



## Inflammation and Its Association with Appetite and Quality of Life of Patients on Maintenance Hemodialysis

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### Abstract

A study was conducted to evaluate the inflammatory status in maintenance hemodialysis (MHD) patients and correlate with self reported appetite and their health related quality of life. Ninety patients on MHD for 6 months and above (56 males and 34 females; mean age  $52.6 \pm 11.7$  years; mean dialysis vintage  $20.99 \pm 12.08$  months) were studied. Serum inflammatory markers TNF- $\alpha$  and hs CRP, self reported appetite using Appetite and Diet Assessment Tool and health related quality of life by Health survey for dialysis patients – Short form 36 (SF 36) were assessed. The mean serum TNF- $\alpha$  and hs CRP levels were  $39.798 \pm 15.19$  pg/mL and  $10.158 \pm 2.82$  mg/L respectively. Appetite was very good for 14.4% patients, good and fair for 47.8%, poor and very poor for 37.8% patients. Poorer the appetite significantly higher was the TNF-  $\alpha$  and hs CRP levels ( $P < 0.0001$ ). The mean score of total physical component of the QOL was  $40.64 \pm 10.8$ , total mental component was  $37.56 \pm 13.2$  and the mean overall QOL score was  $39.0 \pm 11.9$ . TNF –  $\alpha$  had a highly significant negative correlation with total physical component ( $r = -0.713$ ;  $P < 0.0001$ ), total mental component ( $r = -0.727$ ;  $P < 0.0001$ ), and overall quality of life scores ( $r = -0.735$ ;  $P < 0.0001$ ). Similarly hs CRP also had a highly significant negative correlation with total physical component ( $r = -0.481$ ;  $P < 0.0001$ ), total mental component ( $r = -0.515$ ;  $P < 0.0001$ ), and overall quality of life ( $r = -0.508$ ;  $P < 0.0001$ ). Poorer the appetite lower were the mean QOL scores. Patients on MHD suffer an inflammatory state which is strongly associated to anorexia and poor quality of life. Interventions to decrease inflammation may improve appetite and health related quality of life of these patients.

**Key words:** inflammation, appetite, quality of life, hemodialysis.

## INTRODUCTION

The prevalence of chronic inflammation is very high in ESRD patients (30–50%), and chronic inflammatory state is a major contributor of renal cachexia and protein energy malnutrition in patients on maintenance hemodialysis, all of which are key factors to cause poor clinical outcomes and also negatively impact their health related quality of life.<sup>[1]</sup>

Inflammation, which is characterized by an increase in cytokines, such as interleukins or tumor necrosis factor- $\alpha$ , is present in many patients with chronic kidney disease before they start and while they are on dialysis.<sup>[2]</sup> The inflammatory cytokines may alter the feeding behavior by causing not only nausea and vomiting but also decreased gastric motility and emptying or by modifying gastric acid secretion, thus resulting in renal cachexia. Also it is hypothesized that the cytokines released during inflammation may act on the central nervous system to alter the release and function of a number of key neurotransmitters, thereby altering appetite and resulting in renal cachexia.<sup>[3]</sup>

Apart from these causes, non-dialysis-related factors and the dialysis procedure per se may be responsible for the high prevalence of inflammation in ESRD patients on maintenance hemodialysis. Inflammation in ESRD may also be caused by oxidative stress which is again a major contributing factor of malnutrition. Recently, the Hemodialysis<sup>[4]</sup> and the Nutritional and Inflammatory Evaluation of Dialysis<sup>[5]</sup> studies, determined the intensity of a patient's self reported appetite using a simple, standardized questionnaire. There were some consistent and some contradictory results about the appetite evaluation and its relation to inflammation in patients undergoing hemodialysis.

The subjective or self-reported state of well being also known as "health related quality of life" (QoL), is a major prognostic measure in CKD patients on MHD.<sup>[6]</sup> Patients undergoing chronic hemodialysis have been reported to have a poorer QoL and the QoL scores also correlate with measures of appetite and inflammatory status,

which *per se* are strong predictors of longevity in this patient population.<sup>[7,8]</sup> An abnormally low appetite and PEM may be risk factors in dialysis patients for unfavorable prognostic outcomes as poor QOL, and increased hospitalization and mortality.<sup>[9]</sup>

To our knowledge, there is a dearth of data on the association of inflammation with appetite and quality of life patients on MHD, especially in South Indian population. Hence, a cross sectional study was attempted to explicate the effect of inflammation on self reported appetite and Health related QOL of patients on MHD.

## MATERIALS AND METHODS

A cross sectional study was conducted in the dialysis unit of a tertiary care teaching hospital in South India, after obtaining the approval of the Institutional Ethics Committee and the consent of the study participants.

**Study population:** 90 patients undergoing maintenance hemodialysis were screened for eligibility.

### Inclusion criteria:

1. Patients above 18 years of age, undergoing hemodialysis for at least 6 months
2. Patients on oral diet
3. Patients undergoing twice/thrice weekly maintenance hemodialysis

### Exclusion criteria:

1. Patients with inflammatory diseases, smoking history, acute illness, overt infectious complications and known malignancies
2. Patients on concurrent use of glucocorticoids and Immunosuppressive agents
3. Patients undergoing once weekly hemodialysis
4. Patients on enteral or parenteral nutrition

### **Methods adopted:**

#### **Data collection:**

A detailed history elucidation including the demographic data (age, sex, weight in kg, height in cm), were obtained. Further details on co morbidities and duration of dialysis, were

obtained from the patients' medical records. The dialysis adequacy (Kt/V) was determined from pre and post dialytic BUN levels and the pre and post dialysis weights as described by Daugridas JT.<sup>[10]</sup>

Blood sample collection:

To execute the study specific investigations, 5 ml of venous blood samples were collected from the case and the control groups after a overnight fast before the initiation of the dialysis session, placed in appropriate tubes for separation of serum and then stored at  $-70^{\circ}\text{C}$  until analyzed for serum inflammatory cytokines TNF- $\alpha$  and hs CRP levels.

Estimation of the following was done using commercial kits according to the manufacturer's instructions.

1. Serum Tumor necrosis factor (TNF)  $\alpha$  by enzyme linked immunosorbent assay using DRG International Inc., USA, Human TNF-alpha ELISA Kit -The minimum detectable dose of TNF-  $\alpha$  is typically less than 12 pg/ml.
2. Serum hs CRP by immunoturbidimetric method using Daiichi kit (Daiichi pure Chemicals Co. Ltd., Tokyo, Japan).

#### **Appetite assessment:**

The patients were subjected to the first three questions of APPETITE AND DIET ASSESSMENT TOOL (ADAT)<sup>[11]</sup> for assessment of self reported appetite and Health Survey for Dialysis Patients – Short Form 36 (SF 36)<sup>[12]</sup> for the assessment of health related quality of life.

APPETITE AND DIET ASSESSMENT TOOL (ADAT) is a 44 item, self-administered questionnaire divided into three sections. Questions are about the patient's general level of appetite, recent changes in dry weight, dietary compliance, need for assistance with food shopping and meal preparation, common food practices and the patient's perceptions of food enjoyment and diet satisfaction. The answers to the appetite questions are scored as 1. Very good, 2. Good, 3. Fair, 4. Poor and 5. Very poor, based on Likert five point grading scale. The first three ADAT questions are directly related to appetite.

The first question is "During the past week, how would you rate your appetite?" The second and third questions focus on the change in appetite in the past week and, if so, had appetite increased, remained the same, or decreased. The study patients were made to answer the first three questions of the ADAT and the appetite levels of the study patients were graded based on their response. Based on their appetite status, patients were categorized in to three groups as *very good*, *good and fair*, *poor and very poor*.

The Health Survey for Dialysis Patients - SF 36 consists of 36 items categorized under eight scales of self reported health status as Physical functioning (PF), role functioning/ physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role functioning/ emotional (RE) and mental health(MH). These scales are scored from 0 to 100, with higher scores indicating better function. Two normalized scores representing overall physical component summary (PCS) and mental component summary (MCS) are calculated using 1 to 5 scales of physical and 6 to 8 scales of mental functioning respectively.

These questionnaires were answered by the patients either at the time of or within a week of blood sample collection. The questionnaires were answered independently by the patients after explanation of those tools by the investigator. Those who required assistance were assisted by the investigator.

#### **Statistical analysis:**

The analysis was performed using SPSS 16.0 version. Categorical variables were expressed as frequency and percentage. Continuous variables were expressed as mean  $\pm$  standard deviation. The statistical analysis of differences in serum levels of inflammatory markers TNF-  $\alpha$ , hs CRP and the health related QOL scores with respect to appetite was done using one way ANOVA with Tukey's Post-Hoc test. Pearson's correlation was used to analyse the association between serum concentrations of inflammatory markers and QOL. A P value of  $< 0.05$  was considered statistically significant.

## RESULTS

The study was conducted in 90 patients (55(61%) males and 35(39%) females) undergoing twice/thrice weekly maintenance hemodialysis.

The age range of the patients was 18 to 73 years and the mean age was  $52.62 \pm 11.7$  years. Majority of the study subjects were in the age range of 46 to 65 years (68.9 %). The primary causes of renal disease were diabetic nephropathy in 43.3% patients, hypertensive nephropathy in 30%, polycystic kidney disease in 12.2 %, glomerulonephritis in 10% pyelonephritis in 3.4% and neurogenic bladder in 1.1% patients.

The mean dialysis vintage of the patients was found to be  $20.99 \pm 12.08$  months. The mean dialysis adequacy (Kt/V) was found to be  $1.38 \pm 0.09$ . The mean serum levels of inflammatory markers TNF  $\alpha$  and hs CRP were found to be  $39.798 \pm 15.19$  Pg/mL and  $10.158 \pm 2.82$  mg/L respectively.

The self reported appetite of the patients based on the ADAT was found to be very good for 13 (14.4%) patients, Good and fair appetite for 43(47.8%) patients, poor and very poor for 34 (37.8%) patients. There was a significant difference in the mean serum TNF-  $\alpha$  and hs CRP levels based on the self reported appetite ( $P < 0.0001$ ). Poorer the appetite, significantly higher was the levels of serum TNF-  $\alpha$  and hs CRP (Table 1).

The mean scores of the QOL scales are given in table 2. The total mental component of the quality

of life scores were found to be lesser than that of the total physical component of the QOL scores. The overall quality of life was also lower for the study population.

The mean QOL score of total physical component was found to be  $52.308 \pm 6.23$  for 13 patients with very good appetite,  $44.559 \pm 7.50$  for 28 patients with good and fair appetite and  $31.215 \pm 7.95$  for 49 patients with poor and very poor appetite. Similarly the mean QOL score of total mental component was  $51.446 \pm 7.17$ ,  $42.520 \pm 9.52$  and  $25.991 \pm 9.48$  and the overall mean QOL score was found to be  $51.843 \pm 6.47$ ,  $43.566 \pm 8.25$  and  $28.320 \pm 8.39$  for patients with very good, good and fair, poor and very poor appetite respectively. Patients with good appetite reported high scores for QOL scales than the patients with poor appetite. There was a statistically significant difference in the health related QOL of patients based on their appetite ( $P < 0.0001$ ) as explained in Table 3.

Table 4 explains the association of the markers of inflammation with the QOL scales. TNF –  $\alpha$  had a statistically significant negative correlation with total physical component ( $r = - 0.713$ ;  $P < 0.0001$ ), total mental component ( $r = - 0.727$ ;  $P = 0.003$ ), and overall quality of life ( $r = - 0.735$ ;  $P < 0.0001$ ). Similarly hs CRP also had a statistically significant negative correlation with total physical component ( $r = - 0.481$ ;  $P < 0.0001$ ), total mental component ( $r = - 0.515$ ;  $P < 0.0001$ ), and overall quality of life ( $r = - 0.508$ ;  $P < 0.0001$ ).

**TABLE 1: INFLAMMATORY MARKERS VS APPETITE**

Inflammatory markers	Self reported appetite			P value
	Very good	Good & Fair	Poor & Very poor	
TNF- $\alpha$ (pg/ml)	$35.28 \pm 16.01$	$40.13 \pm 13.67$	$50.49 \pm 12.99$	0.008*
hs CRP (mg/L)	$8.92 \pm 2.36$	$10.31 \pm 2.70$	$12.89 \pm 2.31$	<0.0001**

\*\* $P < 0.001$  highly significant; \*  $P < 0.01$  significant

**TABLE 2: MEAN SCORES OF THE QOL SCALES**

QOL Components	Mean ± Std. deviation
Physical functioning	37.664 ± 13.93
Role physical	38.75 ± 11.20
Bodily pain	39.26 ± 10.99
General health	41.05 ± 9.56
Vitality	36.35 ± 12.79
Social functioning	34.87 ± 13.69
Role emotional	35.57 ± 12.79
Mental health	40.64 ± 10.79
Total Physical component	40.64 ± 10.8
Total Mental component	37.56 ± 13.2
Overall QOL SCORE	39.0 ± 11.9

**TABLE 3 - APPETITE AND QOL**

QOL	Appetite			P value
	Very good (n=13)	Good & Fair (n=28)	Poor & Very poor (n=49)	
Total physical component	52.308 ± 6.23	44.559 ± 7.50	31.215 ± 7.95	< 0.0001**
Total mental component	51.446 ± 7.17	42.520 ± 9.52	25.991 ± 9.48	
Overall QOL	51.843 ± 6.47	43.566 ± 8.25	28.320 ± 8.39	

**TABLE 4: ASSOCIATION OF QOL SCALES WITH TNF – A AND HS CRP**

QOL Components	TNF – α		hs CRP	
	r	P	r	P
Physical functioning	-0.656	<0.0001**	-0.421	<0.0001**
Role physical	-0.642	<0.0001**	-0.497	<0.0001**
Bodily pain	-0.672	<0.0001**	-0.437	<0.0001**
General health	-0.677	<0.0001**	-0.477	<0.0001**

Vitality	-0.603	<0.0001**	-0.397	<0.0001**
Social functioning	-0.624	<0.0001**	-0.412	<0.0001**
Role emotional	-0.666	<0.0001**	-0.470	<0.0001**
Mental health	-0.718	<0.0001**	-0.432	<0.0001**
Total Physical component	-0.713	<0.0001**	-0.481	<0.0001**
Total Mental component	-0.727	<0.0001**	- 0.515	<0.0001**
Overall QOL SCORE	-0.735	<0.0001**	- 0.508	<0.0001**

P<0.0001\*\* is considered highly significant

## DISCUSSION

The present study was done to assess the self reported appetite and health related QOL of the patients on MHD and correlate them with serum TNF –  $\alpha$  and hs CRP levels as they are the markers of inflammation. This study showed an increase in the inflammatory markers in patients with poor and very poor appetite and also established significant relation between self-reported appetite, inflammation and health related QOL in patients undergoing hemodialysis.

In the present study, patients on MHD had significantly high mean serum levels of TNF–  $\alpha$  and hs CRP based on their appetite. About 30–65% of maintenance dialysis patients have low-grade chronic inflammation.<sup>[13]</sup> Inflammation may induce additional catabolism in CKD patients, as shown by Avesani et al.<sup>[14]</sup> Besides being catabolic; inflammation is also responsible for anorexia. The threshold of CRP threshold to define inflammation remains unclear, and varies between 5 and 10 mg/l among studies. In many reports, other inflammatory markers such as interleukin-1, interleukin - 6, or TNF- $\alpha$  have been shown to be elevated and elicit comparable side effects.<sup>[15,16]</sup>

Considering that lack of appetite is one of the manifestations of uraemia and chronic inflammation in patients on MHD, it seems plausible to expect that this symptom may be improved by increasing the dialysis adequacy. In

the present study, the dose of dialysis adequacy (Kt/V) was found to be appropriate but it did not have a significant effect on the appetite and the inflammatory status of the MHD patients. Similarly age and dialysis vintage also had no significant effect on appetite and inflammatory status. A study conducted by Lopes et al<sup>[17]</sup> reported an absence of association between Kt/V, dialysis vintage and other dialysis related factors with lack of appetite. In contrast, some studies have reported a strong association between loss of appetite, malnutrition, inflammation and dialysis related factors like dialysis vintage, dialysis dose (Kt/V), urea reduction rate and protein catabolic ratio.<sup>[18]</sup>

The positive association between appetite and QOL is similar to that reported by Kalantar et al.<sup>[9]</sup> Intuitively, a good appetite is an important component of a satisfactory QOL. Another important finding of the study was the negative correlation between inflammation and QOL. Markers of inflammation and appetite are significant predictors of QOL in dialysis patients. Appetite status is the missing link between inflammation and protein energy malnutrition and a key indicator of general health and of QOL thus playing a pivotal role in the clinical outcome of the patients on MHD.<sup>[19,20]</sup>

The major limitation of the study is its small sample size and the cross sectional study design. Hence a longitudinal study in a larger population

would warrant the role of these inflammatory markers as strong predictors of anorexia and poor QOL in patients on chronic hemodialysis.

## CONCLUSION

It is evident that end-stage renal disease (ESRD) is a state of chronic systemic inflammation and there exists a strong association between anorexia, inflammation and a poor health related QOL. Early detection of anorexia, periodic assessment of appetite and initiating necessary therapeutic intervention to combat inflammation would be of greater impact on the health related quality of life of patients undergoing maintenance hemodialysis.

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