The Evaluation of Increase in Hemodialysis Frequency on C-Reactive Protein Levels and Nutritional Status

Ali Akbar Rashidi [1], Ali Reza Soleimani [2], Hassan Nikoueinejad[3], and Shokooh Sarbolouki[2]

[1] *Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran.*

[2] *Kashan Dialysis Center, Kashan University of Medical Sciences, Kashan, Iran*

[3] *Department of Immunology, School of Medicine, Kashan University of Medical Sciences, Kashan, Iran*

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Abstract- Malnutrition and inflammation are the most important causes of cardiovascular disease in hemodialysis patients. This study was conducted to evaluate the effect of increase in hemodialysis frequency on C-reactive protein (CRP) level and nutritional markers in contrast to previous routine method. 18 hemodialysis patients with a mean age of 53±16 years were randomly selected in this before-and-after clinical trial. The patients under a standard hemodialysis of 3 times/4 h per week were converted to 4 times/4 h for a period of 6 weeks. The CRP, albumin, triglyceride, total cholesterol, LDL, HDL serum levels, anthropometric indices and 24-h diet recall intake was assessed before and after of the period. The data were analyzed using paired t-test, and *P*-value less than 0.05 was considered significant. All patients completed the study. Mean weight, body mass index and serum albumin increased while serum CRP level decreased significantly after the intervention ($P<0.03$). Triglyceride, total cholesterol, LDL, HDL, as well as energy, protein and fat intake had no significant change before and after the study. Increase in dialysis frequency decreased systemic inflammation and improved the nutritional state of hemodialysis patients. Therefore, it may decrease the risk of cardiovascular events in these patients.

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Keywords: CRP; Hemodialysis; Nutritional status

Introduction

Hemodialysis was applied for the end-stage renal disease (ESRD) patients for the first time at the beginning of 1960s. Today, conventional hemodialysis is performed 3 times a weeks each 3-4 hours in which mortality rate remains high (approximately 18-20% per year). Considerable complications are associated with hemodialysis including frequent and extended hospitalizations as well as relatively poor functional status and health-related quality of life (1,2). This procedure has got two common other disadvantages including energy-protein malnutrition and inflammation which are common risk factors of morbidity and mortality, including cardiovascular death (3-9), with a prevalence of 18-75% (9) and 35-65% (10,11) among hemodialysis patients, respectively. In dialysis patients, some frequently used indicators of malnutrition are decreased dietary protein and energy intake, reduced body mass index (BMI), and low serum concentrations of albumin and cholesterol. The indicators of inflammation in dialysis patients are the elevated acute-phase reactant of serum C-reactive protein (CRP) and the decreased acute-phase reactant of albumin (9). Hypoalbuminemia and increased serum CRP levels are strong predictors of poor clinical outcome and death in dialysis patients (9,12-15). Also hypoalbuminemia is known as a malnutrition and inflammation marker (9,16-19). Serum CRP which increases about 35% in dialysis patients (7-8) is a sensitive marker of systemic inflammation (20) as well as a predisposing factor to atherosclerotic cardiovascular disease (21). There is a major overlap among the above-mentioned indicators of protein-energy malnutrition and inflammation (22,23). It means that many conditions leading to malnutrition may also cause inflammation; consequently, the strong association between these two phenomena may be an explanation for high mortality rate in dialysis patients (1, 15). Discovering assessment factors that show poor dialysis outcome is of utmost importance (24). The key

Corresponding Author: Hassan Nikoueinejad
Department of Immunology, School of Medicine, Kashan University of Medical Sciences, Kashan, Iran
Tel: +98 913 1615530, Fax: +98 361 5551112, E-mail: hnikuinejad@yahoo.com

to improve survival in dialysis patients may lie in interventions that modify the conventional cardiovascular risk factors, mainly inflammation and malnutrition (15). To modulate such risk factors, we may require a different dialysis prescription to test the benefit of different therapeutic interventions such as increasing dialysis frequency. In other words, it is needed to determine the optimal dose of dialysis. However, solute removal can be dramatically augmented by increasing the frequency of hemodialysis sessions (4 times per week) (25). Therefore, in this study, we evaluate the effect of dialysis frequency increase on CRP, nutritional markers including albumin, triglyceride (TG), total cholesterol (T. Chol), LDL, HDL, and anthropometric markers in patients under treatment with hemodialysis.

Materials and Methods

This is a before-and-after clinical trial carried out on 18 randomly selected hemodialysis patients in Kashan dialysis center. All included patients completed a written consent. The study was approved by the Medical Ethical Committee of Kashan University of Medical Sciences. The undergone patients carried such conditions as 1) they were not in the list of kidney transplantation, 2) had no infectious or inflammatory disease, 3) were not hospitalized in the last month, 4) and were under treatment with standard hemodialysis 4 hours 3 time per week. Then they were converted to hemodialysis 4 hours 4 times per week for 6 weeks. Serum concentration of CRP, albumin, TG, T. Chol, LDL, HDL, anthropometric measurements as well as 24 h food intake for three days a week were assessed before and after the conversion. Serum concentration of CRP was measured using the method of immunonephlometry (MININEPH™, Binding Site Ltd, Birmingham, UK)(13), and the measurement of serum albumin was done by bromocresol green (26). Weight and height of people were assessed (using Seca 725 Gmbh & co., Germany) and BMI was calculated according to weight/(height)^2 formula. All data were analyzed with the paired t-test (software SPSS version 16.0 for Windows, Polar Engineering and Consulting, USA). The results were reported by mean ± SD and the *P*-value less than 0.05 was considered significant in all tests.

Results

A total of 18 patients were enrolled, 12 women (66.7%) and 6 men (33.3%) with mean age of 53±16 years. Median time on dialysis therapy was 48 months at baseline. The majority of patients had diabetes (50%) (Table 1). In contrast to baseline, mean body weight increased after the intervention (67.1±13.4 vs 67.6±13.5, respectively; *P*=0.02). Body mass index (BMI) was 27.5±7.1 at baseline and increased significantly to 28.3 ± 6.9 after the intervention (*P*=0.03). Mean serum albumin at baseline and after the intervention was 3.7±0.3, 4±0.3 g/dl respectively (*P*=0.01). Serum concentrations of CRP increased significantly from 13.4±14.7 at baseline to 7.7±7.2 mg/l after the intervention (*P*=0.03) (Table 2). There was no significant improvement in the rate of energy and protein intake from the baseline till after the intervention (Table 3).

Table 1. Baseline hemodialysis patients characteristics.

Characteristics	n=18
Age (years)	53 ± 16
Men (%)	6 (33.3)
Women (%)	12 (66.7)
BPS	13.6±20.9
BPD	12.0±7.8
Duration on dialysis (month)	48 (18-78)
Cause of end-stage renal disease (%)	
Diabetes	50
Hypertension	27.8
Unknown	22.2

Table 2. Effects of increasing frequency hemodialysis on CRP and nutritional markers.

	Baseline	After 6 weeks	*P*-value
Weight (kg)	67.1±13.4	67.6±13.5	0.02
BMI (kg/m^2)	27.5±7.1	28.3±6.9	0.03
Albumin (g/dl)	3.7± 0.3	4.0±0.3	0.01
Kt/v	1.1 ±0.05	1.24±0.09	0.04
Triglycerides (mg/dl)	145.5±104.2	170.5±97.7	0.078
T.Cholesterol (mg/dl)	125.0±52.2	135.1±36.3	0.276
LDL Cholesterol (mg/dl)	72.5±29.4	64.8±21.2	0.450
HDL Cholesterol (mg/dl)	27.7±12.2	30.3±12.6	0.329
CRP(mg/l)	13.4±14.7	7.7±7.2	0.03

Table 3. Daily nutrient intake before and after 6 weeks in hemodialysis patients.

	Baseline	After 6 weeks	*P*-value
Energy (kcal/day)	1630.8±554.7	1679.6±456.5	0.684
Energy (kcal/kg/day)	24.6±12.6	25.9±10.8	0.489
Carbohydrate (g/day)	247.9±89.9	237.5±66.2	0.616
Protein (g/day)	49.6±15.6	55.3±20.5	0.332
Protein (g/kg/day)	0.74±0.3	0.86±0.4	0.219
Fat (g/day)	50.6±25.7	57.7±26.9	0.245

Values are means ± SD of the data.

Discussion

Conversely, certain markers that predict a low likelihood of cardiovascular events and improve survival in the general population, such as decreased BMI or lower serum cholesterol levels become strong risk factors for cardiovascular morbidity and death in hemodialysis patients. Paradoxically, some indicators of over-nutrition such as obesity and hypercholesterolemia appear to be protective features associated with greater survival among dialysis patients. The phenomenon of risk factor paradox is caused because of a condition that potentially attenuates the magnitude of protein-energy malnutrition or inflammation (10,15). Such attenuation which should be favorable to dialysis patients was seen in this study. Our survey revealed some beneficial aspects of using more frequent dialysis method than conventional one. There are a few other studies clarifying some other beneficial aspects of such methods (27-31). Our results showed that increasing hemodialysis frequency improved weight and BMI of the patients. Numerous studies have provided evidence that hemodialysis patients who have gained a moderate weight (32) and larger BMI measurements (33-35) are more likely to survive. However, mortality risk increases significantly among patients whose BMI decreases by more than 3.5% (36). In line with our results, Galand *et al.* showed that more dialysis frequency increases significantly the body weight, BMI and serum albumin of the patients (37). Although, in our study, there is no significant increase in energy, protein and fat intake, the increase of weight is probably due to increasing absorption of nutrients, more efficiently removal of serum anorectic compounds, and increasing the appetite (38). In fact, increasing dialysis frequency enables the ultrafiltration rate to be decreased, increases inter-dialysis weight gain and reduces the risk of dialysis-induced hypotension (39).

Our patients gained a serum albumin about 4 g/dl after the intervention. Such gain is perfect since it has been shown that an increase in serum albumin over time, especially to values greater than 3.8 g/dl, has the strongest correlation to prospective survival and can potentially save 15,000-20,000 lives per year among dialysis patients in the US (40). In the complete DOPPS I cohort, the mortality risk in patients with a serum albumin concentration less than 3.5 g/dl (35 g/l) was 1.38 times more (41). In spite of our study as well as ones conducted by Galand *et al.* and Yung *et al.* (42), Goldfarb *et al.* (43) observed no significant difference in albumin serum concentration along with the increase of the hemodialysis frequency.

In line with our results, other studies show that increasing dialysis dose above adequate level do not have a favorable effect on protein intake or on the nutritional status (13,44,45). Although statistically insignificant, energy and protein intake increased after 6 weeks in our study. Increased dialysis frequency seems to increase appetite and food intake in hemodialysis patients, ultimately leading to improved patient nutritional status (13). This becomes more important when considering that the hemodialysis procedure *per se* is also capable of enhancing the energy expenditure (46). Recommended energy and protein intake for hemodialysis patients is 35 kcal/kg/day and 1 g/kg/day respectively (47), but in our study the mean energy and protein intake was about 25 kcal/kg/day 0.8 g/kg/day respectively, demonstrating the malnutrition in our patients. A better energy and protein intake achieved by more frequent dialysis can at least fulfill part of insufficient intake. The maintenance of nitrogen balance depends on energy intake; therfore, the more energy to intake the more protein to maintain and to prevent negative nitrogen balance. Many factors affect protein metabolism in hemodialysis patients and cause increased catabolism as well as reduced fat free mass (44).

Our intervention resulted in less serum CRP concentration. Interventions like ours, daily dialysis-based ones could potentially improve clinical outcome of dialysis patients; yet, they are not scientifically proved (15,48). Inflammation, as a risk factor of cardiovascular events, is a leading cause of death in hemodialysis patients (49-51). Mortality rate among hemodialysis patients with CRP>10 mg/dl is 3.5 times higher than others (49). Inflammation is not only catabolic but may also induce protein–energy wasting due to a reduction in appetite (52). Indeed, any 1 mg/l CRP elevation results in a 30 kcal increase in daily energy expenditure (53). Besides being catabolic, inflammation is also responsible for anorexia. In patients on maintenance hemodialysis, serum CRP is negatively linked with appetite (54,55). Thus, more dialysis times seem advantageous in respect of less CRP level and cardiovascular risk. In conclusion, an overall view to our results while cosidering complicated clinical condition of hemodialysis patients reveals that our intervention could hardly be promising alone. It is unlikely that only one single medication or intervention will be found to correct malnutrition and inflammation along with improving survival of the hemodialysis patients. In other words, we suggest that our intervention in addition to other medications or interventions would be promising in this area.

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