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Role of Protein-Restricted diet supplemented with Ketoanalogue in Dialysis Patients

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1. INTRODUCTION

Dialysis patient lose protein during dialysis along with inability of the body to use and process amino acids due to kidney disease leading to requirement of higher protein demand than the average healthy adult. In the pre-dialysis and dialysis period the dietary approach in the different phases of chronic renal insufficiency (CRI) has been highly controversial. Lack of protein in dialysis patient will result in the development of PEM, increased mortality and decreased physical functioning and quality of life [1,2]. It is highly important to assess the nutritional status and to identify patients at risk to prevent and treat malnutrition in dialysis patients.

2. NUTRITIONAL ASPECT IN DIALYSIS

It is common to find malnutrition among patients on maintenance hemodialysis. In patients with advanced renal failure at the beginning of dialysis treatment the prevalence of malnutrition was found to be around 40%. Evidence of wasting was indicated in various epidemiological studies using classic measures of nutritional status, it showed wasting in approximately 18–75% of patients with chronic kidney disease undergoing maintenance dialysis therapy. Signs of malnutrition have also been observed in 10–70% of hemodialysis patients and in 18–51% of patients on continuous ambulatory peritoneal dialysis. Other studies demonstrated mild-to-moderate malnutrition in one-third of patients and severe malnutrition in 6–8% patients. Serum albumin levels are highly predictive nutritional markers for morbidity and mortality— a decrease from 4.0 to 3.5 g/dL or from 4.0 to 3.0 g/dL results in a 2 or 5 times higher mortality rate respectively. , This observation emphasizes the importance of nutritional concerns in the management of chronic kidney disease.

The National Kidney Foundation–Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) guideline recommends a dietary protein intake of 1.2 g/Kg body weight/day for hemodialysis patients, 1.3 g of protein/Kg body weight/day for peritoneal dialysis, 35 kcal/Kg body weight/day for patients aged <60 years and 30–35 kcal/Kg body weight/day for those patients aged >60 years [2].

RESIDUAL RENAL FUNCTION

RRF is important in patients of CKD, and recent studies have also found that it is an essential predictor of patient survival in dialysis patients rather than the overall clearance adequacy (RRF plus dialysis). In dialysis patients RRF plays a major role in inhibiting inflammation, maintaining balance between serum phosphate and calcium, and maintaining nutritional status.

Dietary protein intake (DPI) is the major determinant of the amount of nitrogen excreted as urea by the kidney. Decreased protein intake has been associated with a retardation of kidney function loss in pre-dialysis CKD patients, an effect presumably mediated by lowering the requirement for renal nitrogen clearance and/or a reduction in proteinuria, as well as other factors. To preserve RRF a low-protein diet is recommended to CKD patients pre-dialysis, whereas current recommendations are for a DPI of no less than 1.2 g of protein/Kg ideal body weight (IBW)/day to prevent protein-energy wasting (PEW). The recommended high protein intake is twice as high as for patients during the late predialysis stage, is difficult to achieve, and may additionally promote the deterioration of metabolic abnormalities (e.g., hyperphos-

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phatemia, dyslipidemia, metabolic acidosis) and the decline in RRF. Low-protein diets in pre-dialysis CKD patients are supplemented with ketoanalogues, this is done not only for nutrition safety but also because of their independent impact on RRF.

KETOANALOGUES

Ketoanalogoues (keto acids) are de-aminated amino acids, which mean that they are simply carbon chains lacking any amino group. These keto acids do not contain nitrogen. At the same time, the keto acids are acceptors for amino groups and can be rebuilt to the corresponding amino acid in the body. The main advantage is that keto acids do not contain nitrogen and do not generate nitrogenous by-products, which have to be excreted via the kidney. This saving of nitrogen is associated with a direct inhibition of the genesis of urea and subsequently a decreased workload of the kidney (Figure 1).

LOW PROTEIN DIET AND KETOANALOGUES (KA) IN DIALYSIS PATIENTS: SOME EVIDENCE

Current studies during the pre-dialysis phase of CKD have disclosed that a protein-restricted diet supplemented with KA can improve several metabolic dysfunctions, lower urea levels, and maintain a sound nutritional condition for these patients. However, until now there have been only a few studies with a limited sample size available that have evaluated the safety and efficacy of protein-restricted diets plus KA supplementation on the clinical outcome of dialysis (hemodialysis [HD] and peritoneal disease [PD]) patients.[10]

The first prospective, randomized, single-center trial on the efficacy of different kinds of protein-restricted diets in PD patients has been performed by Jiang et al.10 In 60 patients, randomized into 3 groups, the nutritional status and RRF in PD patients was evaluated. Group I was advised to follow a low protein diet (LPD) (0.6 to 0.8 g protein/Kg body weight/day) supplemented with KA (0.12 g/Kg body weight/day); group II was advised to follow a LPD (0.6 to 0.8 g protein/Kg body weight/day); and group III was advised to follow an unrestricted protein intake (1.0 to 1.2 g protein/Kg body weight/day) for 12 months. Main outcomes were renal (e.g., RRF, glomerular filtration rate) as well as nutritional and biochemical parameters (e.g., serum albumin, SGA, normalized protein catabolic rate, etc). At the end of the study, the nutritional parameters albumin and pre-albumin showed stable or slightly improved values with no significant differences between the groups. A decrease in RRF, estimated glomerular filtration rate, and Kt/V within the study period could be seen in every treatment group; however, after 12 months, the degree of decline was significantly less in group I (LPD supplemented with KA) as compared with the 2 other groups. In conclusion, a diet containing 0.6 g of protein/Kg of ideal body weight/day is safe. A combination with KA supplementation is associated with an improved preservation of RRF in maintenance PD. Recently Jiang et al11 also evaluated beneficial effects of LPD + KA in suppressing peritoneal transport rate in peritoneal dialysis (PD) patients. It was a supplemented analysis to their previous published trial mentioned above. Variations of peritoneal transport rate were assessed in this study, while baseline D/Pcr (dialysate-to-plasma concentration ratio for creatinine at 4 hour) and D/D0glu (dialysate glucose at 4 hour to baseline dialysate glucose concentration ratio) were similar, D/Pcr in group sLP was lower, and D/D0glu was higher than those in the other two groups ($P < 0.05$) at 12th month. D/D0glu increased ($P<0.05$), and D/Pcr tended to decrease, ($P = 0.071$) in group sLP. They have concluded that low-protein diet with KA may benefit PD patients by maintaining peritoneum at a lower transport rate.[11]

Li H et al also evaluated the effects of short-term restriction of dietary protein intake (DPI) supplemented with KA on hyperphosphatemia in maintenance hemodialysis (HD) patients. For 8 weeks 40 MHD patients with uncontrolled hyperphosphatemia were randomized to either low DPI with keto acid-supplemented (sLP) or normal DPI (NP) group. Later the sLP group was shifted to NP for another 8 weeks. Low-protein diet (LPD) was individualized with total caloric intake 30-35 kcal/kg/day, protein intake of 0.8 g/kg/day and phosphate intake of 500 mg/day, a KA dosage of 12 pills per day was also provided. Calcium phosphorous metabolism index and nutritional index (serum albumin, total protein, somatometric measurements, 3-day diaries and Mini-Nutritional Assessment score) was recorded. At the end of the first 8 weeks in the sLP group compared to the basal value and the NP group ($p < 0.001$) serum phosphorus level and calcium-phosphate product were significantly decreased. It was concluded that while keeping stable nutritional status among MHD patients, short-term restriction of DPI supplemented with KA could decrease hyperphosphatemia and calcium-phosphate product. [11,12]

In a pilot study of a randomized, double-blind, multicenter clinical trial to evaluate the safety and efficacy of a restricted protein diet supplemented with a keto acid on the preservation of RRF and nutritional

status in CAPD patients conducted by the Nephrology Department at Sun Yat-sen University, Guangzhou, P.R. China.They randomized 40 CAPD patients into 2 groups–38 patients completed a 6-month follow-up: 20 patients in group I received a protein-restricted diet (0.6 to 0.8 g/Kg /day) supplemented with keto acid, and 18 patients were on a routine protein diet group (1.0 to 1.2 g/Kg/day) (group II). On comparison a significant improvement in hyperphosphatemia ($P < 0.05$), body mass index, serum albumin, blood urea nitrogen (BUN), serum creatinine, RRF, and urine volume was seen in group I.

CONCLUSION

A protein-restricted diet in combination with Keto/amino acid supplements is recommended for RRF protection and malnutrition improvement. However, in the future, more randomized controlled trials are needed to explore the efficacy and safety of this nutritional treatment concept.

CASE STUDY

Case 1. Keto analogues in CKD II-III secondary to chronic glomerulonephritis

A 40 yrs old gentleman was diagnosed to have CGN–CKD-II in 2007, while being investigated for hypertension and proteinuria. His Sr. creatinine was 1.6 mg% and eGFR 55.5 ml/min. He was started on restricted dietary schedule of 0.7 g/kg proteins, phosphate binders and antihypertensives. He followed the treatment very religiously and blood pressure was controlled. In next 18 months (April 2009), his renal functions deteriorated (Sr. Creatinine 2.9 mg%, eGFR 30.6 ml/min; CKD-III) despite diet and blood pressure control.

He was started on ketoanalogues (Ketosteril) 6 tab/day in April, 2009. During the next four years, his renal functions stabilized (Creatinine 2.8 mg%, eGFR 35.2 ml/min). There is gain in weight of 8 kg, his lean body mass has improved as assessed by triceps skin fold thickness (TSF) and mid arm upper circumference (MAUC). His parathyroid levels have improved from 588 pg/ml to 96 pg/ml; and his albumin, calcium and phosphorus have remained stable during this period. His hemoglobin has improved and there is not only stabilization of renal functions but improvement in eGFR also (30.6 ml/min in April in 2009, 35.97 ml/mg in Feb, 2013) after initiation of ketoanalogues.

Conclusion

Regular use of ketoanalogues along with protein restricted diet with adequate control of blood pressure resulted in good preservation of renal functions without causing malnutrition. Hemoglobin, lean body mass, parathyroid functions improved and his albumin, calcium, phosphorous remained in normal range.

Case 2. Ketoanalogues in Diabetic Kidney disease

Mr. SS, a 65 yrs old male, diabetic for 20 yrs presented with CKD in July, 2007. His sugar and blood pressure were uncontrolled and had Sr. Creatinine of 5.2 mg% (eGFR 19.2 ml/min). He had anemia, whereas calcium and phosphorous were in range. In August 2009, he was started on ketoanalogues (Ketosteril) 6 tablets/day along with protein restricted diet (0.7 g/kg). His Sr. Creatinine was 5.9 mg/dl, eGFR 16.9 ml at initiation of this therapy. He took medicines regularly, though his follow-up was not regular. He presented after 15 months (Nov, 2010) with acute on CKD due to pneumonia and sepsis. Sr. Creatinine was 7.34 mg% (eGFR 13.6 mg/min). After control of sepsis, his renal functions improved. After one month i.e., December, 2010 his Sr. creatinine was 3.4 mg/dl, and eGFR 29.2 ml. In June, 2012 sr. creatinine was 4.05 (eGFR 26.7 ml) and in Jan, 2013 i.e., after 3½ yrs of ketoanalogues use his sr.creatinine is 5.13 mg% with eGFR 19.9 ml/min. His HBA1C remained in range of 6.5–7%, Sr. protein, calcium, phosphorous and lipids remained in range. His hemoglobin has improved from 9.9 g% to 11 g% and he has gained 6 kg weight in last 3½ years.

Conclusion

In diabetic kidney disease, ketoanalogues along with protein restriction have useful role in preservation of renal failure, even if started late (Stage IV).They were associated with good sugar control as shown by HBA1C; lipids, calcium, phosphorous and serum protein remained in normal range. There was improvement in nutritional status as determined by good appetite, general well-being, increase in lean body mass and weight gain.

Case 3. Ketoanalogues in CKD-V

AG, a 70 yrs old male, hypertensive for 15 years was diagnosed to have chronic kidney disease stage-V (eGFR 11.3 ml/min) and was started on dialysis thrice/week (12 hrs/week) in August 2008 at some other hospital. He came for a second opinion in October 2008, his serum creatinine was 9.4 mg % and had volume depletion which was restored. Patient was managed conservatively as there was no emergent indication for dialysis. In next 4-5 days with volume repletion his sr.creatinine came down to 7.8 mg% and he was discharged with an AV fistula & 6 tablets of ketoanalogues (Ketosteril) along with protein restricted diet (0.6 g/kg/body weight). He was followed every fortnight for next 8 weeks. His sr.creatinine and

eGFR improved (5.77 mg%, 19.7 ml). For one year (Dec 2010) his sr.creatinine and eGFR remained stable 5.5 mg, 20.1 ml/min. In June 2011 he had pulmonary infection and acute on CKD. He was maintained on dialysis for three weeks and then again he was off dialysis and maintained reasonable renal functions till Jan 2012 (sr.creatinine 7.2 eGFR 16.7 ml). However in May 2012, his eGFR decreased to 11.5 ml and started complaining of anemia, anorexia and weakness; and hence was started on regular dialysis.

During ketoanalogues treatment, his calcium, phosphorous, protein, hemoglobin and nutritional status improved and maintained good quality life without dialysis for almost 2½ years.

Conclusion

Elderly people with CKD can be started on ketoanlaoues to postpone dialysis or those who don't want to go for dialysis. However, a regular timely detection of any complication is required for initiation of dialysis at an appropriate time.

Case 4. Ketoanalogues in CKD-V patients on CAPD

RV, a 47 yrs old man underwent kidney transplant from his father in 1994. He remained well till 2008, when he developed chronic allograft nephropathy and by Jan 2011, he developed CKD-V. He was started on CAPD (three exchanges/day) as there was no alternative family donor for 2nd transplant and there was no vascular access. Till Oct 2011, he remained reasonably well. However, he started developing weakness, loss of weight, pallor and hypoproteinemia. Dose of CAPD was increased to 4 exchanges/day and high protein diet counseling done repeatedly. However, there was no improvement in general condition and nutritional status worsened further with >10% weight loss.

In Jan 2012, he was started on ketonanlogues (Ketosteril) 6 tab/day. In the next two months, he started feeling better, appetite improved and gained 2 kg dry weight; Sr. protein also improved. By December 2012 i.e., one year of ketoanalogues his Hb rose to 11 g%, Sr.albumin 3.4 mg% &and had gained 6 kg body weight.

Conclusion

Ketoanalogues have a beneficial role in patients on CAPD, who are not doing well. Addition of these supplements improves appetite, general well-being and nutritional status as assessed by weight gain, improvement in hemoglobin and serum protein in the patient.

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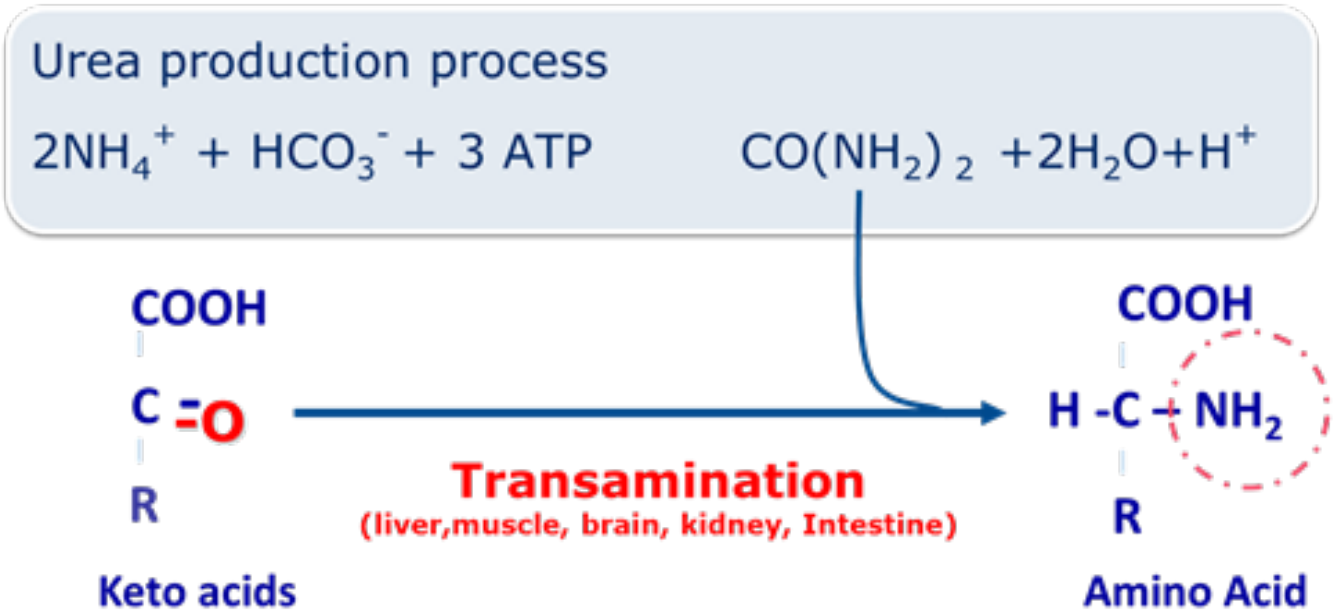

Figure 1: Mechanism of action of ketoanalogues

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Table 1: Keto analogues in CKD II-III secondary to chronic glomerulonephritis

	Feb 13	Dec 12	July 12	Jan 12	Aug 11	Jan 11	June 10	Oct 09	April 09	July 08
Weight	72	71	73	72	70	71	70	67	64	64
MAUC	29	28	29	30	30	–	31	31	30	30
TSF	11	10	10.5	10	11	–	11.5	11	10	11
BUN	22.7	–	22.7	–	–	26.2	22.4	–	–	18
Creatinine	2.78	2.89	2.82	2.89	2.99	3.24	3.3	3.28	2.9	1.6
Calcium	9	9.2	–	9.6	9.4	9.8	7	10	8.4	9.2
Phosphorus	3.5	3.4	–	3.1	3	3.9	2.9	2.6	3.2	2.1
Albumin	3.5	–	3.4	–	–	3.5	–	3.4	–	3.4
Cholesterol	155	168	170	170	–	134	130	178	150	140
Triglyceride	170	150	183	–	–	142	100	–	–	–
PTH	–	94.6	120	–	–	178	588	588	–	167

MAUC: mid arm upper circumference; TSF: triceps skinfold thickness; BUN: blood urea nitrogen; PTH: Parathormone

Table 2: Ketoanalogues in Diabetic Kidney disease

	Jan 13	June 12	Dec 11	April 11	Nov 10	Aug 09	April 08	July 07
Weight	78	76	74	72	72	74	72	72
MUAC	33	34	32	32	33	32	32	32
TSF	10.5	10	10.5	10.5	11	10.5	10	10.5
BUN	30		30	33	39	57.2	–	–
Creatinine	5.13	4.05	3.57	3.02	7.34	5.93	4.8	5.2
Calcium	9.6	9.6	8.6	8.5	9.9	9.9	9.9	–
Phosphorus	3	3.2	3.1	3.5	5.3	5.2	4.5	5
Albumin	3.6	3.5	–	3.4	–	3.5	3.2	2.8
Cholesterol	168	156	–	172	154	72	–	168
Triglyceride	120	–	142	–	–	–	180	–
PTH	–	94	–	–	120	–	–	178
HBA1c	6.8	–	6.8	–	6.8	7.2	–	8.8

Table 3: Ketoanalogues in CKD-V

	May 12	Nov 11	June 11	Dec 10	April 10	Oct 09
Wt	86	84	82	82	83	77
MUAC	33	32	30	32	–	30
TSF	11	11	10.5	11	–	10.5
BUN	98	–	115	102	90	200
Creatinine	8.22	7.46	7.85	5.54	5.99	9.4
Calcium	7.6	–	8.1	–	–	7.6
Phosphorus	6.5	–	7.2	152	–	9.4
Albumin	3.2	–	3.4	–	3.4	2.8
Cholesterol	166	156	170	–	140	124
Triglyceride	–	–	140	–	123	135
PTH	98	–	100	–	97	–

Table 4: Ketoanalogues in CKD-V patients on CAPD

	Dec 2012	October 2012	July 2012	April 2012	Jan 2012
Wt	69	67	66	65	63
MUAC	29	27	26	29	24
TSF	10	9	8	–	7
BUN	145	–	121	–	150
Creatinine	3.4	5.4	5.8	6.1	6.7
Calcium	9.0	8.5	7.1	–	6.8
Phosphorus	5.8	6.9	–	7.8	9.1
Albumin	3.4	3.0	2.8	2.5	2.2
Cholesterol	167	177	–	140	144
Triglyceride	–	145	155	123	165
PTH	110	–	97	–	129