Protein Intake and the Nutritional Status in Patients with Pre-dialysis Chronic Renal Failure on Unrestircted Diet

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Objectives : *Malnutrition is known to be highly associated with morbidity and mortality in dialysis patients. Malnutrition may begin to develop in patients with chronic renal failure(CRF) before they need dialysis. In this study, the nutritional status of patients with moderate to severe CRF on unrestricted diet was evaluated.*

Methods : *We measured dietary protein intake(DPI, g/kg/day) in 64 patients with CRF and 42 normal controls(N). Nutritional indices such as serum albumin(SA, g/dl), transferrin(TF, mg/dl), prealbumin(PA, mg/dl) and insulin-like growth factor-1(IGF-1, ng/ml) were measured to evaluate the visceral proteins, and creatinine-height index(C-H, g/d/m) to evaluate the somatic proteins.*

Results : *Mean DPI was 0.80 ± 0.27(S.D.) in CRF and 1.07 ± 0.30 in N($p<0.0001$). DPI was lower than 0.6 in 15 CRF patients(23%). Serum albumin, transferrin and C-H were significantly lower in CRF patients than in N($p<0.01$). In patients with CRF, nutritional indices were significantly worse with lower DPI($<0.6g/kg/d$, n=15) than higher DPI($>0.6g/kg/d$, n=49)(SA 2.9 ± 0.7 vs. 3.6 ± 0.8, $p<0.005$; TF 147 (134-179) vs. 220(182-264), $p<0.0005$; PA 24 ± 8 vs. 32 ± 9, $p<0.001$; IGF-1 123 (66-261) vs. 226(140-344), $p<0.05$; C-H 0.52 ± 0.15 vs. 0.87 ± 0.23, $p<0.0001$). CRF patients with nephrotic range proteinuria($>3.5g/d$, n=19) had lower SA (2.8 ± 0.6 vs. 3.8 ± 0.8, $p<0.0001$) and PA(27 ± 9 vs. 32 ± 9, $p<0.05$). CRF patients with diabetes mellitus(n=20) showed worse nutrition than non-diabetic patients(SA $2.8 \pm 0.6g/dl$ vs. $3.8 \pm 0.8g/dl$, $p<0.0001$; TF 176mg/dl(148-214) vs. 220mg/dl(175-266), $p<0.05$; PA $24 \pm 10mg/dl$ vs. $33 \pm 8mg/dl$, $p<0.0005$; IGF-1 138ng/ml(69-269) vs 231ng/ml(140-364), $p<0.05$; C-H 0.66 ± 0.23 vs. 0.85 ± 0.5, $p<0.005$).*

Conclusion : *A significant protein malnutrition prevails in patients with pre-dialysis CRF on unrestricted diet, especially with low protein intake. The effort to detect and correct malnutrition should be made in patients with CRF even before initiation of maintenance dialysis.*

Key Words : *Chronic renal failure, Nutrition, Protein intake*

INTRODUCTION

Recent studies have shown that malnutrition is an important risk factor for the development of morbidity and mortality in patients on maintenance dialysis[1-4]. Malnutrition is known to be associated with more frequent infection or cardiovascular disease which are the major causes of death in

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these patients[5-8]. A significant proportion of patients on maintenance dialysis have been demonstrated to have malnutrition as measured by anthropometric measurements or biochemical parameters[9-11], but they might have begun to suffer from malnutrition even before the institution of dialysis. The evidence for malnutrition was reported to be present in patients who are commencing maintenance dialysis therapy[12]. Detection and appropriate management of nutritional problems seems to be required even before the initiation of maintenance dialysis.

There are not sufficient data about the nutritional status of patients with pre-dialysis chronic renal failure. Protein and calorie intake were reported to be low in a study[13] of a small number of patients with early renal failure. In the report of the Modification of Diet in Renal Disease Study[14], it was concluded that patients with chronic renal insufficiency who are not in need of maintenance dialysis therapy, in general, do not suffer from protein calorie malnutrition. However, patients with advanced malnutrition were excluded from the study and the prevalence of malnutrition seems to be underestimated.

In this study, we measured the amount of protein intake of 64 patients with moderate to severe renal insufficiency who were clinically stable and had been on an unrestricted diet, and evaluated various nutritional indices in relation to protein intake, degree of renal insufficiency, amount of proteinuria and underlying renal disease.

MATERIALS AND METHODS

1. Subjects

Sixty four consecutive adult patients(46 men and 18 women, mean age 53 ± 14(SD) years) with pre-dialysis chronic renal failure(creatinine clearance less than 60ml/min) who visited the nephrology clinic of Asan Medical Center and 42 healthy subjects (24 men and 18 women, mean age 45 ± 14(SD) years) as control were included. Twenty patients were diabetics(non-insulin dependent) and 19 patients had nephrotic range proteinuria(>3.5g/day). All patients had been on

an unrestricted calorie and protein intake.

2. Methods

Serum albumin, transferrin, prealbumin and insulin-like growth factor I(IGF-1) were measured to evaluate the visceral proteins, and creatinine-height(C-H) index to evaluate the somatic proteins.

Serum albumin was measured by bromocresol green method using Hitachi 735-40 autoanalyser (Hitachi Ltd. Tokyo, Japan). Transferrin and prealbumin were measured by nephelometeric immunoassay with Beckman Array System (Beckman Instrument, CA, USA) and Behring nephelometer 100 analyser(Behring wake AG Diagnostica, Malburg, Germany). IGF-1 was measured by two site immunoradiometric assay using commerical kit(DSL-5600, ActiveTM IGF-1-coated tube IRMA, Diagnostic system laboratory Inc, Texas, USA). Total CO_2 was measured by ion selective electrode.

Twenty-four-hour urine urea nitrogen was measured by enzyme method(NADH-NAD) with Hitachi 736-40 autoanalyser and 24hr urine protein by trichloroacetic method with spectrophotometer (Shimadgu CL-750, Japan).

Body mass index(BMI) was calculated by dividing the weight, in kilograms, by the square of the height, in meters. Dietary protein intake(DPI, g/kg/day) and C-H index(g/d/m) were calculated from the 24hr urine nitrogen and creatinine excretion using the following formula[15, 16].

DPI=$6.25 \times$(24hr urinary nitrogen$+0.031$g/kg$\times$ body weight)/ideal body weight

C-H index=actual 24hr urinary creatinine excretion/normal value for height and sex

The degree of renal insufficiency was defined as follows : moderate renal insufficiency; Ccr 25-60ml/min, severe renal failure; Ccr less than 25ml/min. The amount of protein intake in CRF patients was divided into two groups : lower protein intake; <0.6g/kg/day, higher protein intake; >0.6g/kg/day. Various nutritional indices were compared in relation to protein intake, degree of renal insufficiency, amount of proteinuria and underlying renal disease. The correlations between DPI or creatinine clearance and nutritional parameters w ere also analysed.

3. Statistical Analysis

DPI, serum albumin, prealbumin and C-H index are presented as mean with standard deviation. Transferrin and IGF-1 are presented as median with interquartile range. Comparisons of value between two groups were performed by unpaired t-test or Mann-Whitney U test as appropriately. The correlation between DPI or creatinine clearance and nutritional parameters was calculated using Spearman's rank correlation test. The statistical significance was defined as $p < 0.05$.

RESULTS

Mean DPI was significantly lower in chronic renal failure(CRF) patients(n=64, 0.80 ± 0.27g/kg/day) compared with normal subjects(n=42, 1.07 ± 0.30g/kg/day)($p < 0.0001$). Fifteen(23%) CRF patients had DPI lower than 0.6g/kg/day. Mean serum albumin(3.5 ± 0.8g/dl), C-H index(0.79 ± 0.26g/d/m) and median value of transferrin[207mg/dl(157-245)] were also significantly lower in CRF patients compared with normal subjects[4.5 ± 0.4g/dl, $p < 0.0001$; 1.03 ± 0.22g/d/m, $p < 0.0001$; 292mg/dl(258-316), $p < 0.0001$]. (Table 1) Thirty(47%) CRF patients had serum albumin level lower than 3.5g/dl.

Patients with moderate CRF(n=17) had less protein intake (0.88 ± 0.29g/kg/day) than normal subjects($p < 0.05$). Serum albumin(3.9 ± 0.8g/dl, $p <$

0.001), transferrin[243mg/dl(158-277), $p < 0.005$] and C-H index (0.91 \pm 0.20g/d/m, $p < 0.05$) were also lower in these patients than in normal subjects.

CRF patients with nephrotic range proteinuria($>$3.5g/d, n=19) had lower serum albumin(2.8 ± 0.6g/dl vs. 3.8 ± 0.8g/dl, $p < 0.0001$) and prealbumin (27 ± 9mg/dl vs. 32.9mg/dl, $p < 0.05$) than those with proteinuria less than nephrotic range(Table 2).

CRF patients with lower DPI(n=15, <0.6kg/kg/d) showed significantly worse nutritional indices than patients with higher DPI(n=49, >0.6kg/kg/d) [serum albumin 2.9 ± 0.7g/dl vs. 3.6 ± 0.8g/dl, $p < 0.005$; transferrin 147mg/dl(134-179) vs. 220mg/dl(182-

Table 2. Nutritional Indices of Patients with Chronic Renal Failure : Nephrotic vs Non-nephrotic

	Nephrotic Proteinuria (n=19)	Non-Nephrotic proteinuria(n=45)	p value
Proteinuria(g/day)	6.8 ± 2.4	1.5 ± 1.0	-
Ccr(ml/min)	17 ± 7	20 ± 11	NS
DPI(g/kg/day)	0.77 ± 0.18	0.82 ± 0.31	NS
Total CO_2(mEq/L)	21 ± 3	20 ± 4	NS
BMI(kg/m^2)	23 ± 3	23 ± 3	NS
Albumin(g/dl)	2.8 ± 0.6	3.8 ± 0.8	<0.0001
Transferrin(mg/dl)	184(149-220)	217(162-264)	0.07
Prealbumin(mg/dl)	27 ± 9	32 ± 9	<0.05
IGF-1(ng/ml)	190(93-313)	192(129-446)	NS
C-H index(g/d/m)	0.77 ± 0.24	0.80 ± 0.27	NS

Table 1. Nutritional Indices of Patients with Chronic Renal Failure and Normal Subjects

	CRF patients (n=64)	Normal subjects (n=42)	p value
DPI(g/kg/day)	0.80 ± 0.27	1.07 ± 0.30	<0.0001
Proteinuria(g/day)	3.0 ± 2.9	0.1 ± 0.1	<0.0001
Total CO_2(mEq/L)	20 ± 4	24 ± 2	<0.0001
Albumin(g/dl)	3.5 ± 0.8	4.5 ± 0.4	<0.0001
Transferrin(mg/dl)	207(157-245)	292(258-316)	<0.0001
Prealbumin(mg/dl)	30 ± 9	29 ± 7	NS
IGF-1(ng/ml)	190(123-338)	216(151-325)	NS
C-H index(g/d/m)	0.79 ± 0.26	1.03 ± 0.22	<0.0001

Abbreviation : BMI, body mass index; DPI, dietary protein intake; IGF-1, insulin-like growth factor-1; C-H index, creatinine-height index

Table 3. Nutritional Indices of Patients with Chronic Renal Failure According to Dietary Protein Intake

	Lower DPI (<0.6g/kg/d) (n=15)	Higher DPI (>0.6g/kg/d) (n=49)	p value
DPI(g/kg/day)	0.50 ± 0.10	0.90 ± 0.24	-
DM/NonDM	6/9	14/35	NS
Ccr(ml/min)	15 ± 11	21 ± 10	0.06
Proteinuria(g/day)	3.3 ± 2.5	3.0 ± 3.0	NS
Total CO_2(mEq/L)	20 ± 4	20 ± 4	NS
BMI(kg/m^2)	20 ± 2	23 ± 3	<0.0001
Albumin(g/dl)	2.9 ± 0.7	3.6 ± 0.8	<0.005
Transferrin(mg/dl)	147(134-179)	220(182-264)	<0.0005
Prealbumin(mg/dl)	24 ± 8	32 ± 9	<0.001
IGF-1(ng/ml)	123(66-261)	226(140-344)	<0.05
C-H index(g/d/m)	0.52 ± 0.15	0.87 ± 0.23	<0.0001

264), $p < 0.0005$; prealbumin $24 \pm 8mg/dl$ vs. $32 \pm 9mg/dl$, $p < 0.001$; IGF-1 123ng/ml(66-261) vs. 226ng/mg(140-344), $p < 0.05$; C-H index $0.52 \pm 0.15g/d/m$ vs. $0.87 \pm 0.23g/d/m$, $p < 0.0001$] although there was no significant difference in the amount of proteinuria between the two groups($3.3 \pm 2.5g/$ day vs. $3.0 \pm 3.0g/day$) (Table 3).

Diabetic patients(n=20) had worse nutrition than non-diabetic patients[serum albumin $2.8 \pm 0.6g/dl$ vs. $3.8 \pm 0.8g/dl$, $p < 0.0001$; transferrin 176mg/dl (148-214) vs. 220mg/dl(175-266), $p < 0.05$; prealbumin $24 \pm 10mg/dl$ vs. $33 \pm 8mg/dl$, $p < 0.0005$; IGF-1 138ng/ml(69-269) vs. 231ng/ml(140-364), p < 0.005).

Diabetic patients had more severe proteinuria ($5.1 \pm 3.2g/day$ vs. $2.1 \pm 2.2g/day$, $p < 0.0001$) and less intake of dietary protein ($0.70 \pm 0.16g/kg/day$ vs. $0.85 \pm 0.31g/kg/day$, $p < 0.05$) than non-diabetic patients(Table 4).

In the analysis of correlation, DPI was significantly related with serum albumin(r=0.52, $p < 0.0001$), transferrin(r=0.51, $p < 0.0001$), prealbumin(r= 0.55, $p < 0.0001$), IGF-1(r=0.40, $p < 0.005$) and C-H index(r=0.67, $p < 0.0001$) in CRF patients(Table 5). DPI(r=0.44, $p < 0.0005$), serum albumin(r=0.39, $p < 0.005$), prealbumin(r=0.30, $p < 0.05$), transferrin(n= 0.27, $p < 0.05$) and C-H index(r=0.51, $p < 0.0001$) were positively correlated with creatinine clearance in CRF patients, but IGF-1 were not.

DISCUSSION

The results of the present study reveal that a high proportion of patients with pre-dialysis chronic

Table 4. Nutritional Indices of Patients with Chronic Renal Failure : Diabetic vs Non-diabetic

	Diabetic (n=20)	Non-diabetic (n=44)	p value
Ccr(ml/min)	14 ± 8	21 ± 11	<0.05
DPI(g/kg/day)	0.70 ± 0.16	0.85 ± 0.31	<0.05
Proteinuria(g/day)	5.1 ± 3.2	2.1 ± 2.2	<0.0001
Total CO_2(mEq/L)	21 ± 3	19 ± 4	NS
BMI(kg/m^2)	21 ± 3	23 ± 3	<0.05
Albumin(g/dl)	2.8 ± 0.6	3.8 ± 0.8	<0.0001
Transferrin(mg/dl)	176(148-214)	220(175-266)	<0.05
Prealbumin(mg/dl)	24 ± 10	33 ± 8	<0.0005
IGF-1(ng/ml)	138(69-269)	231(140-364)	<0.05
C-H index(g/d/m)	0.66 ± 0.23	0.85 ± 0.25	<0.005

Table 5. Correlation Coefficients between Nutritional Indices and Parameters of Patients with Chronic Renal Failure(r_s and p value are presented)

	SA	TF	PA	IGF-1	C-H
BMI	0.32	0.31	0.35	--	0.49
	<0.05	<0.05	<0.01	--	<0.0001
DPI	0.52	0.51	0.55	0.40	0.67
	<0.0001	<0.0001	<0.0001	<0.005	<0.0001
Ccr	0.39	0.27	0.29	--	0.51
	<0.005	<0.05	<0.05	--	<0.0001
Proteinuria	-0.68	-0.40	-0.30	--	--
	<0.0001	<0.005	<0.05	--	--
Total CO_2	--	--	--	--	--
	--	--	--	--	--
SA	--	0.68	0.65	0.44	0.49
	--	<0.0001	<0.0001	<0.0005	<0.0001
TF	--	--	0.56	0.45	0.37
	--	--	<0.0001	<0.0005	<0.005
PA	--	--	--	0.48	0.53
	--	--	--	<0.0005	<0.0001
IGF-1	--	--	--	--	0.29
	--	--	--	--	<0.05

Abbreviation : SA, serum albumin; TF, transferrin; PA, prealbumin; IGF-1, insulin-like growth factor-1; C-H, creatinine-height index; BMI, body mass index; DPI, dietary protein intake; Ccr, creatinine clearance

renal failure on unrestricted diet take low protein and have worse nutritional indices.

The finding of this study is quite different from the previous observation[14] that patients with chronic renal insufficiency who were not on maintenance dialysis do not develop protein calorie malnutrition. This discrepancy may be due to the different inclusion criteria considering that patients with advanced malnutrition were excluded from participation in the previous study. Our result shows that patients with chronic renal insufficiency tend to reduce protein intake if they are left on an unmodified diet. This tendency was observed even in patients with moderate renal insufficiency and was definite in patients with severe renal failure. This is also consistent with the report of Guarnieri et al[13] that protein intake was reduced in 8 patients with early renal failure on an unrestricted diet.

Low protein intake was associated with significant worsening of various nutritional indices in this study. Protein restriction has been the main focus of recent studies in the nutritional management of chronic renal failure since there was substantial evidence that low protein diet may slow the rate of progression of renal falilure in patients with moderate chronic renal insufficiency[17-22]. The protein requirement in pre-dialysis patients with chronic renal failure was suggested to be 0.55 to 0.60g/kg/day with about two-thirds of the protein being of high biologic value[23]. One concern about prolonged protein restriction was that it may cause protein malnutrition. Some reported that prolonged protein restriction was associated with change in several indices of nutrition such as fall in serum protein, urea, phoshorus and reduction of muscle mass[13, 14, 24, 25]. Others reported that low protein diet did not cause protein malnutrition or could prevent and correct malnutrition rather than cause it[17, 26-29].

The recent report of the Modification of Diet in Renal Disease Study[30] of a large number of patients with chronic renal insuffciency demonstrated only a small difference between the diet groups in changes in weight and serum concentrations of albumin, transferrin and cholesterol. In view of these results, the deficient protein intake might have contributed in part to the worse

nutritional indices in the patient group with low protein intake, but the impact does not seem to be great. On the other hand, low protein intake may reflect the inadequate total nutritional intake. Although the calorie intake was not calculated in our patients, previous reports[13, 14] that patients with lower glomerular filtration rate tended to have lower energy intake support this possibility.

Patients with nephrotic proteinuria also had worse nutritional indices despite similar dietary protein intake and creatinine clearance compared with those who had mild proteinuria. In contrast to dietary protein intake, however, heavy proteinuria was accompanied by reduction in serum albumin and prealbumin only. The correlation of nutritional indices was also less prominent with the amount of proteinuria than with dietary protein intake. These findings suggest that reduced dietary intake may have a more important role in causing nutritional deficit in these patients than the amount of proteinuria.

Diabetic pateints had worse nutritional indices with less protein intake than non-diabetic patients. This may be in part due to the inclusion of patients with more advanced renal failure. In addition, the heavy proteinuria is known to persist until the renal insufficiency progresses to end-stage. Diabetic patients in this study also had more severe proteinuria. Anorexia and other symptoms caused by diabetic gastroenteropathy can reduce their oral intake, too. These factors also could contribute to their poor nutrition.

Malnutrition is known to be associated with increased morbidity and mortality in dialysis patients. Our results demonstrate that nutritional problems begin to develop even in the stage of moderate renal insufficiency and become significant before initiation of dialysis therapy if appropriate intervention to prevent malnutrition is not done. Malnutrition developed before maintenance dialysis may have an adverse effect on the morbidity and mortality of dialysis patients.

Nutritional indices which can detect even an early change are needed for appropriate intervention of malnutrition. However, it has some limitations in applying the currently available indices in the assessment of the nutritional status of patients with chronic renal failure. Traditionally

well known anthrophometric measurements have some flaws in detecting the early malnutrition in patients who are not at their estimated dry weight[12]. Therefore, C-H index or biochemical parameters may be more useful and easy in assessing the nutritional status, especially in edematous patients. Serum albumin level has been regarded as a good nutritional indicator in persons with normal kidney, but is also affected by renal disease in CRF patients, thus making the interpretation of it difficult. Due to the relatively long half-life and the vast capacity of the liver to synthesize it, the level of serum albumin responds slowly to nutritional changes[31]. As tools for early detection of malnutrition, many kinds of nutritional markers have been suggested. Recently, pre-albumin level was suggested as a sensitive marker for early malnutrition in hemodialysis patients[32]. However, its usefulness to detect the malnutrition in pre-dialysis condition was not widely studied. Prealbumin is metabolized and excreted by the kidney[12]. Therefore, the level of prealbumin might be influenced by the renal function. Serum transferrin level is also used as a tool for early detection of malnutrition[33], but it can be affected by iron status. IGF-1 has been shown to be a good indicator of malnutrition in hemodialysis patients[34], but may also be influenced by the renal function[34, 35] C-H index has been used as an indicator of muscle mass[36]. The interpretation of C-H index is somewhat complicated in severe renal failure in view of the fact that creatinine degradation tends to rise when serum creatinine level is above 10mg/dl[37]. For now, no single index can correctly represent the nutritional status of patients with chronic renal failure, and serial monitoring of several nutritional parameters is needed for better detection of malnutrition.

In conclusion, a high proportion of patients with pre-dialysis chronic renal failure seems to have nutritional problems, as assessed by anthropometric and biochemical nutritional indices when they are left on an unmodified diet. Malnutrition may have an adverse effect on morbidity and mortality in the long run. The effort to detect and correct malnutrition should be made in patients with chronic renal failure even before initiation of maintenance dialysis.

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