PN should be tapered gradually towards the use of enteral feeding or dietary intake if suitable.

12. Summary

CKD Patients are sensitive to PEW, and adequate nutritional therapy can yield remarkable improvements in the symptoms of the disease, quality of life, morbidity, mortality and the progression of renal failure. Evaluation of nutritional state in CKD and assessment of dietary intake, including supplements and compliance are steps of crucial importance. The principal causes involve poor dietary intake, abnormal metabolism of amino acids, proteins, lipids and carbohydrates, and metabolic acidosis promoting catabolism. In many complicated CKD patients the main reason for PEW is chronic inflammation**.**

Key words: chronic kidney disease (CKD), protein-energy wasting (PEW), nutrition, diet, enteral, parenteral nutrition.

13. References

1. Lowrie E G, Lew N L: Death risk in hemodialysis patients: the predictive value of commonly measured variables and on evaluation of death rate differences between facilities. Am J Kidney Dis 1990; 15: 458-82.
2. Stenvinkel P, Heimbiirger O, Lindholm B. Wasting, but not PEW, predicts cardiovascular mortality in end-stage renal disease. Nephrol Dial Transplant 2004; 19: 2181-2183.
3. National Kidney Foundation I. Kidney Disease-Dialysis Outcome Quality Initiative: K/DOQI Clinical Practice Guidelines for nutrition in chronic renal failure. Am J Kidney Dis 2000; 35: S1-S140.
4. Uhlig K, Macleod A, Craig J et al. Grading evidence and recommendations for clinical practice guidelines in nephrology. A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2006; 70: 2058-2065.
5. Levey AS, Eckardt KU, Tsukamoto Y et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int 2005; 67: 2089-2100.
6. Mak RH, Cheung W. Energy homeostasis and cachexia in chronic kidney disease. Pediatr Nephrol 2006; 21: 1807-1814.
7. Lindholm B, Heimbiirger O, Stenvinkel P. What are the causes of protein-energy PEW in chronic renal insufficiency? Am J Kidney Dis 2002; 39: 422-425.
8. Detsky AS, Me Laughlin JH, Jeejeeboy KN: What is subjective global assessment of nutritional status. JPEN 1987; 11: 8-13.
9. Steiber AL, Kalantar-Zadeh K, Seeker D et al. Subjective Global Assessment in chronic kidney disease: a review. J Ken Nutr 2004; 14: 191-200.
10. Madore F, Wuest M, Ethier JH: Nutritional evaluation of hemodialysis patients using an impedance index. Clin Nephrol 1994; 41(6): 377-382.
11. Gentile MG, D'Amico G: How to measure and how to improve dietary compliance. Contr Nephrol 1990; 98: 1-8.
12. Toigo G, Situlin R, Carraro M, Faccini L, Russo M, Tamaro G, Collari P, Sergiani GF, Guarnieri G. Evaluation of dietary compliance in patients on chronic renal failure on conservative treatment: comparison of methods to assess dietary intake. Contri Nephrol 1990; 81: 16-24.
13. Heymsfield SB, Tighe A, Wang ZM. Nutritional assessment by anthropometric and biochemical methods. In "Modern nutrition in health and disease", Shils ME, Olson JA, Shike M (Eds), Lea and Febiger, Philadelphia, 1994, 812-841.

14. Fouque D, Aparicio M. Eleven reasons to control the protein intake of patients with chronic kidney disease. Nat Clin Pract Nephrol 2007; 3: TX 383-392.
15. Aparicio M,Chauveau P,Combe Ch. Low protein diets and outcome of renal patients.J Nephrol 2001,14:433-439.
16. Di Iorio B.R, Minutolo R, De Nicola L et al: Supplemented very low protein diet ameliorates responsiveness to erythropoietin in chronic renal failure. Kidney Int 2003, 64:1822-1828.
17. Joint WHO/FAO Expert Consultation on Diet Nutrition and the Prevention of Chronic Diseases. Diet, Nutrition and the Prevention of Chronic Diseases: Report of a Joint WHO/FAO Expert Consultation. World Health Organization: Geneva, Switzerland, 2003.
18. Guarnieri G, Toigo G, Situlin R, Carraro M, Tamaro G: The assessment of nutritional status in chronically uremic patients. Contr Nephrol 1989; 72: 73-103.
19. Wiecek A, Kokot F, Chudek J, et al The adipose tissue a novel endocrine organ of interest to the nephrologist. Nephrol Dial Transplant. 2002 17:191-19.
20. Szolkiewicz M, Sucajtys E, Wolyniec W, et al (2005) Mechanisms of enhanced carbohydrate and lipid metabolism on adipose tissue in uraemia. J Ren Nutrition. 2005 15(1):166-172.
21. Axelsson J, Heimbűrger O, Lindholm B et al Adipose tissue and its relation to inflammation: the role of adipokines. J Renal Nutr, 2005 15, 1: 131-136.
22. Iseki K, Kawazoe N, Fukiyama K. Serum albumin is a strong predictor of death in chronic dialysis patients. Kidney Int 1993; 44: 115-119.
23. Ikizler TA, Greene JH, Wingards RL, Parker RA, Hakim RM: Spontaneous dietary protein intake during progression of chronic renal failure. J Am Soc Nephrol 1995; 6: 1386-91.
24. Kaysen GA, Gambertoglio J, Jiminez I et al. Effect of dietary protein intake on albumin homeostasis in nephrotic patients. Kidney Int 1986; 29: 572-577.
25. Kaysen GA. Biological basis of hypoalbuminemia in ESRD. J Am Soc Nephrol 1998; 9: 2368-2376.
26. Kopple JD, Mehrotra R, Suppasyndh O et al. Observations with regard to the National Kidney Foundation K/DOQI clinical practice guidelines concerning serum transthyretin in chronic renal failure. Clin Chem Lab Med 2002; 40**:** 1308-1312.
27. Cano NJ. Metabolism and clinical interest of serum transthyretin (prealbumin) in dialysis patients. Clin Chem Lab Med 2002; 40**:** 1313-1319.
28. Chertow GM, Ackert K, Lew NL et al. Prealbumin is as important as albumin in the nutritional assessment of hemodialysis patients. Kidney Int 2000:58:2512-2517.
29. Beddhu S, Kaysen GA, Van G et al. Association of serum albumin and atherosclerosis in chronic hemodialysis patients. Am J Kidney Dis 2002; 40**:** 721-727.
30. Kopple JD. Use and limitations of the Balance Technique. JPEN, 1987,11,798-85S.
31. Guarnieri G, Toigo G, Situlin R, Faccini L, Coli U, Landini S, Bazzato G, Dardi F, Campanacci L. Muscle biopsy studies in chronically uremic patients: evidence for PEW. Kidney Int 1983, 24 (SI6), S187-S193.
32. Pollock CA, Ibels LS, Alien BJ, Ayass W, Caterson RJ, Waugh DA, Macadam C, Pennock Y, Mahony JF: Total body nitrogen as a prognostic marker in maintenance dialysis. J Am Soc Nephrol 1995; 6: 82-88.
33. Toigo G, Situlin R, Carraro L, Faccini L, Russo M, Tamaro G, Collari P, Sergiani G, Guarnieri G. Evaluation of dietary compliance in patients with chronic renal failure on conservative treatment: comparison of methods to assess dietary intake. Contr Nephrol 1990, 81: 16-24.

34. Mitch W E, Goldberg A L,: Mechanisms of Muscle Wasting, the rule of the Ubiquitin-Proteasome pathway. N Engl J Med 1996; 335(25): 1897-1905.
35. Maroni BJ: Requirements for protein, calories and fat in the predialysis patients. In: Nutrition an the kidney. Boston; Little, Brown and Company 1993; Mitch W E, KlahzS(Eds), 185-212.
36. Sharma AM, Chettey VT Obesity, hypertension and insulin resistance. Acta Diabetol. 2005 42, Suppl 1:S3-8.
37. Teplan V, Schück O, Hanzal V, Hajny J, Horackova M, Ryba M, et al Obesity and progression of chronic renal insufficiency: Czech long-term prospective double-blind randomized multicentre study. Vnitrni lekarstvi (Internal Medicine). 2006 52,6:571-576.
38. Zoccali C, Mallamaci F, Tripetpi G Adipose tissue as a source of inflammatory cytokines in health and disease: focus and-stage renal disease. Kidney Int. 2003 63, Suppl 84: 65-68.
39. Sciaqua A, Candigliota M, Ceravolo R, et al Weight loss in combination in human obesity. Diabetes Care 2003; 26:1673-1678.
40. Workeneh BT, Rondon-Berrios H, Zhang L et al. Development of a diagnostic method for detecting increased muscle protein degradation in patients with catabolic conditions. J Am Soc Nephrol 2006; 17: 3233-3239.
41. Keshaviah PR, Nolph KD, Moore HL et al. Lean body mass estimation by creatinine kinetics. J Am Soc Nephrol 1994; 4: 1475-1485.
42. Kaysen GA, Zhu F, Sarkar S et al. Estimation of total-body and limb muscle mass in hemodialysis patients by using multifrequency bioimpedance spectroscopy. Am J Clin Nutr 2005; 82: 988-995.
43. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease.Kidney Int 2008,73:391-398.
44. Kopple JD, Gao XL, Qing DP. Dietary protein, urea nitrogen appearance and total nitrogen appearance in chronic renal failure and CAPD patients. Kidney Int 1997; 52: 486-494.
45. Pecotts-Filho R, Lindholm B, Stenvinkel P. The PEW, inflammation, and atherosclerosis (MIA) syndrome—the heart of the matter. Nephrol Dial Transplant 2002; 17(Suppl 11): 28-31.
46. Kalantar-Zadeh K, Mehrotra R, Fouque D et al. Metabolic acidosis and PEW-inflammation complex syndrome in chronic renal failure. Semin Dial 2004; 17: 445-465.
47. Bajardi P, Dionisio P, Valenti M, Cornelia C, Caramello E, Bergia R, Cravero R, Stramignoni E, Pellerey M, Berto IM: Monitoring of central venous dual-lumen catheter placement in haemodialysis: improvement of a technique for the practising nephrologist. Nephrol Dial Transpl 1995; 10 (11) p2118-21**.** The modification of diet in renal disease study: design, methods and results from the feasibility study. Am J Kidney Dis 1992; XX (1): 18-33.
48. Axelsson J, Qureshi AR, Divino-Filho JC et al. Are insulin-like growth factor and its binding proteins 1 and 3 clinically useful as markers of PEW, sarcopenia and inflammation in end-stage renal disease? Eur J Clin Nutr 2006; 60: 718-726.
49. Kaysen GA. Diabetes, a cause of progressive sarcopenia in dialysis patients? Kidney Int 2005; 68: 2396-2397.
50. Mak RH, Rotwein P. Myostatin and insulin-like growth factors in uremic bsarcopenia: the yin and yang in muscle mass regulation. Kidney Int 2006; 70: 410-412.

51. Vesani CM, Kamimura MA, Draibe SA et al. Is energy intake underestimated in nondialyzed chronic kidney disease patients? J Ren _ Mutr 2005; 15: 159-165.
52. Bergstrom J: Nutrition and mortality in hemodialysis. J Am Soc Nephrol 1995; 6: 1329-41.
53. Toigo G,Oldrizzi I,Situlin R,Tamato G,Faccini L,Russo M,Campanacci L,Rugiu C,Maschio G,Guarnieri G.Nutritional and metabolic effect of ten years of protein restricted diet in patients with early renal failure.Contr Nephrol 1989,75:194-202.
54. Bergstrom J: Why are dialysis patients malnourished? Am J Kidney Dis 1995, 26, 229-241.
55. Attmann P O: Long-term treatment with low protein diet in uremia. Contrib Nephrol 1986; 53: 128-136.
56. Zoccali C, Mallamaci F, Tripepi G, et al Adiponectin, metabolic risk factors, and cardiovascular events among patients with and stage renal disease. J Am Soc Nephrol. 2002 13:134-141.
57. Kaysen GA, Eiserich JP. The role of oxidative stress-altered lipoprotein structure and function and microinflammation on cardiovascular risk in patients with minor renal dysfunction. J Am Soc Nephrol 2004; 15: 538-548.
58. Himmelfarb J, Stenvinkel P, Ikizler TA et al. The elephant in uremia:oxidant stress as a unifying concept of cardiovascular disease in uremia. Kidney Int 2002; 62: 1524-1538.
59. Kilpatrick RD, McAllister CJ, Kovesdy CP et al. Association between serum lipids and survival in hemodialysis patients and impact of race. J Am Soc Nephrol 2007; 18: 293-303.
60. Kalantar-Zadeh K, Kopple JD, Kilpatrick RD et al. Association of morbid V^X obesity and weight change over time with cardiovascular survival in hemodialysis population. Am J Kidney Dis 2005; 46: 489-500.
61. Reaich D, Channon SM, Scrimgeour CM, Goodship TH. Ammonium chloride-induced acidosis increases protein breakdown and aminoacid oxidation in humans. Am J Physiol 1992, 263: E735-E739.
62. Bologa RM, Levine DM, Parker TS et al. Interleukin-6 predicts hypoalbuminemia, hypocholesterolemia, and mortality in hemodialysis patients. Am J Kidney Dis 1998; 32: 107-114.
63. Teplan V, Schück O, Konotek A, et al. Enhanced metabolic effect of erythropoietin and keto acids in CKD patients on low-protein diet: Czech multicenter study. Am J Kidney Dis 2003, Suppl 1,41:S26-S30.
64. Aparicio M, Gin H, Potaux L, et al: Effect of a ketoacid diet on glucose tolerance and tissue insulin sensitivity. Kidney It 1989; 36 (S27): 231-235.
65. Hansen H.P., Tauber-Lassen E., Jensen B, Parving H.H. Effect of dietary protein restriction on prognosis with diabetic nephropathy. Kidney Int 2002, 62:220-228
66. Kopple JD. Nutrition, diet and the kidney. In "Modern nutrition in health and disease", Shils ME, Olson JA, Shike M (Eds). Lea and Febiger, Philadelphia, 1994, 1102-1134.
67. FAO, WHO, UNU: Energy and proteins requirements in technical report. Series 724, World Health Organization, Geneva 1985; 1-110.
68. Pedrini M T, Levey A S, Lasu J, Chalmers T C, Wang P H: The effects of dietary protein restriction on the progression of diabetic and non diabetic renal disease: A meta-analysis. Ann Intern Med 1996; 124: 627-632.
69. Fouque D, Laville M, Boissel R, LabeeuwM, Zech PY. Controlled low protein diets in chronic renal insufficiency: meta-analysis. BMJ 1992; 304:216-220.

70. Fouque D, Vennegoor M, ter Wee P et al. EPBG guideline on nutrition. Nephrol Dial Transplant 2007; 22(Suppl 2): ii45-ii87.
71. Attman P-O, Ewald J, Isaksson B. Body composition during long-term treatment of uremia with aminoacid supplemented low-protein diet. Am J Clin Nutr 1980; 33: 801-810.
72. Walser M: Effect of Ketoanalogues in chronic renal failure and other disorders. Am J Clin Nutr 1989; 49: 17-22.
73. Klahr S: Role of dietary protein and blood pressure in the progression of renal disease. Kidney Int 1996; 49: 1783-86.
74. Cupisti A, Morelli E, Meola M, Barsotti M et al. Vegetarian diet alternated with conventional low-protein diet for patients with chronic renal failure. J Ren Nutr 2002,12:32-37.
75. Teplan V Pharmacological features of keto amino acid therapy. Am J Nephrol; 2005 25, Suppl 1: 13-14.
76. Teplan V, Schück O, Horackova M, Skibova J, Holecek M Effect of keto acid-amino acid supplement on the metabolism and renal elimination of branched-chain amino acids in patients with chronic renal insufficiency on a low protein diet. Wien Klin Wochensch; 2000 112/20,876-881.
77. Klahr S, Morrissey J. Progression of chronic renal disease. Am J Kidney Dis 2003,Suppl 1,41:S3-S7.
78. Kopple JD,Mofeon FJ,Shaib JK.Effect of energy intake on nitrogen metabolism in nondialyzed patients with chronic renal failure.Kidney Int 1986,29:734-742.
79. Schneeweiss B, Graninger W, Stockenhuber F, Druml W, Ferenci P, Eichinger S, Grimm G, Laggner AN, Lenz K: Energy metabolism in acute and chronic renal failure. Am J Clin Nutr 1990; 52: 596-601.
80. Fouque D, Peng SC, Shamir E et al. Recombinant human insulin-like growth factor-1 induces an anabolic response in malnourished CAPD patients. Kidney Int 2000; 57**:** 646-654.
81. Kalantar-Zadeh K. Causes and consequences of the reverse epidemiology of body mass index in dialysis patients. J Ren Nutr 2005; 15: 142-147.
82. Klahr S, Levey A S, Beck G J, Caggiula A W, Hunsicker L, Kusek J W, Striker J: The effect of protein dietary restriction and blood-pressure control on the progression of chronic renal failure. New Engl J Med 1994; 330(13): 877-884.
83. D'Amico G, Gentile M G, Fellin G, Manna G, Cofano F: Effect of dietary protein restriction on the progression of renal failure: a prospective randomized trial. Nephrol Dial Transpl 1994; 9: 1590-94.
84. Petersen J C, Adler S, Borkart J M, Greene T, Herbert Lee A, Hunsicker 1 G, King A J, Klahr S, Massry S G, Seifter J L: Blood Pressure Control, Proteinuria and the progression of renal disease. Ann Intern Med 1995; 123: 754-62.
85. Maschio G, Oldrizzi L, Rugiu C: Dietary factors and progression of diabetic nephropathy. Acta Diabetol 1992; 47: 7-24.
86. Jungers P, Hannedouche T, Itakura Y, Albouze G, Descamps-Latscha B, Man NK. Progression rate to end-stage renal failure in non diabetic kidney disease: a multivariate analysis of determinant factors. Nephrol Dial transpl 1995, 101353-60.
87. Samuelsson O, Aurell M, Knight-Gibson C, Alaupovich P, Attman P-O. Apolipoprotein-B-containing lipoproteins and the progression of renal insufficiency. Nephron 1993: 63:279-285.
88. Keane WF, Mulcahy WS, Kasiske BL, Kirn Y, O'Donnell MP. Hyperlipidemia and progressive renal disease . Kidney Int 1991, 39 (S31), S41-S48.

89. Loghman-Adam M. Role of Phosphate retention in the progression of renal failure. J Lab Clin Med 1993, 122: 16-26.
90. Massry SG, Fadda GZ. Chronic renal failure is a state of cellular calcium toxicity. Am J Kidney Dis 1993, 21: 81-86.
91. Combe C, Morel D, de Precigout V, Blanchetier V, Bouchet JL, Potaux L, Fournier A, Aparicio M: Long term control of hyperparathyroidism in advanced renal failure by low-phosphorus low protein diet supplemented with calcium (without changes in plasma calcitrol). Nephron 1995; 70: 287-95.
92. Massry SG and Kopple JD: Requirements for calcium, phosphorous and Vit D. In: Nutrition and the Kidney. Boston; Little, Brown and Company 1993; Mitch W E, Klahz S eds. 96-113.
93. Gentile MG, Fellin G, Manna GM, D'Amico G, Testolin G, Porrini P, Simonett P. Vitamin A and retinol binding protein in chronic renal insufficiency Int J Artif Org 1988, 11,403-404.
94. Kopple J D, Mercuric K, Blumenkrantz M J, Jones M R, Roberts C, Card B, Saltzman R, Casciato D A, Swenseid M A: Daily requirement for pyridoxine supplement in chronic renal failure. Kidney Int 1981; 19: 694-704.
95. Gilmour E R, Hartley G H, Goodship T H: Trace elements and vitamins in renal disease. In: Nutrition and the Kidney. Boston; Little, Brown and Company 1993; Mitch W E, Klahz S eds. 114-31.
96. Stein G, Schon S, Sperschneider H, Richter R, Funfstiick R, Giinter K. Vitamin status in patients with chronic renal failure. Contr Nephrol 1988, 65: 33-37
97. Gentile M G, Manna G M, D'Amico G, Testolin G, Porrini M, Simonetti P: Vitamin nutrition in patients with chronic renal failure and dietary manipulation. Contr Nephrol 1988; 65: 43-50.
98. Mahajan SK et al. Zinc deficiency: a reversible complication of uremia.. Am J ClinNutr 1982, 36, 1177.
99. Stec J, Podsacka L, Paykovekava O, Kollar M: Zinc and copper metabolism in nephrotic syndrome. Nephron 1990; 56:186.
100. Kallistratos G, Evangelou A, Seferiadis K, Vezyraki P, Barboutrs K: Selenium and hemodialysis: serum selenium levels in healty persons, non cancer and cancer patients with chronic renal failure. Nephron 1985. 41: 217-222.
101. Kalantar-Zadeh K, Fouque D. Nutritional management of chronic kidney disease. N Engl J Med 2017 Nov 2;377(18):1765-1776.

