Impact Of Malnutrition And Comorbidities On Survival Of Peritoneal Dialysis Patients
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Abstract:
Protein energy malnutrition (PEM) and muscle wasting are present in a large proportion of patients with chronic kidney disease. Peritoneal dialysis (PD) is an established modality of renal replacement therapy worldwide. Comorbidities and malnutrition are common and highly prevalent at the commencement of PD therapy. PEM and associated co-morbid conditions are amongst the several important factors affecting the survival of these patients. Major co-morbidities such as cardiovascular disease and diabetes mellitus have strong influence on mortality. Co-morbid conditions and clinical outcomes are closely associated. The associated co-morbidities in PD patients are not only important risk factors for increased morbidity and mortality, but also for the development of malnutrition. The prevalence of malnutrition in patients with comorbidities is high, compared with patients without comorbidities. Co-morbidities in PD patients can vary both in number and severity. Therefore the confounding effect of comorbidities should be quantified or stratified to assess its impact on various clinical outcomes including survival of these patients. Malnutrition and comorbidities either independently or in combination affect the survival of these patients. Patients with both malnutrition and comorbidities showed the worst survival. Nutritional assessment and nutritional counselling should be done periodically to improve the nutrition status of PD patients. Associated comorbidities should be properly treated to improve clinical outcomes in these patients.

Keywords: Peritoneal Dialysis, Malnutrition, Co-morbidities, Survival

Introduction:
Protein energy malnutrition (PEM) and muscle wasting are present in a large proportion of patients with chronic kidney disease (CKD). This may be a consequence of urernia per se or related to co-morbid conditions(1). End-Stage Renal Disease (ESRD) patients suffer from multiple nutritional and metabolic abnormalities, leading to significant changes in their nutrition status and complications of malnutrition (2).

Prevalence of Malnutrition:
Table 1 shows the prevalence of malnutrition in different studies reported from different part of the world. The
Table 1: Prevalence Of Malnutrition In Different Studies

<table>
<thead>
<tr>
<th>References</th>
<th>Patients</th>
<th>Age</th>
<th>Region</th>
<th>MALNUTRITION %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Mild-Moderate</td>
</tr>
<tr>
<td>Young et al, 1991 (7)</td>
<td>224</td>
<td>53.4</td>
<td>Europe and North America</td>
<td>32.6</td>
</tr>
<tr>
<td>Cianciaruso et al, 1995 (11)</td>
<td>224</td>
<td>60.2</td>
<td>Italy</td>
<td>34.9</td>
</tr>
<tr>
<td>CANUSA, 1996 (6)</td>
<td>680</td>
<td>54.3</td>
<td>Canada, USA</td>
<td>44.6</td>
</tr>
<tr>
<td>Chung et al, 2000 (14)</td>
<td>91</td>
<td>47.9</td>
<td>Korea</td>
<td>44.9</td>
</tr>
<tr>
<td>Kumano and Kawaquchi, 2000 (15)</td>
<td>239</td>
<td>50.0</td>
<td>Japan</td>
<td>26.2</td>
</tr>
<tr>
<td>Wang et al, 2001 (16)</td>
<td>242</td>
<td>55.0</td>
<td>Hong Kong</td>
<td>40.1</td>
</tr>
<tr>
<td>Kang et al, 2002 (17)</td>
<td>127</td>
<td>50.7</td>
<td>Korea</td>
<td>34.7</td>
</tr>
<tr>
<td>Prasad et al, 2008 (13)</td>
<td>283</td>
<td>50.0</td>
<td>India</td>
<td>67.8</td>
</tr>
</tbody>
</table>

Causes Of Malnutrition:

Malnutrition is multifactorial and is often associated with reduced food intake (18). The major causes have been shown in fig.1. Inadequate food and nutrients intake, increased losses of nutrients in PD effluent and increased catabolism associated with renal failure are the main reasons of development of malnutrition in these patients. The possible causes of decreased energy and protein intake in PD patients are uremia per se; gastrointestinal symptoms like nausea, vomiting, altered taste, constipation, gastroparesis and abdominal discomfort; medications; peritonitis and other infections; other comorbid illnesses; dialysate glucose absorption; unpalatable or inadequate diet; and sometimes continuation of pre-dialysis protein restricted diet. Associated

Fig1: Major Causes Of Malnutrition In PD Patients.
Comorbid conditions or superimposed illness, endogenous uremic toxins, drug-nutrient interactions, endocrine disorders, psychological and socioeconomic factors may also contribute to the development of malnutrition (19). Persistent metabolic acidosis increased catabolism and thus also contribute to development of malnutrition (20,21,22). Losses of proteins into dialysate reported to be approximately 5 to 15 g/d in PD and protein losses increase with episodes of peritonitis (23). Loss of amino acids in peritonial effluent also significantly contributes to daily loss of nutrients. Absorption of dialysate glucose and abdominal distension by the dialysate fluid further decrease the appetite leading to decreased nutrient intake (24,25).

**Diagnosis of Malnutrition:**

The diagnosis of malnutrition is not straightforward. The details of diagnosis of malnutrition are beyond the scope of the present review. No single measure can provide a comprehensive evaluation of the nutrition status of PD patients (26). It cannot be assessed properly with a single test or by an evaluation at a single time point. The frequency of using these measures has not been verified, but a 6 monthly review is desirable. Serum albumin, pre-albumin, creatinine and creatinine index, dietary interviews and diaries, protein equivalent of nitrogen appearance (nPNA), subjective global assessment (SGA), anthropometry and dual-energy X-ray photon absorptiometry (DEXA) are all measures utilized to assess nutritional status. The patients should be screened for malnutrition with a combination of nutritional measures on a regular basis (23). Assessment of nutritional status is of utmost importance for the diagnosis and prevention of protein-energy malnutrition, evaluation of nutritional requirements, development of alternative patient specific nutritional therapies, comparing the changes in nutritional status with baseline and previous values for future evaluation and finally monitoring of the effects of the treatment (27).

**Classification Of Malnutrition:**

Protein malnutrition, energy malnutrition, and protein energy malnutrition are the important types of malnutrition are associated with PD. Low muscle mass and low serum proteins is caused by protein malnutrition. Energy malnutrition usually results in decreased body weight, low fat mass, and low carbohydrate stores. Majority of these patients show a combination of protein and energy malnutrition (27). Stenvinkel et al proposed two types of malnutrition: the first one that is associated with poor nutritional intake because of uremic syndrome per se and it improves with dialysis; and the second type is often associated with significant comorbidity and inflammation and it is refractory to improvement with dialysis (28). The major differences between these two types of malnutrition have been shown in table 2.

**Table 2: Summary Of The Differences In Clinical And Biochemical Characteristics Between Two Types Of Malnutrition**

<table>
<thead>
<tr>
<th></th>
<th>TYPE 1 Malnutrition</th>
<th>TYPE 2 Malnutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. Albumin</td>
<td>Normal / Low</td>
<td>Low</td>
</tr>
<tr>
<td>Co-Morbidity</td>
<td>Uncommon</td>
<td>Common</td>
</tr>
<tr>
<td>Presence of Inflammation</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Food intake</td>
<td>Low</td>
<td>Low / Normal</td>
</tr>
<tr>
<td>Resting energy expenditure</td>
<td>Normal</td>
<td>Elevated</td>
</tr>
<tr>
<td>Oxidative stress</td>
<td>Increased</td>
<td>Markedly</td>
</tr>
<tr>
<td>Protein catabolism</td>
<td>Decreased</td>
<td>Increased</td>
</tr>
<tr>
<td>Reversed by Dialysis &amp; Nutrition</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Impact of malnutrition on clinical outcomes and survival of PD patients:

Renal patients with malnutrition or any parameter indicating the compromised nutrition status are associated with increased morbidity and mortality (29). Certain measures of nutrition status are closely associated with clinical outcome (30-32). A close relationship between malnutrition,
hospitalization, and mortality has been documented in various studies (32,33). Subjective Global Assessment (SGA) of nutrition status is strongly associated with survival of PD patient (6,7). However it is difficult to distinguish definite nutrition-related causes for morbidity or mortality. Malnutrition is rarely reported as a direct cause of death, however there is evidence to support that the nutrition status in renal failure patients plays a crucial role in the outcome of these patients (34).

The famous CANUSA Study Group (35) has observed that there is 25% increase in the relative risk of mortality with each one unit decrease in the SGA score. The 2-year patient-survival rates in patients with normal nutrition, mild to moderate malnutrition, and severe malnutrition were 80.5%, 77.3%, and 47.2%, respectively (35). A 1% difference in % LBM is associated with a 3% change in the relative risk of death (6). Other studies also supported the evidence that malnutrition at the initiation of chronic dialysis therapy is a significant risk factor for mortality during the subsequent follow-up (36,37). In our published data (38), we have also observed that the mean survival (patient-months) in patients with normal nutrition [58 (95% CI 51.9 - 65.7)] was superior to malnourished patients [42 (95% CI 37- 47; p=0.001)] (Fig.3). The relative risk of death in patient with malnutrition [RR 3.2 (95% CI 1.6 - 6.3), p=0.001] was significantly high, compared to that of patients with normal nutritional status.

Chung et al (14) have also reported the malnutrition as a significant predictor of mortality in a study on 91 consecutive PD patients. The 2-year patient survival was significantly superior in normal patients compared to that of malnourished patients (91.7% versus 67.1%, p = 0.02). They have also reported that patients with normal nutritional status had significantly higher fat free edema free body mass, % lean body mass, blood urea nitrogen, and serum albumin as compared to that of malnourished patients.

CANUSA study group have also shown that serum albumin level is a powerful predictor of mortality in PD patients (6). Lower serum albumin level was associated with increased technique failure and hospitalization rates in PD patients (6, 35). Several other studies also shown that low serum albumin is a predictor of patient and technique survival in PD patients (39,40). However, the use of serum albumin alone as marker of nutrition status is limited because of fluctuations in serum albumin level due to catabolic state and hydration status. National Kidney Foundation–Kidney Disease Outcomes and Quality Initiative (NKF-KDOQI) nutrition guidelines recommended the use of additional markers to complement serum albumin (41). The Kidney Disease Outcomes Quality Initiative (KDOQI) guideline also recommends various parameters for monitoring the nutritional status, such as serum albumin, subjective global assessment, anthropometry, and body composition (42).

Several scoring systems other than SGA have been used for nutrition status assessment in PD patients. We have first time used Nutrition Risk Index (NRI) to determine the nutrition risk in 283 ESRD patients on PD. The mean survival of the patients with normal nutritional status was superior to
patients with mild-moderate malnutrition and severe malnutrition based on NRI. NRI has high sensitivity of 92.9%, a low specificity of 32.39%, positive predictive value (PPV) 80.41% and negative predictive value (NPV) 60.53%. The study revealed that NRI cannot be used as a screening tool for assessment of nutritional status in PD patients (43).

A recent study involving Onodera's prognostic nutritional index (OPNI) which was based on serum albumin level and total lymphocyte count, indicates that a low OPNI was associated with poor nutrition status and high mortality in a 522 PD patients (44). Chen et al used PNI protein nutrition index—a index based on serum albumin, nPNA and %LBM to predict survival in 552 PD patients and documented that Nutritional status at initiation of PD can predict long-term mortality during PD, independent of age and comorbidities. On multivariate analysis, only age, comorbidity index and PNI were found to be independent predictors of mortality. They also observed a increase in the comorbidity index by a score of 1 was associated with a 160% increased risk of mortality, and an increase in PNI by a score of 1 was associated with 16% decreased risk of mortality (45). In spite of being a important predictor of mortality, malnutrition, however, is not reported as the direct cause of death (46).

Impact Of Comorbidities On Survival Of PD Patients: Co-morbid illnesses are the medical conditions other than the index disease, that is, kidney failure, are highly prevalent in patients with CKD and dialysis population. Comorbidities at start of dialysis is also a strong predictor of mortality (47). It is an inevitable prognostic factor, and case-mix comorbidity has a profound influence on outcomes of PD patients (48,49).

Defining an individual's risk for case-mix severity is challenging and one individual may have multiple comorbidities with different severity (50,51), therefore quantification and stratification of comorbidities is important in clinical practice. Chung et al (14) reported that diabetics PD patients had significantly lower %LBM and serum albumin concentration compared to non diabetics (p < 0.05), and more diabetics died during observation than non diabetics (20% vs 12.2%, p = 0.39), but presence of diabetes was not an independent factor determining death. In a study by Park et al (52) on 212 PD patients, diabetes mellitus, cardiovascular disease, serum albumin, and old age were shown to be independent predictors of mortality on Cox proportional hazard analysis. Similar to that we have also observed that diabetes, comorbidities, peritonitis, malnutrition, and residual glomerular filtration rate are the major factors predicting survival of PD patients. We have observed that the median survival of diabetics PD was significantly inferior to non diabetic PD patients [(34.5 versus 59 patient months) p = 0.001]. The patient survival of diabetic versus non-diabetic PD patients at 1, 2, 3, 4, and 5 years was 85% versus 96%; 62% versus 82%; 48% versus 72%; 39% versus 62%; and 34% versus 42%, respectively. The survival remains numerically inferior, but statistically similar between diabetic and non-diabetic PD patients after adjusting for comorbidities on Kaplan–Meier survival analysis. (3) Major co morbidity categories such as cardiovascular disease and diabetes mellitus have strong influence on mortality (53). About 40% increase in the annual mortality in diabetics patients compared to non-diabetic patients with stage 5 CKD have been reported.(54,55) Several other studies (56-60) have also reported that patient survival is lesser and relative risk of mortality is greater in diabetic patients compared to that of non-diabetic PD patients and these differences has been attributed to the high prevalence of associated co-morbidities in diabetic patients. (61) Report of the United States Renal Data System (USRDS) 1997 (62) also showed a sharp differences in survival between diabetic and non-diabetic ESRD patients. We have reported (38) that the mean survival of patients with comorbidities was significantly lesser than that of patients without comorbidities in our PD patients (Fig. 4).
Figure 4: Kaplan Meier survival analysis showing survival of patients with and without comorbidities

The relative risk of death in patients with comorbidities was significantly high, compared to that of patients without comorbidities [RR= 3.1 (95% CI 1.8–5.3), p = 0.001] (38).

Association Between Comorbidities And Malnutrition Malnutrition:

The associated co-morbidities in PD patients are not only important risk factors for increased morbidity and mortality, but also for the development of malnutrition. The presence of comorbidities also influences nutrition status of patients either through reduced nutritional intake or increased catabolism, resulting in depleted energy stores, loss of somatic protein, and decreased visceral protein. (63,64) In our own study, we observed that of the 342 patients, 186 (54.4%) had one or more comorbidities. Of the 186 patients with comorbidities, 160 (86%) were malnourished, and only 26 (14%) had normal nutrition status. Of 156 patients without comorbidities, only 95 (61%) were malnourished, and 61 (39%) had a normal nutritional status. The relative risk of developing malnutrition in patients with co-morbidities was significantly high, compared to the patients without any associated co-morbidities [RR= 3.9 (95% CI 2.3–6.6) p=001].(38) Diabetes per se is an important co morbidity and increases the cardiovascular risk in CKD of patient.(65) Chung et al in their study on 213 PD patients have reported that higher percentage of diabetic patients had both cardiovascular disease and protein energy wasting (PEW) compared to that of the non-diabetic patients (66).

Quantification or Stratification of Comorbidities in PD Patients:

Co-morbidities in dialysis patients can vary both in number and severity. Comorbid conditions and clinical outcomes are closely associated. Therefore the confounding effect of comorbidities should be quantified or stratified to assess its impact on various clinical outcomes in PD patients. Adjustment for the case-mix will allow fair comparisons and reduce the chances of bias in survival studies. Khan, (48) Charlson (67) and Davies indices (49) are amongst the commonly used indices to assess co-morbidities in ESRD patients.

Quantification and adjustment of comorbidities in survival analysis of PD patients is important (67-69). Fried et al in a prospective study on 415 incident PD patients compared the Charlson comorbidity index (combines comorbidity and age) and Davies score (comorbidity score without age), and they have reported that both the comorbidity scores were significant predictors of outcomes(70). Charlson comorbidity index appeared to be the stronger predictor for mortality while the Davies score was a stronger predictor of hospitalizations. Khan et al (48) have observed that the patient survival was significantly different between the low, medium, and high risk groups using all three methods of risk stratification in 1407 patients who commenced renal replacement therapy in five European countries. In our own study of 373 PD patients, we compared the survival in low, medium and high risk groups of patients using Khan Comorbidity index. We observed that the mean survival (patient-months) of our patients in the low risk group was [(51, 95% CI 45.6 - 56.4) better than that of the medium
Comorbidities are strongly associated with both initial malnutrition and poor clinical outcomes. In our own published data (38) we have observed that risk for mortality was 6.6 times high in patients with both malnutrition and comorbidity and 3.5 times high in patients with normal nutrition and comorbidity and 2.9-fold high in patients with malnutrition without comorbidity as compared to that of patients with normal nutrition and without comorbidity. The risk ratio of mortality in patients with both malnutrition and co-morbidities was 3.7 times higher than in patients with normal nutrition and co-morbidities alone. Malnutrition and comorbidities together have the significant impact on mortality (38). Patients with both malnutrition and comorbidities showed the worst survival. The mean actuarial survival in group 1 (normal nutrition without comorbidities) was [62(95% CI 55 - 70) patient-months; in group 2 (normal nutrition with comorbidities), 46 (95% CI, 37 to 55) patient-months; in group 3 (malnutrition without comorbidities), 46 (95% CI, 40 to 52) patient months; and in group 4 (malnutrition with comorbidities), 37 (95% CI, 32 to 43) patient months (p=0.0001). The Kaplan Meier survival curves for patients in four different groups are shown in fig. 5.

Figure 5: Kaplan Meier Survival Analysis Showing Survival Of Patients In Four Different Groups With And Without Comorbidities And Malnutrition.
In a study on 213 incident PD patients, Chung et al showed that three-year patient survival rate in patients without cardiovascular disease and protein energy wasting was 96% compared to only 22% in patients with both cardiovascular disease and protein energy wasting and 51% in patients with cardiovascular disease and protein energy wasting alone. The risk for mortality was three times higher in diabetic patients with both cardiovascular disease and protein energy wasting compared to diabetic patients without cardiovascular disease and protein energy wasting after adjusting for age, gender and RRF. There was no significant difference in the survival of diabetic and non-diabetic patients without CVD and PEW. Survival was superior in diabetic patients without cardiovascular disease and protein energy wasting compared to nondiabetic patients with cardiovascular disease and protein energy wasting. (66) Previous study by Chung et al (73) also supported the fact that the combined presence of malnutrition and co-morbidities increase the mortality risk in PD patients.

Energy And Protein Requirement In PD Patients:

Assessment of nutrition status is of paramount importance because of the close association of nutrition status and morbidity and mortality of PD patients. In India, prevalence of malnutrition is high at initiation of PD and the periodic assessment of nutrition status and dietary counselling help in improving the nutrition status of PD patients.(13). Every PD patient should receive intensive nutritional counselling by a dietitian, based on an individualized plan of care developed before or at the time of commencement of therapy. The plan of care should be updated every 3-4 months. Counselling may lead to improved dietary compliance [41]. It is very important to have the knowledge of energy and protein requirements for PD patients to impart proper and adequate nutritional counselling and achievement of optimum nutritional status to improve overall clinical outcomes in PD patients. The panel of experts from the Nutrition National Kidney Foundation / Kidney Disease Outcome Quality Initiative (K-DOQI) (42) recommended a total daily energy intake of 35 kcal/kg/d for individuals < 60 years of age and 30-35 kcal/kg/d for individuals >60 years including both diet and the energy derived from the glucose absorbed from the peritoneal dialysate. KDOQI panel recommend protein intake of 1.2 to 1.3 g/kg/d for adults PD patients (42). Adequate dietary protein intake is important in achieving nitrogen balance and preventing malnutrition in continuous ambulatory peritoneal dialysis patients (74,75).

Conclusion:

Comorbidities and malnutrition are common and highly prevalent in ESRD patients at the commencement of PD Therapy. Malnutrition is often associated with comorbidities and is an important predictor of mortality. The prevalence of malnutrition in patients with comorbidities is high, compared with patients without comorbidities. Comorbidities should be quantified or stratified in these patients. Malnutrition and comorbidities either independently or in combination affect the survival of these patients. Patients with the combined presence of malnutrition and comorbidities have the worst survival. Nutritional assessment and nutritional counselling should be done periodically to improve the nutrition status of PD patients.

References:


52. Hyeong Cheon Park, Shin Wook Kang, Kyu Hun Choi, Sung Kyu Ha, Dae Suk Han, Ho Yung Lee. Clinical outcome in continuous ambulatory peritoneal dialysis patients is not influenced by high peritoneal transport status. Perit Dial Int 2001;21(Suppl3),S80-S85.


