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Dietary inflammatory index is associated with serum C-reactive protein and protein energy wasting in hemodialysis patients: A cross-sectional study

Mevlude Kizil[1§], M. Merve Tengilimoglu-Metin[1], Damla Gumus[1], Sumeyra Sevim[1], İnci Turkoglu[1] and Fahri Mandiroglu[2]

[1]Department of Nutrition and Dietetics, Faculty of Health Sciences, Hacettepe University, 06100 Sıhhiye, Ankara, Turkey
[2]RFM Hemodialysis Units, Ankara, Turkey

BACKGROUND/OBJECTIVE: Malnutrition and inflammation are reported as the most powerful predictors of mortality and morbidity in hemodialysis (HD) patients. Diet has a key role in modulating inflammation and dietary inflammatory index (DII) is a new tool for assessment of inflammatory potential of diet. The aim of this study was to evaluate the application of DII on dietary intake of HD patients and examine the associations between DII and malnutrition-inflammation markers.
SUBJECTS/METHODS: A total of 105 subjects were recruited for this cross-sectional study. Anthropometric measurements, 3-day dietary recall, and pre-dialysis biochemical parameters were recorded for each subject. Subjective global assessment (SGA), which was previously validated for HD patients, and malnutrition inflammation score (MIS) were used for the diagnosis of protein energy wasting. DII was calculated according to average of 3-day dietary recall data.
RESULTS: DII showed significant correlation with reliable malnutrition and inflammation indicators including SGA ($r = 0.28$, $P < 0.01$), MIS ($r = 0.28$, $P < 0.01$), and serum C-reactive protein (CRP) ($r = 0.35$, $P < 0.001$) in HD patients. When the study population was divided into three subgroups according to their DII score, significant increasing trends across the tertiles of DII were observed for SGA score ($P = 0.035$), serum CRP ($P = 0.001$), dietary energy ($P < 0.001$), total fat ($P < 0.001$), saturated fatty acids ($P < 0.001$), polyunsaturated fatty acids ($P = 0.006$), and omega-6 fatty acids ($P = 0.01$) intakes.
CONCLUSION: This study shows that DII is a good tool for assessing the overall inflammatory potential of diet in HD patients.

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INTRODUCTION

Protein energy wasting (PEW) and inflammation generally occur concomitantly in HD patients, known as malnutrition inflammation complex syndrome (MICS) or malnutrition inflammation atherosclerosis (MIA) associated with high mortality and poor clinical outcome [1,2]. In particular, the cardiovascular mortality rate among patients with chronic kidney disease (CKD) is high and approximately 50% of all deaths in maintenance hemodialysis (HD) patients are attributable to cardiovascular diseases (CVD) [3,4]. PEW and chronic systemic inflammation are considered the main mediators of increased cardiovascular disease risk in HD patients [5]. In particular, elevated serum C-reactive protein (CRP) level is a strong risk factor for development of cardiovascular disease [6,7] and high CRP level is linked to endothelial injury and impaired vasodilation which may lead to glomerular damage and progressive loss of kidney function [8].

Diet has a key role in immunonutrition and several specific nutrients influence nutritional, immunological, and inflammatory parameters [9]. Dietary inflammatory index (DII) is a new tool based on an extensive literature search involving epidemiologic, animal, and cell culture studies on the effect of diet on inflammation and dependent on whole diet and not limited to macronutrients and micronutrients, also including dietary components such as spice and tea [10,11]. It reflects inflammatory weights of a number of dietary components and indicated that DII was able to predict serum CRP level [12]. In addition, the construct validation of the DII with serum CRP, interleukin-6 (IL-6), and tumor necrosis factor alpha receptor 2 (TNFα-R2) was recently reported [13].

In HD patients, assessment of nutritional status is critical for increasing quality of life and improving clinical outcomes. Body mass index (BMI), subjective global assessment (SGA), malnutrition inflammation score (MIS), serum albumin, and dietary intake assessments are commonly used nutritional assessment tools in these patients. However, validated SGA for HD patients and MIS are considered good predictors for malnutrition [14,15]. Inflammation and insufficient dietary intake are important reasons for malnutrition but the inflammatory potential of

§ Corresponding Author: Mevlude Kizil, Tel. 90-312-3051094, Fax. 90-312-3091310, Email. mkizil@hacettepe.edu.tr
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whole dietary intake of these patients has not yet been investigated. To better our knowledge, the efficiency of the new dietary assessment in evaluation of pro-inflammatory and anti-inflammatory nutrients should be investigated for different chronic diseases. The aim of this cross sectional study was to evaluate the application of DII on dietary intake of HD patients and examine the associations between DII and malnutrition-inflammation markers.

SUBJECTS AND METHODS

Subjects

This cross sectional study was conducted on 105 HD patients recruited from the RFM hemodialysis unit, Ankara, Turkey between April and October 2014. Inclusion criteria were age over 20 years, maintained HD therapy at least 3 months. Exclusion criteria were as follows: communication problems, cognitive limitations, diagnosis of cancer in any organs, hepatic insufficiency, acute or chronic pancreatitis, irritable bowel syndrome or prolonged gastrointestinal symptoms and other inflammatory diseases.

All patients underwent regular maintenance dialysis sessions at least 4 h and three times per week. Dialysis adequacy was calculated in terms of Kt/V urea for each patient according to pre- and post-dialysis serum urea concentration, length of dialysis session, post dialysis weight, and ultra-filtration volume. All patients received adequate dialysis therapy according to their Kt/V values.

The study protocol was approved by the Ethical Committee of Hacettepe University (number 16969557-423). Written informed consent was obtained from all patients and the study was conducted in accordance with the Helsinki Declaration.

Nutritional assessment

Study participants were interviewed after their HD session about socio-demographic characteristics (age, gender, marital status, education level, etc.), medical diagnosis or being treated for chronic conditions, and other potential covariates. Dietary assessment was performed using three days dietary recalls with two non-dialysis days and one dialysis day. For accuracy of portion size, standardized photographs specifying a common portion size were used for each food or beverage consumed.

Validated SGA and MIS were used for the diagnosis of PEW and nutritional assessment of patients [14,15]. SGA consists of 7 questions indicating weight change during the past six months, dietary intake, gastrointestinal symptoms, functional capacity, and co-morbidities, physical examination included assessing loss of subcutaneous fat, muscle wasting, and nutrition associated alterations in fluid balance, edema and/or ascites. Each SGA component was rated on a scale of 1 (normal) to 5 (very severe). The sum of all seven SGA components ranges from 7 to 35; a higher total score reflects a more severe degree of PEW [14]. On the SGA a score ranging from 7 to 13 was considered as normal status, while a score $\geq$ 14 was considered as PEW [16].

MIS consists of seven SGA components and three new items; BMI, serum albumin, and total iron binding capacity. Each MIS component has four levels of severity from 0 (normal) to 3 (very severe). The sum of all 10 MIS components ranges from 0 to 30; a higher total score indicates a more severe degree of PEW [15]. Based on MIS, a score ranging 0 to 7 was considered as normal status, while a score $\geq$ 8 was considered as PEW [16].

Anthropometric measurements

Anthropometric measurements except pre-dialysis weight were obtained immediately after the HD session. Dry weight, height, waist circumference, hip circumference, mid upper arm circumference (MAC), and triceps skinfold thickness (TSF) were measured using standard techniques and BMI was calculated as dry weight divided by height squared. TSF and MAC were measured on the non-fistula side using a Holtain Skinfold Caliper with a precision of 0.2 mm and non-elastic tape to the nearest 0.1 mm, respectively.

Biochemical parameters

In this cross sectional study, routinely analyzed pre and/or post dialysis levels of serum albumin, total protein, serum CRP, hemoglobin, serum potassium, phosphor, sodium, calcium, urea, creatinine, and blood lipids were recorded from patients' files.

Dietary inflammatory index

The design and development of the DII has been described previously [11]. Briefly, DII is a scoring algorithm based on a 1943 literature review published from 1950 to 2010 evaluating the effect of diet on six inflammatory biomarkers; IL-1β, IL-4, IL-6, IL-10, TNF-α, and CRP. Forty-five food parameters including various macronutrients, micronutrients, flavonoids, and individual food items associated with these inflammatory biomarkers were scored according to whether they increased (+1), decreased (-1) or had no effect (0) on inflammation. An overall food parameter specific inflammatory effect score was calculated for each food item. The higher DII score reflects the more pro-inflammatory diet, while more negative values represent more anti-inflammatory diets. It was also reported that the DII score could take on values ranging +8 (maximally pro-inflammatory) to -9 (maximally anti-inflammatory).

In this study, 25 food parameters were available from dietary intake data, including mean daily intakes of energy, protein, carbohydrate, fat, saturated fat, polyunsaturated fatty acids (PUFA), monounsaturated fatty acids (MUFA), omega-3 fatty acids, omega-6 fatty acids, cholesterol, vitamin A, carotene, vitamin E, vitamin B_1, vitamin B_2, niacin, vitamin B_6, vitamin B_{12}, folic acid, vitamin C, magnesium, iron, zinc, fiber, and caffeine were used for the calculation of DII. Table 1 shows the inflammatory effect scores for dietary components used for calculation of DII in this study population. All food parameter DII scores were summed to obtain the overall DII score for each patient.

Statistical analysis

Data were analyzed for the normality of distribution using the Shapiro-Wilks test and expressed as mean $\pm$ SD. The categorical variables were shown as number and/or percentage. The study population was divided into three subgroups according to their DII score and analysis of covariance (ANCOVA)

Table 1. Inflammatory effect scores for dietary components used for calculation of DII

Food parameters	Inflammatory effect score*
Energy (kcal)	0.180
Protein (g)	0.021
Carbohydrate (g)	0.097
Total fat (g)	0.298
Saturated fat (g)	0.373
Polyunsaturated fatty acids (g)	-0.337
Monounsaturated fatty acids (g)	-0.009
Omega-3 fatty acids (g)	-0.436
Omega-6 fatty acids (g)	-0.159
Cholesterol (mg)	0.110
Vitamin A (RE)	-0.401
Carotene (μg)	-0.584
Vitamin E (mg)	-0.419
Vitamin B_1 (mg)	-0.098
Vitamin B_2 (mg)	-0.068
Niacin (mg)	-0.246
Vitamin B_6 (mg)	-0.365
Vitamin B_{12} (mg)	0.106
Folic acid (mg)	-0.190
Vitamin C (mg)	-0.424
Magnesium (mg)	-0.484
Iron (mg)	0.032
Zinc (mg)	-0.313
Fiber (g)	-0.663
Caffeine (g)	-0.110

* A negative value indicates anti-inflammatory effect and a positive score indicates pro-inflammatory effect.

was used for testing the differences across DII tertiles, with gender, education level, and marital status as covariates. Partial correlation coefficient was used to assess the relationship between DII and some nutritional assessment parameters controlling for gender, education level, and marital status. Statistical significance was accepted as $P < 0.05$. Statistical analyses were performed using the IBM SPSS 21.

RESULTS

Characteristics of patients

This cross sectional study consisting of 105 HD patients aged between 23 to 86 years included 68 males. Diabetes Mellitus (37.1%), hypertension (33.3%), idiopathic CKD (5.7%), and other diseases (23.9%) including nephrolithiasis, glomerulonephritis, and polycystic kidney were primary causes of CKD in this study population. The mean dialysis vintage was 6.0 ± 4.8 years and PEW was determined at the rate of 33.3%, 38.6% according to SGA and MIS, respectively. The demographic characteristics of HD patients across the tertiles are shown in Table 2.

Nutritional, biochemical and anthropometric parameters of patients by DII tertiles

DII value was calculated for each HD patient. The mean DII score was 1.76 ± 1.26 (min, - 0.37; max, 4.90). The nutritional status, biochemical, anthropometric and dietary characteristics of HD patients according to tertiles of the DII are shown in Table 3. Significant increasing trends across the tertiles of DII were observed for SGA score ($P = 0.035$), CRP level ($P = 0.001$), dietary energy ($P < 0.001$), total fat ($P < 0.001$), saturated fat ($P < 0.001$), PUFA ($P < 0.01$), and omega-6 fatty acids ($P = 0.01$) intakes. On the other hand, decreasing trends were observed

Table 2. Characteristics of the HD patients

Characteristics	All patients (n = 105)	Tertile 1 (n = 37)	Tertile 2 (n = 33)	Tertile 3 (n = 35)	*P*-value
Age (yrs)*	57.5 ± 12.4	59.4 ± 11.5	59.4 ± 10.8	53.8 ± 14.1	0.094
Male/Female (%)†	64.8/35.2	56.8/43.2	51.5/48.5	85.7/14.3	0.006
Dialysis vintage (yrs)‡	6.0 ± 4.8	5.0 ± 4.3	5.9 ± 3.5	7.0 ± 5.9	0.192
Diabetes mellitus (%)	37.1	40.5	30.3	40	0.679
Marital status (%)†					0.006
Single	7.6	5.4	-	17.1	
Married	84.8	91.9	81.8	80.5	
Divorced	7.6	2.7	18.2	2.9	
Education level (%)†					0.018
Non-literate	11.4	24.3	9.1	-	
Literate	3.8	2.7	3	-	
Primary school	45.7	40.5	60.6	37.1	
Secondary school	11.4	8.1	6.1	20	
High school	20	18.9	9.1	31.4	
Collage	7.6	5.4	12.1	5.7	
Malnutrition (%)†					
SGA ≥ 14	33.3	27	42.4	31.4	0.378
MIS ≥ 8	38.6	31.4	43.8	41.2	0.545

Data are presented as mean ± SD or percentage or number.
* One-Way ANOVA test was used.
† Chi-squared test was used.
‡ Kruskall-Wallis test was used.

Table 3. Characteristics of the patients according to tertiles of dietary inflammatory index

Characteristics	All patients (n = 105)	Tertile 1 (n = 37)	Tertile 2 (n = 33)	Tertile3 (n = 35)	*P*-value*
SGA score	12.6 ± 3.2	11.3 ± 2.7	13.1 ± 3.2	15.1 ± 3.2	0.035
MIS	6.6 ± 3.2	6.0 ± 2.9	6.4 ± 3.3	7.1 ± 3.5	0.075
CRP (mg/L)	17.6 ± 5.3	10.2 ± 4.4	18.1 ± 4.9	25.2 ± 4.6	0.001
Serum albumin (g/dL)	3.9 ± 0.4	4.1 ± 0.7	3.9 ± 0.4	3.9 ± 0.4	0.183
Serum creatinine (mg/dL)	8.7 ± 2.2	8.6 ± 2.7	8.7 ± 2.2	8.8 ± 1.8	0.690
Serum urea (mg/dL)	147.1 ± 43.5	146.8 ± 48.6	149.9 ± 37.2	144.5 ± 44.9	0.807
Total cholesterol (mg/dL)	178.8 ± 40.3	173.5 ± 34.3	188.6 ± 43.1	174.5 ± 42.5	0.281
LDL-cholesterol (mg/dL)	103.8 ± 34.2	95.2 ± 31.5	111.2 ± 36.7	104.9 ± 33.3	0.198
TSF (mm)	12.5 ± 6.5	13.8 ± 6.5	13.4 ± 7.1	11.4 ± 5.9	0.841
MAC (cm)	27.8 ± 4.5	28.7 ± 4.1	28.5 ± 5.2	26.8 ± 4.6	0.816
BMI (kg/m^2)	25.9 ± 4.2	27.0 ± 4.3	25.5 ± 3.7	25.1 ± 4.4	0.182
Energy intake (kcal)	1,345.4 ± 593.6	1,088.7 ± 466.1	1,053.1 ± 316.2	1,884.9 ± 545.3	< 0.001
Total fat intake (g)	58 ± 30.4	46.8 ± 29.5	43.3 ± 13.7	83.3 ± 27	< 0.001
Saturated fat intake (g)	19.8 ± 12.1	14.9 ± 8.3	13.8 ± 6.1	30.4 ± 12.8	< 0.001
PUFA intake (g)	12.8 ± 9.1	11.7 ± 11.3	9.6 ± 6.1	17.0 ± 7.4	0.006
Omega-6 intake (g)	11.5 ± 8.5	10.4 ± 10.3	8.8 ± 6.2	15.0 ± 7.3	0.01

Data are presented as mean ± SD
* *P*-values obtained using covariance analysis adjusted for gender, education level, and marital status.
Tertile 1, < 1.04.
Tertile 2, 1.04 to 2.15.
Tertile 3, ≥ 2.16.
BMI, body mass index; CRP, c-reactive protein; LDL, low density lipoprotein; MAC, mid upper arm circumferences; MIS, malnutrition inflammation score; PUFA, polyunsaturated fatty acids; SGA, subjective global assessment TSF, triceps skinfold thickness.

Table 4. Correlation matrix for malnutrition and inflammation indicators†

Variable	DII	SGA	MIS	CRP	Serum albumin	Serum creatinine	TSF	MAC
SGA	0.28**	-						
MIS	0.28**	0.84***	-					
CRP	0.35***	0.24*	0.34***	-				
Serum albumin	-0.14	-0.27	-0.29**	0.16	-			
Serum creatinine	-0.10	-0.21*	-0.25*	-0.06	0.32	-		
TSF	-0.16	-0.18*	-0.21*	0.01	0.12	0.04	-	
MAC	-0.16	-0.11	-0.14	0.01	0.13	0.22*	0.52***	-
BMI	-0.26**	-0.27**	-0.33***	-0.02	0.12	0.11	0.51***	0.72***

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.
† *P*-values obtained using partial correlation controlling for gender, education level, and marital status.
BMI, body mass index; CRP, C-reactive protein; DII, dietary inflammatory index; MAC; mid upper arm circumference; MIS, malnutrition inflammation score; SGA, subjective global assessment; TSF, triceps skinfold thickness.

for TSF, MAC, and BMI but were not statistically significant ($P > 0.05$).

Correlations between DII and malnutrition-inflammation markers

Correlations between DII and some nutritional assessment parameters are shown in Table 4. DII showed significant positive correlation with CRP (r = 0.35, $P < 0.001$) and negative correlation with BMI (r = -0.26, $P < 0.01$). In addition, strong positive correlation was observed between DII and SGA score (r = 0.28, $P < 0.01$) and MIS (r = 0.28, $P < 0.01$), and SGA score showed positive correlation with CRP (r = 0.24, $P < 0.05$), negative correlation with BMI (r = -0.27, $P < 0.01$) and TSF (r = -0.18, $P < 0.05$). BMI (r = -0.33, $P < 0.001$), TSF (r = -0.21, $P < 0.05$), and serum albumin level (r = -0.34, $P < 0.001$) showed negative correlation, whereas serum CRP (r = 0.34, $P < 0.001$) showed positive correlation with MIS in HD patients.

DISCUSSION

To the best of our knowledge, this is the first study to apply the DII to the diets of maintenance HD patients and examine the association between DII and malnutrition-inflammation markers. The result of this cross-sectional study shows that DII is significantly associated with reliable malnutrition and inflammation indicators including SGA (r = 0.28, $P < 0.01$), MIS (r = 0.28, $P < 0.01$), and CRP (r = 0.35, $P < 0.001$) in HD patients.

PEW is common in HD patients and related to increased mortality and morbidity [1,2]. The pathogenesis of PEW is considered multifactorial. Inadequate food intake by the results of anorexia, altered taste sensation, intercurrent illness, emotional distress or illness, impaired ability to prepare food, unpalatable prescribed diets, hypercatabolism and reduced anabolism, dialysis procedure, chronic inflammatory state, and endocrine disorders of uremia were reported as major causes of PEW [17].

Approximately 40% of patients undergoing maintenance dialysis suffer from varying degrees of PEW [18,19]. Similarly, in this study, PEW was observed in 33.3%, 38.6% of HD patients according to SGA and MIS, respectively. In addition, SGA score ($P = 0.035$) and CRP levels ($P = 0.001$) showed significant increasing trends across the tertiles of DII. Therefore, these findings confirm the hypothesis for the associations between pro-inflammatory diet, PEW, and elevated CRP. Interestingly, we found no association between MIS and CRP. However, previously MIS was found to be associated with serum interleukin-6 (IL-6), CRP, nutritional status, and quality of life in HD patients [20].

The modulating role of diet on inflammation has been shown in several studies and association of specific dietary components with lower or increased levels of inflammation has been reported [21]. The DII represents a new tool for assessing the inflammatory potential of the diet that can be applied to any population in which dietary data have been collected [10,11]. It also has the potential to be used for evaluating and guiding individuals in decreasing levels of inflammation and possibly reduce the risk of certain chronic conditions [11]. Dietary compounds with anti-inflammatory and anti-oxidative properties have an important role in the reduction of inflammation and cardiovascular risk [22]. Several studies have also shown that dietary interventions might mitigate chronic inflammation. Potential anti-inflammatory and anti-oxidative agents including vitamin E, vitamin C, vitamin A/carotenoids, fish oil, and carnitine have been studied in CKD patients in order to reduce inflammation [23]. Flaxseed oil [24] and pomegranate juice [25] interventions were recently reported to decrease inflammation and oxidative stress in HD patients, while saturated fatty acids, high glycemic index foods and high omega-6/omega-3 ratio are associated with increased levels of inflammation [26]. Similarly, in our study, dietary total fat ($P < 0.001$), saturated fatty acids ($P < 0.001$), PUFA ($P = 0.006$), and omega-6 fatty acids ($P = 0.01$) intakes were higher in Tertile 3 (more pro-inflammatory diet), especially dietary total fat and saturated fatty acid intakes were main contributors to high DII score. In addition, total fat ($r = 0.24$ $P < 0.05$) and saturated fatty acids intake ($r = 0.28$ $P < 0.01$) showed positive correlation with serum CRP level (data not shown), in well agreement with other studies showing the association between saturated fatty acids intake and CRP [27,28]. In addition, association of increased levels of serum CRP with the nutritional status was demonstrated in HD patients and serum CRP values were 2.5 fold higher in wasted patients compared with well-nourished ones [29].

Adequate energy intake is essential for prevention of PEW in HD patients but macro and micronutrient contributions to energy intake are also important. Many dietary factors affect inflammation, especially western type diet, rich in refined grains, red and processed meat, saturated fatty acids increases levels of inflammation. In this respect, in our study we observed that patients, with a high DII score also have worse nutrition status, despite intake of more dietary energy. This is because the pro-inflammatory nutrients, particularly total fat and saturated fatty acid intakes are also high in the 3rd tertile. Hence, we can suggest that more energy intake is not solely adequate to ensure good nutrition status. In order to fight PEW in HD patients, the contributions of macro and micronutrients to the energy intake should be considered.

As mentioned before, CKD is characterized by chronic systemic low-grade inflammation [30], which increases the release of inflammatory cytokines including IL-6 and tumor necrosis factor-α, leading to increased synthesis of CRP [31]. The causes of inflammation in HD patients are complex and multifactorial, including the repeated contact of blood mononuclear cells with dialysis tubes and dialyzer membranes, impurities in the dialysis water and/or dialysis solution, oxidative and carbonyl stress, increased release and decreased clearance of inflammatory cytokines, clinical or subclinical infection of the vascular access port, malnutrition, and increased oxidative stress [24]. However, according to the findings of this study, consumption of a pro-inflammatory diet, particularly high in fat and saturated fat might be another reason for inflammation.

BMI is a commonly used anthropometric indicator of PEW in HD patients and considered a predictor of poor outcome and high mortality [2,32]. However, it is argued that BMI does not assess central adipose tissue associated with cardiovascular disease and inflammation [29]. Likewise, in the current study BMI failed to assess inflammatory state of subjects. Similar to our results, it was reported that the severity of inflammation was not related to BMI even in normal, overweight, and obese HD patients [33].

The current cross-sectional study has some limitations. First, dietary data were collected according to 3-day dietary recall, therefore, the actual dietary intakes of subjects might have been underestimated and herbs and spice were excluded in the calculation of DII due to lack of dietary intake information. Second, we only examined the association between DII and CRP as a systemic inflammatory marker; association between other pro-inflammatory cytokines and DII can be examined in future studies. Third, despite small sample size ($n = 105$), the current study has strength to show the association between DII and malnutrition-inflammation markers in HD patients.

In conclusion, DII is a new index associated with inflammatory cytokines including CRP and IL-6 [11,34], increased odds of asthma [35], colorectal cancer risk [36,37], prostate cancer among Italian men [38], risk of pancreatic cancer [39], and length of hospitalization among surgical patients treated for colorectal cancer [40]. The findings of this study demonstrate the evidence of a new tool for assessing the overall inflammatory potential of diet in HD patients. This study also suggests the application of DII for assessment of nutritional and inflammatory status as a target for reducing morbidity and mortality.

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