The Changing Role of Dietary Protein Restriction in Management of Chronic Kidney Disease (CKD)

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Abstract
In the last 5 to 6 decades there has been a marked variation in use of dietary protein restriction (DPR) in treatment of patients with chronic kidney disease (CKD). Before availability of renal replacement therapy (RRT), DPR restriction was widely practised in uraemic patients to reduce generation of nitrogenous waste products and ameliorate uraemic symptoms. With availability of RRT, the interest in DPR was lost. There was a resurgence of interest in DPR when animal experimental studies suggested that DPR can retard the progression of CKD. Then there was concern about worsening nutritional status with DPR. This article reviews how the role of DPR in treatment of CKD as perceived by physicians has varied over the years and suggests a strategy that should be followed in India considering that RRT is available to a very small percentage of cases developing end stage kidney disease (ESKD).

Introduction

Kidneys perform the important function of excreting nitrogenous waste products and regulating the volume and composition of body fluids. When kidney function is impaired, these functions are affected. There is retention of nitrogenous waste products and disturbance in fluid, electrolyte and acid-base balance. Dietary modification can minimise these changes. Hence dietary modification is important in management of patients with chronic kidney disease (CKD). In dietary modification, protein restriction, which was once the main modification for patients with CKD, is now of debatable value. This article discusses how the role of dietary protein restriction, as perceived by medical fraternity, has changed over the years.

Role of Dietary Protein Restriction before the Availability of Renal Replacement Therapy (RRT) – Before 1960

About 65 years ago, using analogy of myocardial hypertrophy in response to systemic hypertension, Addis reasoned that nephron “overwork” (by maintaining usual protein intake in face of decreased kidney function) could, over time prove maladaptive. He went on to suggest that severity of CKD could be ameliorated by reducing the excretory burden on diseased kidney through dietary protein restriction. Indeed, in absence of availability of any form of renal replacement therapy (RRT), dietary protein restriction was the main treatment for CKD.

Role of Dietary Protein Restriction after the Availability of Renal Replacement Therapy (RRT) - After 1960

In the early stages of CKD when the patient would be asymptomatic, dietary protein restriction would be seldom prescribed. A diet restricted in protein would usually be prescribed only when the CKD was advanced and patient symptomatic. A stringent diet at this stage would make it difficult for the patient to follow. Often it would lead to worsening nutritional status and increasing weakness. With the availability of RRT
Role of Dietary Protein Restriction in 1970s

There was resurgence of interest in dietary protein restriction when it was realised that such dietary modification not only reduces generation of end products of protein breakdown but may retard the rate of progression of CKD.

In 1970s it was realised that the progression of CKD involves not only persistence of underlying aetiology but also a set of mechanisms that are a common consequence following long term reduction of renal mass, irrespective of aetiology. The important role of these mechanisms was realised when it was observed that CKD continued to progress even when the aetiology that caused initial kidney injury subsided. For example, women who developed post partum cortical necrosis and stabilised at a lower level of kidney function, went on to have progressive decline in kidney function despite complete resolution of coagulopathy that caused cortical necrosis.

To understand this phenomenon, studies were conducted in animal models in which the functioning kidney mass was surgically reduced. These models have reduced renal mass but no underlying kidney disease.

In 1974, Deen et al. described dynamics of glomerular ultrafiltration in the rat uninephrectomy model. They observed significant haemodynamic changes in the form of renal arteriolar vasodilatation and increased glomerular capillary flow and pressure. This occurred because vascular resistance reduced in the afferent and efferent arterioles, allowing the increase in the glomerular capillary plasma flow rate (QA). Because the decrease in afferent arteriolar resistance (RA) is proportionally greater than that in efferent arteriolar resistance (RE), the hydraulic pressure in the glomerular capillary increases. Together these increases in glomerular plasma flow and glomerular capillary hydraulic pressure (Pc) account for the increase in SNGFR.

In 1975, Shimamura and Morrison described morphological changes in rats in response to decreased kidney mass. They removed 80-85% of kidney mass in adult rats and then performed serial histopathological studies. Progressive glomerulosclerosis developed in initially normal remnant glomeruli. Further, the pace of development of glomerular pathology was directly proportional to the degree of ablated kidney mass.

Hostetter et al performed micropuncture studies in three groups of male Munich-Wistar rats 1 wk after surgery: group I, eight control rats that underwent laparotomy and were fed a normal diet; group II, nine rats that underwent right nephrectomy and segmental infarction of five-sixths of the left kidney and were fed a normal diet; and group III, seven rats in the form of dialysis and transplantation, the interest in dietary protein restriction waned.
that underwent the same renal ablative procedure and were fed a low protein diet. Single nephron glomerular filtration rate (SNGFR) was higher in the remnant kidney of group II rats compared with group I rats due to higher mean glomerular transcapillary hydraulic pressure. Glomeruli in remnant kidneys of group II showed striking alterations in morphology, including epithelial cell protein reabsorption droplets, foot process fusion, and mesangial expansion. Group III rats demonstrated a mean SNGFR not statistically different from that of group I, but significantly less than that of group II rats. The glomerular structural lesions seen in group II were also largely attenuated in group III. The authors suggested that alterations in glomerular haemodynamics associated with renal ablation are accompanied by structural lesions and that sustained single nephron hyperfiltration may have maladaptive consequences by damaging remnant glomeruli.

**Role of Dietary Protein Restriction in 1980s**

Based on observations in animal experimental studies, Brenner et al. proposed a hypothesis. They proposed that when the functioning renal mass is reduced, haemodynamic changes develop in the remnant nephrons. These changes, which partially offset the loss of function that would result, are compensatory or adaptive. It is these adaptive changes that contribute to progressive deterioration in renal function (Figure 1). Restricting dietary protein can minimise the adaptive changes and thereby retard progressive deterioration in renal function.

Brenner’s hyperfiltration hypothesis prompted studies with dietary protein restriction (DPR) in human subjects with CKD. Three forms of nutritional regimens were used:

1. Low-protein diet containing 0.6 gm protein/kg body weight/day of primarily high quality protein
2. A very low-protein diet supplemented with essential amino acids
3. A very low protein diet supplemented with ketoacids

Supplementation with essential amino acids allows prescribing a protein intake below the minimum daily requirement (0.6 g protein/kg/day) because requirements are met by the supplements.

Walser suggested the use of deaminated EAA, the alpha-ketoanalogues, in order to achieve an extreme reduction in protein intake. The alpha-ketoanalogues are simply carbon chains lacking any amino group. These ketoanalogues do not contain nitrogen and do not generate nitrogenous by-products. At the same time alpha-ketoanalogues are acceptors for amino groups and can be rebuilt to corresponding amino acids. In the transamination reaction which leads to this formation, urea-generating non-essential amino acids like glutamine and alanine, are used as amino group donators.

How to assess the effect of DPR on the course of CKD in human subjects? In 1976, Mitch et al. proposed that in patients with CKD, GFR declines at a constant rate. Since GFR is directly proportional to reciprocal of serum creatinine (1/cr), slope of 1/cr vs. time can be used to measure the rate of progression. They further proposed that change of slope after therapeutic intervention could be used to assess the effect of therapeutic intervention.

Figure 2 shows how the effect of therapeutic intervention on the progression of CKD was assessed. To the left of vertical line in the slope of 1/cr vs. time before intervention and to the right is the slope after intervention. If the slope became less steep, it means beneficial effect of the intervention. If the slope becomes more steep, it means detrimental effect of intervention.

**Role of Dietary Protein Restriction in 1990s**

There were 2 major limitations of the studies in human subjects done in 1980s:

1. Use of creatinine as a marker of kidney function and reciprocal of creatinine vs. time to determine rate of decline in kidney function. We now know that creatinine is not an ideal marker of kidney function.
Multiple factors determine S.creatinine level, namely-

a. Creatinine generation (which depends on muscle mass, creatine and creatinine intake in the diet and creatinine synthesis)

b. Creatinine loss (which depends on GFR, Tubular secretion and Extrarenal loss)

c. Volume of distribution

This is explained in Figure 3. The figure shows that there is a constant rate of decline in creatinine clearance (5 ml/min/year). However when creatinine generation is reduced, a plot of reciprocal of creatinine vs. time gives the false impression that rate of decline in kidney function is retarded.

2. Presumption that the rate of decline in 1/cr is constant as proposed by Mitch et al. Shah and Levey have shown that spontaneous changes in the decline of 1/cr do occur. This makes it difficult to determine whether the change in slope is a spontaneous phenomenon or a result of therapeutic intervention. This also makes it inappropriate to use the patient as his own control. Figure 4 shows plot of 1/cr vs. time in a representative case. Panel A shows a single best fit regression line. Panel B shows 2 best-fit regression lines with an intersection at 26 months (vertical dashed line). A spontaneous change in slope has occurred at 26 months without any intervention. Had an intervention been made around that time, change in slope would have been attributed to that.

Keeping in mind limitations of earlier studies, a prospective multi-centre trial - the modification of Diet in Renal Disease (MDRD) Study was performed in the USA. In this study, which was divided in two parts, 585 patients were included in study A and 255 patients were included in study B. Study A included patients with GFR 25 to 55 ml/min and they were prescribed usual (1.3 gm/kg/day) or low protein (0.58 gm/kg/day). Study B included patients with GFR 13 to 24 ml/min and they were prescribed low protein diet (0.58 gm/kg/day) or very low protein diet (0.28 gm/kg/day) supplemented with ketoanalogues. In both Study A and B, diabetics were excluded. Kidney function was assessed from GFR measured as renal clearance of Iothalamate. Figure 5 (a) (b) show the result of MDRD study A and B. It was interpreted that there was some slowing in the rate of decline in GFR in study A and no significant difference in the rate of decline in GFR in study B.

When the MDRD study was published, we were looking at dietary protein intake in our stable patients with CKD stage 4 and 5. We observed that most of our subjects were predominantly vegetarians and their mean ± 1 SD protein intake was 0.64 ± 0.15 gm/kg/day on an unrestricted diet. We extended this study to include larger number of subjects and this again confirmed that their dietary protein intake was low (0.65 ± 0.15) gm/kg/day. Based on the interpretation of MDRD study and our observations of lower protein intake by Indian subjects with CKD stage 4 and 5,
we felt that there was limited role for dietary protein restriction in Indian subjects with CKD.

Role of Dietary Protein Restriction After 2000

In 2002, Kher\textsuperscript{16} reported that less than 10% of ESRD patients in India are fortunate to be able to initiate RRT. A majority of those who initiate are lost to follow up and only about 1% are fortunate to go through transplant. Similar observation was reported by Agarwal.\textsuperscript{17} These observations made us realise that it is very important to retard progression of CKD and delay the need for RRT in Indian subjects with CKD.

We reviewed the MDRD study A and felt that dietary protein restriction does significantly retard the rate of progression of CKD. This is shown in Figure 6. The figure shows that in study A patients, there was a rapid decline in kidney function in subjects with low protein diet for the first four months. This was haemodynamically mediated. After 4 months the rate of decline in kidney functions in patients with protein restriction was slower than in those on usual protein diet. Had the study been continued further, it would have been possible to appreciate beneficial effect of dietary protein restriction.\textsuperscript{18}

Indeed, secondary analysis of the MDRD study A and felt that dietary protein restriction does significantly retard the rate of progression of CKD. This is shown in Figure 6. The figure shows that in study A patients, there was a rapid decline in kidney function in subjects with low protein diet for the first four months. This was haemodynamically mediated. After 4 months the rate of decline in kidney functions in patients with protein restriction was slower than in those on usual protein diet. Had the study been continued further, it would have been possible to appreciate beneficial effect of dietary protein restriction.\textsuperscript{18}

A meta-analysis\textsuperscript{20} to assess the efficacy of dietary protein restriction in previously published studies of diabetic and nondiabetic renal diseases also suggests beneficial effect of dietary protein restriction. A total of 1413 patients in five studies on nondiabetic renal disease (mean length of follow-up, 18 to 36 months) and 108 patients in five studies of type I diabetes mellitus (mean length of follow-up, 9 to 35 months) were included in this study. The relative risk for progression of renal disease in patients receiving a low-protein diet was compared with patients receiving a usual-protein diet. In five studies of nondiabetic renal disease, a low-protein diet significantly reduced the risk for renal failure or death (relative risk, 0.67 [95% CI, 0.50 to 0.89]. In five studies of insulin-dependent diabetes mellitus, a low-protein diet significantly slowed the increase in urinary albumin level or the decline in glomerular filtration rate or creatinine clearance (relative risk, 0.56 [CI, 0.40 to 0.77]. Tests for heterogeneity showed no significant differences in relative risk among studies of either diabetic or nondiabetic renal disease. No significant differences were seen between diet groups in pooled mean arterial blood pressure (diabetic and nondiabetic patients) or glycosylated haemoglobin level (diabetic patients only). The authors concluded that dietary protein restriction effectively slows the progression of both diabetic and nondiabetic renal diseases.

Prakash et al\textsuperscript{21} conducted a randomised. Double-blind, placebo controlled trial to evaluate efficacy of VLPD supplemented with KA in patients with CKD. Thirty-four patients were randomised to 2 comparable groups in terms of age, sex distribution, aetiology of CKD, blood pressure control, use of angiotensin converting enzyme inhibitors, GFR and body mass index (BMI). Subjects randomly received either 0.6 gm/kg/day protein plus placebo (n = 16) or 0.3 gm/kg/day protein plus placebo (n = 18).
**Fig. 6**: Because of initial rapid decline in GFR which was haemodynamically mediated, although subsequent rate of decline was slower in subjects prescribed a low protein diet (solid line), the absolute decrease in GFR was not significantly different when compared to subjects allowed usual protein diet over a follow-up period of 36 months (F36). If the study had been continued further, it would have been possible to see the beneficial effect of low protein diet (LPD) compared to usual protein diet (UPD).

protein plus tablets of KA (Ketosteril; Fresenius Kabi, Germany) for 9 months. The mean GFR at baseline in the KA group and control group was 28.1 ± 8.8 and 28.6 ± 17.6 ml/min/1.73 m² respectively. At the end of the study it was 27.6 ± 10.1 and 22.5 ± 15.9 ml/min/1.73 m² respectively. Thus there was a significant drop in GFR in the control group. In both groups there was no significant change in the BMI after the study.

Based on above observations, we feel that dietary protein restriction retards rate of progression of CKD. In addition, it minimises metabolic changes. Because of both these factors, it delays need for RRT. The benefit is likely to be much more when dietary protein restriction is introduced at an early stage of CKD.

It is important to select the subjects properly. Dietary protein restriction should not be prescribed to those with stable (non-progressive) CKD; to those with poor appetite, weight loss and BMI < 17.5 kg/m²; to those with comorbid conditions like infection, malignancy and cardiac failure; to those who are soon to go for kidney transplant.

The biggest concern about prescribing dietary protein restriction is the risk of malnutrition. This actually is not due to decreased protein intake but due to decreased energy intake. In the MDRD study, before the patients were randomised to different diet groups it was observed that energy intake declined before the patients were randomised to different diet due to decreased energy intake. In the MDRD study, actually is not due to decreased protein intake but protein restriction is the risk of malnutrition. This likely to go for kidney transplant.

In summary, role of dietary protein restriction in management of patients with CKD has waxed and waned over the last few decades. Before the availability of RRT, DPR was the main treatment for patients with CKD. With availability of RRT its role waned. There was resurgence of interest in DPR when it was observed in animal studies that DPR retards the rate of progression of CKD. This enthusiasm was blunted by initial interpretation of MDRD study that DPR is of limited value. Reanalysis of MDRD study and meta-analysis of studies of DPR suggest a beneficial effect of DPR in retarding progression of CKD with little risk of malnutrition.

What should be our approach at present? Considering that DPR retards progression of CKD and decreases generation of nitrogenous waste products, it should be prescribed to delay the need for RRT. This has an important practical implication for an economically poor country like ours where RRT is available to a very small percentage of patients developing end stage kidney disease. It should be stressed that DPR should be prescribed from an early stage (stage 3) of progressive CKD to achieve substantial benefit of DPR and patients should be properly selected.

**References**

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