Seasonal Variation of Nutritional Status and Oxidative Stress in Haemodialysis Patients - Are They Related?

Tanja Ilic Begovic
    University Hospital Split

Josipa Radic (✉ josiparadic1973@gmail.com)
    Sveuciliste u Splitu Medicinski fakultet   https://orcid.org/0000-0003-2645-7597

Mislav Radic
    University Hospital Split

Darko Modun
    Sveuciliste u Splitu Medicinski fakultet

Ana Seselja-Perisin
    Sveuciliste u Splitu Medicinski fakultet

Leida Tandara
    University Hospital Split

Abstract

Background

Seasonal variations in body composition and parameters that reflect nutritional status are well established in haemodialysis (HD) patients. However, no study has assessed changes in oxidative stress (OS). The objectives of our study were to assess seasonal variations in OS, body composition and other nutritional parameters, as well as their interactions.

Methods

Seasonal variations in fat tissue mass (FTM), fat tissue index (FTI), adipose tissue mass (ATM), lean tissue mass (LTM), lean tissue index, body cell mass (BCM and overhydration (OH), OS (the blood levels of derivatives of reactive oxygen metabolites (d-ROMs), thiobarbituric reactive substances (TBARS), plasma protein reduced thiol content (THIOLS) and ferric reducing ability of plasma (FRAP) were measured) and other nutritional parameters were assessed in 45 HD patients aged 70 (60.5-76.5) years.

Results

Significantly increase in FTM (P=<0.001), FTI (P=<0.001) and ATM (P=<0.001) and significantly decrease in LTI (P=<0.001), LTM (P=<0.001), BCM (P=<0.001) and OH (P=0.004) over season was found. Also, significantly seasonal variations in d-ROMs (P=0.02) and THIOLS (P=0.02) were found. Statistically significant predictor of LTM and BCM was d-ROM (β =-0.57 (95% CI -1.08 to -0.06); P=0.03; β =-0.04 (95% CI -0.075 to -0.006); P=0.02). Furthermore, statistically most significant predictor of d-ROM was hip circumference (β =2.66 (95% CI 0.28 to 5.04); P=0.03), while for THIOLS it was WHtR (β=251(95% CI 16.6 to 477.2); P=0.03) and serum prealbumin level (β=263 (95% CI 6.8 to 521.1); P=0.04).

Conclusions

These results suggest seasonal variations of OS in HD patients and possible interaction between OS and nutritional status in HD patients.

Background

Despite modern renal replacement therapy and pharmacological interventions end stage renal disease (ESRD) is still associated with disproportionately high mortality. Leading cause of this excess mortality and morbidity is cardiovascular disease which accounts for 40%-50% deaths (1). „Traditional" risks for cardiovascular disease fail to explain the full range of cardiovascular burden of chronic kidney disease (CKD) patients (2) and there are many on-going researches trying to explain the role and contribution of nutritional status, oxidative stress (OS), inflammation and other „non-traditional" factors to this excessive mortality in CKD. In a large cohort of haemodialysis (HD) patients, significant seasonal variations in overall and cardiovascular mortality were observed, which were consistent over different climatic regions.

Other physiologic and laboratory parameters were also seasonally different. Results showed that mortality differences were related to seasonality of physiologic and laboratory parameters (3).

During the last two decades, OS has become the center of attention as a novel, nontraditional risk factor for inflammation, atherosclerosis and chronic kidney disease (CKD) progression (4). Furthermore, OS is increased at the very early stages of CKD, (5) is augmented in parallel to deterioration of renal function, (6) and is further exacerbated by the HD procedure (7,8). Therefore, HD procedure itself contributes to inflammation and OS stress (8). It is well known that HD is characterized by excessive OS for several reasons. Firstly, multiple comorbidities that usually accompany HD patients like dyslipidemia, hypertension, metabolic syndrome, diabetes mellitus, advanced age, and atherosclerosis trigger pro-oxidant activity (9). Secondly, in HD patients, antioxidant defense mechanisms are impaired (4). Thirdly, the chronic inflammation that characterizes HD patients is directly linked with OS (10). Also, it is well known that several HD procedure-related factors are implicated in the pathogenesis of OS. Duration of dialysis therapy, iron infusion, anemia, presence of central venous catheter, and bioincompatible dialyzers are several factors triggering the development of OS (9). Finally, the HD procedure per se seems to activate prooxidant mechanisms (11) and every HD session is characterized by further loss of antioxidants molecules (eg. vitamins and trace elements). Convective and diffusive losses of vitamin C during haemodiafiltration session is a contributive factor to oxidative stress in HD patients (12). Many dietary restrictions in HD patients as well as the high prevalence of malnutrition may also result in reduced intake of nutritional factors (eg. vitamin C, D, E) (13) leading to significant depletion of antioxidant defense mechanisms.

Protein energy wasting (PEW) is one of the most common comorbidities observed in ESRD on chronic HD (14). It is well known that a multitude of factors can affect the nutritional and metabolic status of patients with ESRD, including decreased dietary nutrient intake, catabolic effects of renal replacement therapy, systemic inflammation, metabolic and hormonal derangements, and comorbid conditions such as diabetes and depression (15). PEW is associated with poor quality of life, complications and increased risk of mortality (16).

Since poor nutritional status is associated with increased death risk in HD patients (17) measuring reliable markers of PEW may lead to timely interventions for individuals at risk. Hypoalbuminemia is currently the most commonly used surrogate of PEW in HD patients and has a strong association with increased mortality in this population of patients (18) even though a low serum albumin appears to be a strong marker of inflammation rather than nutritional status (14). Several studies have advocated the use of serum prealbumin, as a better surrogate of nutritional status in this patient population (14,19).

Body composition has been shown to be an important parameter related to outcome in dialysis patients. Alterations in body composition are very common in dialysis patients, in particular loss of lean tissue mass (LTM) which is induced by PEW and highly associated to morbidity and mortality (20).

Various clinical and laboratory parameters were found to differ between seasons and previous studies have shown seasonal variations in blood pressure level (21), body mass composition and hydration state

(22), interdialytic weight gain (3,23), body weight (24), calcium phosphate metabolism (25), clinical and laboratory variables that reflect nutritional status (26) and even cognitive impairment, depression, sleep disorders and quality of life (27) in maintenance HD patients.

To our knowledge there is no study focusing exclusively on seasonal variations of OS in maintenance HD patients. Considering the importance of OS and malnutrition in this population of patients the aim of this study was to define more precisely the seasonal variation of OS, body composition, anthropometry and laboratory parameters that reflect nutritional status in maintenance HD patients living in Dalmatia, South Croatia, as well as their interaction.

Methods

Study participants

This study was conducted at the dialysis unit of the Department of Nephrology and Dialysis, University Clinical Hospital Centre, in Split. In total, a selected population of 45 adults (15 females and 30 males) on maintenance haemodialysis (HD) patients were included.

Eligible participants were enrolled if they met the following inclusion criteria: (i) aged 18 years or more, (ii) stable duration of maintenance HD of more than six months with a three times weekly dialysis program before study entry, (iii) continuity of HD regimen and (iv) those patients have never changed their modality of dialysis treatment (from peritoneal dialysis to HD). None of the patients received antibiotics, cytotoxic drugs, blood transfusions or corticosteroids during the 3 months prior to and during participation in the study. We also excluded those patients who had an implanted pacemaker or cardioverter defibrillator, stents or limb amputation; patients with liver cirrhosis and active underlying malignant disease or active infection at the beginning of the study; and patients who refused to participate in the study.

The causes of ESRD were arterial hypertension in 20 (44.5%) patients, diabetes mellitus in 7 (15.5%), chronic glomerulonephritis in 4 (8.9%), polycystic kidney disease in 5 (11.1%), and unknown in 9 (20%).

The fulfilment of these criteria was determined by interviewing both participants and their relatives, as well as by reviewing participants' medical records.

The assessment of nutritional status, body mass composition, anthropometric measurements and blood sampling was performed in HD patients before the midweek HD session. Measurements were taken in July, October and January; altogether in 135 HD sessions. Blood was taken just prior to connecting the subject to the dialysis machine and before administering heparin. For determining the post HD blood urea concentration, a blood sample was obtained from the arterial line 2 min after the blood pump was reduced to 50 mL/min (slow-flow technique). All patients were receiving conventional 4 h HD, three times weekly, with bicarbonate dialysate at a flow rate of 500 mL/min and low molecular weight heparin as standard anticoagulation. The dialysis methods and pharmacological therapy have not changed

(erythropoietin dose and dose of bone metabolism drugs were changed with dosage adjustment according to clinical guidelines) for the analysed months. High-flux polysulfone dialyzers (Fresenius Medical Care, Bad Homburg, Germany) were used mainly for HD.

All participants were informed of the purpose and nature of the study and provided written consent. The study protocol was accepted by the Hospital Ethics Committee of the University Hospital Centre Split (class 500-03/14-01/40, number: 2181-147-01/06/J.B.-14-2).

Biochemical and haematological analysis

Concentrations of total iron binding capacity (µmol/L), urea (mmol/L), creatinine (µmol/L), uric acid (µmol/L), serum albumin (g/L), phosphates (mmol/L) and C-reactive protein (CRP) (mg/L) were determined by standard laboratory methods.

The following parameters were determined by immunoturbidimetry: high sensitivity CRP (hsCRP) (mg/L) (Beckman Coulter, AU680, USA) and prealbumin (g/L) (Cobas Integra, Roche Diagnostics, Germany). A complete blood count was obtained with a hematology analyzer (Advia 120, Siemens, Erlangen, Germany).

Assessment of nutritional status

There is not a single measurement that provides complete assessment of the nutritional status of HD patients. To assess nutritional status in HD patients in this study, anthropometric measurements; the malnutrition inflammation score (MIS); the dialysis malnutrition score (DMS); body mass composition monitoring and laboratory parameters that reflect nutritional status such as serum albumin and prealbumin were used.

The following anthropometric parameters were collected for each study subject: height (cm), dry weight (kg), triceps skin fold (mm), waist circumference (WC), hip circumference (HC) and mid-upper arm circumference (MUAC). Additionally, waist-to-height ratio (*WHtR*) and BMI were calculated for each study subjects. The subjects stood upright, facing forward with their shoulders relaxed, and measures were taken with flexible, nonstretchable measuring tape.

The MIS assessment was performed according to the description by Kalantar-Zadeh et al. (28). The MIS is measured on a 4-point scale and is a quantitative nutrition screening tool consisting of four main parts: patients' related medical history, physical examination, BMI and laboratory parameters. The sum of all components ranges from 0 to 30, and a higher score reflects a more severe degree of malnutrition and inflammation. The MIS was found to significantly correlate with hospitalization; mortality; and indices of nutrition, inflammation, and anaemia (29, 30).

Dialysis Malnutrition Score (DMS) consists of seven features; weight change, dietary intake, GI symptoms, functional capacity, co-morbidity, subcutaneous fat and signs of muscle wasting. Each component has a score from 1 (normal) to 5 (very severe). Thus the malnutrition score (sum of all seven components) is a number between 7 (normal) and 35 (severely malnourished). Lower score denotes tendency towards a normal nutritional status. A higher score is considered to be an indicator of the presence of malnutrition elements i.e. protein energy malnutrition (31).

The assessment of body mass composition was carried out using the Body Composition Monitor portable device (Fresenius Medical Care), which works on the principle of bioimpedance spectroscopy (32). The Body Composition Monitor is a valid method for assessing and monitoring hydration and nutritional status in haemodialysis patients (6). Measurements using the Body Composition Monitor (according to the manufacturer's instructions) were made before the midweek dialysis session. Patients were in the supine position for approximately 5 min before the measurement. All Body Composition Monitor measurements were performed by the same trained operator with the study participant in the supine position on a nonconductive bed in resting conditions. Body Composition Monitor measurements included the following variables: overhydration volume (OH) (L), lean tissue mass (LTM) (kg), lean tissue index (LTI) (kg/m^2), fat tissue mass (FTM), (kg), fat tissue index (FTI), (kg/m^2), adipose tissue mass (ATM) (kg) and body cell mass (BCM) (kg) (33).

Oxidative stress

The blood levels of derivatives of reactive oxygen metabolites (d-ROMs) as indicator of protein oxidation and thiobarbituric reactive substances (TBARS) as indicator of lipid oxidation were measured for all study subjects. Total antioxidant capacity, as plasma protein reduced thiol content (THIOLS) and ferric reducing ability of plasma (FRAP) were also measured.

The d-ROM assay is intended to measure the concentration of total hydroperoxides in serum or heparin plasma. The method was first described by Alberti et al. (34). It is based on the following principle. In an acidic buffered solution (pH = 4.8), iron ions are released from the serum (plasma) proteins and catalyze the in vitro transformation of hydroperoxides into alkoxyl and peroxyl radicals, which further react with the chromogen N,N-diethyl-p-phenylenediamine. The concentration of the colored complex is directly proportional to the concentration of the hydroperoxides that are present in the sample. The absorbance was measured at 505 nm, and the results are expressed in Caratelli units (CARR U). One CARR U corresponds to 0.08 mg/100 mL H2O2. The characteristics of the assay were evaluated and validated by Verde et al. (35), who reported that the assay is reliable even in patients with hyposideremic anemia.

The total antioxidant capacity, as the FRAP value, was measured. FRAP was measured by the ferric reducing/antioxidant and ascorbic acid (FRASC) assay (36). In this assay, the samples are treated with or without ascorbate oxidase, and antioxidants in the sample are evaluated as reductants of Fe3+ to Fe2+, which is chelated by tripyridyltriazine (TPTZ) to form an Fe2+−TPTZ complex absorbing at 593 nm. Absorbance was monitored with a UV−Vis spectrophotometer equipped with a six-cell holder and a

thermostatically controlled bath. The results were compared with a standard curve prepared daily with different concentrations of vitamin C (ascorbic acid) and expressed as micromoles of vitamin C equivalents. The validity of this method for determination of vitamin C in heparinized human plasma has been shown previously (37).

The assay for plasma protein reduced thiol content (THIOLS) measures the major source of reducing equivalents (or antioxidant capacity) available in the plasma. Thiol groups were assayed according to the method of Ellman (38) as modified by Hu (39), as described in Himmelfab et al.(40). Briefly, 2 mL of buffer containing 0.1mol/L Tris,1 mmol/L EDTA, pH 8.2, and 100mL plasma was added to cuvettes, followed by 100uL 10 mmol/L 5dithio-bis (2-nitrobenzoic acid) (DTNB) in methanol. Blanks were run for each sample, prepared as above, with the exception that there was no DTNB in the methanol. Following incubation for 15 minutes at room temperature, sample absorbance was read at 412 nm. Results are expressed as umol/L of glutathione.

TBARS assay is based on reaction of malondialdehyde (MDA), one of end products of lipid peroxidation, with TBA (41). To correct for background absorption, the absorbance values at 572 nm were subtracted from those at 532 nm, which represent the absorption maximum of the TBA:MDA adduct (42). Absorbance was monitored by the above-mentioned UV-spectrophotometer. All measurements were carried out in triplicate. Results were compared with a standard curve prepared daily with different concentrations of MDA and expressed as lmol∕ L MDA.

STATISTICAL METHODS

To discern the mean effect in the numeric variables of the three measurements,with the significance level of 0.05, power 0.95, and the effect size 0.25, the minimum sample size required was 44 subjects (calculated by G * Power 3.1.2, Franz Faul, University in Kiel, Germany). Categorical data are represented by absolute and relative frequencies. Numerical data were described by the median and the limits of the interquartile range. The normality of the distribution of numerical variables was tested by the Shapiro-Wilk test. Differences between numerical variables between measurements were tested by Friedman's test (Post hoc Conover). The correlation between numerical variables was evaluated by Spearman's correlation coefficient ρ (rho). Using multivariate regression analysis (*stepwise*), we determined the predictors that influence oxidative stress. All P values were two-sided. The significance level was set to Alpha = 0.05. MedCalc Statistical Software version 19.1.7 (MedCalc Software Ltd, Ostend, Belgium; https://www.medcalc.org; 2020) was used in the statistical analysis.

Results

Data were processed on 135 single HD treatments involving a group of 45 MHD patients. Baseline demographic data demonstrated (Table 1) that average age of participants was 70 years (range 60.5-76.5 years), 15 (33.3%) were women, and HD vintage was 27 months (range 16-53.5 months). The average MIS at the beginning of study was 8 (range 6-9) and average DMS was 10 (range 9-12). Other

baseline data regarding anthropometric value, body composition parameters, laboratory parameters and parameters of OS for all study participants are shown in **Table 1.**

Seasonal variations in anthropometric and body composition parameters in 135 haemodialysis sessions performed on 45 maintenance haemodialysis patients are shown in **Table 2.** Significant seasonal variations were found for triceps skin fold (P=0.01), WC (P=0.03) and WHtR (P=0.02), respectively. Also, significant seasonal differences were found for body mass composition parameters. Significantly increase in FTM (P=<0.001), FTI (P=<0.001) and ATM (P=<0.001) was found over season. Therefore, significantly decrease in LTI (P=<0.001), LTM (P=<0.001) and BCM (P=<0.001) over season was found. OH significantly decreased (P=0.004) over season with a peaked value in June. In contrast to body mass composition parameters, neither dry weight nor BMI significantly changes over season during 6 months follow up.

Also, significant seasonal variations in biochemical parameters in 135 HD session performed on 45 maintenance HD patients were found as shown in **Table 3.** Significant seasonal difference among all study subject were found in uric acid (P=0.03), pre HD urea (P=0.002), albumin (P=0.001) and prealbumin (P=0.001) level. In contrast, neither serum creatinine level, haemoglobin, CRP nor hs-CRP level varied with the season.

Furthermore, seasonal variations of OS parameters during follow up for all study subjects were analysed as shown in **Table 4.** Significantly seasonal variations in d-ROMs (P=0.02) and THIOLS (P=0.02) value were found. Also, results showed significantly positive correlation between d-ROMs and hs-CRP (ρ=0.361, P=0.03) **(Figure 1)** and significantly positive correlation between dialysis duration and TBARS (ρ=0.324, P=0.02).

Correlations of body mass composition parameters with parameters of nutritional status, other anthropometric and biochemical parameters in January are shown in **Table 5 and Figure 2.** Significantly positive correlations between MUAC, WC, WHtR, hip circumference, BMI and FTI was found (ρ=0.455, P=0.01), (ρ=0.571, P=<0.001), (ρ=0.641, P=<0.001), (ρ=0.648, P=<0.001), (ρ=0.711, P=<0.001), respectively. Also, significantly positive correlation between MUAC, WC, WHtR, hip circumference, BMI and FTM was found (ρ=0.503, P=<0.01), (ρ=0.657, P=<0.001), (ρ=0.631, P=<0.001), (ρ=0.758, P=<0.001), (ρ=0.738, P=<0.001), respectively. Therefore, significantly positive correlation between MUAC, WC, WHtR, hip circumference, BMI and ATM was found (ρ=0.503, P=<0.01), (ρ=0.649, P=<0.001), (ρ=0.624, P=<0.001), (ρ=0.752, P=<0.001), (ρ=0.728, P=<0.001), respectively. Results also showed positive correlation between LTI, LTM, BMC and serum prealbumin level (ρ=0.434, P=0.01), (ρ=0.467, P=0.01), (ρ=0.475, P=0.01), respectively. Significantly negative correlation between OH and serum prealbumin level was found (ρ=-0.369, P=0.03) among all study subjects.

To analyze factors that affect body composition parameters we performed multiple regression analysis. In multivariant analysis (*stepwise method*) statistically most significant predictors of fat tissue indices (FTI, FTM, ATM) was hip circumference (β =0.29 (95% CI 0.12 to 0.47); P=0.002; β =1.3 (95% CI 1.01 to 1.61); P=<0.001; β =1.8 (95% CI 1.41 to 2.19); P=<0.001), respectively. Statistically significant predictor of

LTM and BCM was d-ROM (β =-0.57 (95% CI -1.08 to -0.06); P=0.03; β =-0.04 (95% CI -0.075 to -0.006); P=0.02). Significant predictor of FTI was MIS (β =2.66 (95% CI 0.28 to 5.04); P=0.03), respectively.

Similarly, we also analyzed nutritional factors that affect oxidative stress parameters, we performed multiple regression analysis and univariant analysis of each OS parameter. In multivariant analysis (*stepwise method*) statistically most significant predictor of d-ROM was hip circumference (β =2.66 (95% CI 0.28 to 5.04); P=0.03), for THIOLS it was WHtR (β=251(95% CI 16.6 to 477.2); P=0.03) and serum prealbumin level (β=263 (95% CI 6.8 to 521.1); P=0.04).

Discussion

This study evaluated seasonal variations of nutritional status, anthropometric, body mass composition and OS parameters during 6-months period and their associations in a group of maintenance HD patients living in a mild Mediterranean climate of the Adriatic coast in Dalmatia, South Croatia, Europe. To our knowledge this is the first detailed European report of seasonal variation in OS parameters in maintenance HD patients.

In this population of HD patients, we showed significant seasonal difference among all study subjects in all body mass composition parameters and anthropometric parameters such are triceps skin fold, WC and WHtR.

First of all, OH significantly decreased during 6 months of follow up, especially during first three months (between June and October). Possible explanations for this finding might be

that initial measurement was done at summer month (July) when fluid intake is higher as a consequence of increased thirst and higher ambient temperatures and other possibility is that after initial BIA measurement patients were more aware of OH and became more compliant in next three months. Our results are similar to the results of Broers et al. (22) who found that fluid overload was highest in spring and summer and lowest in winter.

Therefore, body mass composition parameters that represent fat tissue (FTI, FTM and ATM) showed significant seasonal variation during 6 months follow up whereas body mass composition parameters that are predictors of nutritional status (LTI, LTM and BCM) showed significant decrease. Results showed that FTI, FTM and ATM were highest in winter (in January) and lowest in summer (in July) whereas LTI, LTM and BCM were lowest during winter (in January) and highest in summer (June). This pattern of body composition changes was already confirmed in previous studies, showing that with dialysis vintage maintenance HD patients experience loss of muscle mass with increasing fat mass and it is called "sarcopenic obesity" (43, 44). These results are in line with a recent cohort study in which increase in FTI and decrease in LTI were observed within 2 years following the start of dialysis (43). A combination of these two disorders of body composition leads to a higher risk of mortality more than when each pathology occurs separately (44, 45).

As mentioned earlier, anthropometric parameters such are triceps skin fold, WC and WHtR also showed significant seasonal differences during follow up. Possible explanation for this findings in our population of HD patients might be significantly increase in fat mass content during follow up because those HD patients with higher value of WC and WHtR had significantly higher fat tissue content (higher value of FTI, FTM and BCM) after 6 months of follow up (in January). WC (46,47,48,49) and WHtR (48,49,50) are commonly used in HD patients to assess visceral fat, and the predictability of mortality in HD patients further strengthens the role of WC (47). Obese dialysis patients have both a large WC and high percentage of body fat (51).

In this population of HD patients, we did not show significant seasonal differences among all study subject in BMI and dry weight with peak values for both parameters occurring in January. In contrast to results from our study, in previous studies BMI and pre HD weight varied with season but also, like in our study, peaked in January. The difference may be due to older HD patients and shorter HD duration in our study. Body fat mass increase and lean body mass decreased significantly during first year of HD (52). That could be explanation for our findings, and also because of significant increase of fat mass and significant decrease of lean mass and OH, BMI and dry weight did not change significantly during follow up. The study of Broers et (22) all. supported the fact that BMI in cold months is higher due to fat mass. Next to nutritional intake, it is also possible that low physical activity plays a role in peak value of BMI, significantly higher fat mass and lower lean tissue mass in January. It is known that dialysis patients have decreased levels of physical activity, matching a sedentary lifestyle (53). Physical inactivity in dialysis patients is associated with an increased risk for hospitalization and mortality (54,55) and with alterations in body composition and decreased muscle strength (56).

Both albumin and prealbumin levels are sensitive to protein–calorie malnutrition and are negative acute-phase proteins, exhibiting decreases in their serum concentration during episodes of inflammation (57,58). Longitudinal measures of albumin or prealbumin concentrations may provide more information about the risk of adverse outcomes on dialysis than single measures of these proteins (59, 60). Our results showed statistically significant seasonal difference in serum albumin level and serum prealbumin level, with the peak values for albumin occurring in July, and the peak value for prealbumin peaked in January. In contrast to our study in study of longitudinal serum albumin and prealbumin concentrations, (61) found that serum albumin concentrations increased, whereas prealbumin concentrations did not change over time on average. The difference may be due to older HD patients, higher baseline serum albumin, lower prealbumin and CRP level and shorter follow up in our study. Therefore, in our previous study (26) we did not found significant seasonal difference nor difference between cold (December and January) and mild (June and September) months in serum albumin level. Possible explanation for this difference might be that in previous study was higher baseline serum albumin level. In our previous study 70.2 % HD patients had baseline serum albumin level ≥ 38 g/L while in present study 51% HD patients had baseline serum albumin level ≥ 38 g/L. According to consensus of the panel of experts of the International Society for renal Nutrition and metabolism serum albumin level < 38 g/L is one of the biochemical parameters that may be indicative of PEW in individuals with kidney disease (14). The interpretation of serum albumin level is complicated since albumin level concentration is the compound

resultant of inflammation, nutrition, and fluid status (62). Data from previous studies about seasonal variation in albumin level are inconclusive. In contrast to serum albumin, serum prealbumin half-life is relatively short, i.e., 2 to 3 days (63). Hence, it may be a more sensitive indicator of nutritional status than either serum albumin or transferrin (19, 64, 65). In our study those HD patients with higher prealbumin level had significantly higher parameters of body lean mass (LTI, LTM and BCM) and lower proportion of body fat but those correlations were not significant. These results are similar to the results from previous study of Mehdi Rambod (59)where the inverse association between serum prealbumin and the percentage of total body fat was found. They found that in HD patients with higher prealbumin level was a lower proportion of body fat and higher proportion of lean body mass.

Our results showed significant seasonal variation in preHD urea level with peak value in January. This is in line with our previous study where pre HD urea level vas significantly higher in cold months with a peaked value in January (26). The most likely explanation is change in in dietary intake (increased protein intake) in cold months among HD patients. CRP, hsCRP and leukocytes level did not show significant seasonal variation with a peak value in January. Similarly to previous study (62,3) CRP and hsCRP were lower in the summer period. These results may point to a lower risk of infective episodes in summer periods.

Of the other laboratory parameters, serum phosphate levels were not significantly different between the various season observed in our study. It is important to note no reliable data on phosphate binders were available in this study and that in general, seasonal variation in laboratory parameters are not completely consistent between studies (23, 66).

Uric acid level in our study showed significantly seasonal differences, uric acid significantly decreased from June to October. Possible explanation could be change in food intake. Those patients who consumed more fruits and vegetables had a higher uric acid level which could be attributed to an overall higher intake of food and high-purine products (67). Uric acid is a powerful oxygen radical scavenger in hydrophilic environments, and a study on a large cohort showed that low and not high serum uric acid level predicted all-cause and CV mortality (68). Longitudinal changes in serum uric acid seem to track with changes in nutritional status over time, and these changes are associated with survival of patients on maintenance HD. An increase in serum uric acid levels over time is accompanied by improvement of nutritional status and lower mortality rate (69).

To our knowledge this is the first study that evaluated seasonal difference in OS stress parameters in HD patients. Our results showed statistically significant seasonal difference in level of d-ROMs. d-ROMs level increased from June to January, with peaked value in January. The most likely explanation for significantly increase in d-ROMs value during season might be significantly increase in fat content during observed seasons. Univariant regression analysis showed that d-ROM was significantly influenced with FTI, FTM and hip circumference. Furthermore, in multivariant analysis most significant positive predictor of d-ROMs was hip circumference. It is important to note that in our study those HD patients with higher hip circumference had significantly higher fat content (adipose tissue). Also, most significant positive

predictor of fat tissue indices (FTI, FTM, ATM) was hip circumference and statistically significant negative predictor of lean tissue indices (LTM and BCM) was d-ROM. Adipose tissue is a potential source of inflammation in ESRD that is not due to increased adiposity and may contribute to mitochondrial dysfunction in uraemia (70). In line with those finding d-ROMs correlated positively with hsCRP in our population of HD patients. These results suggest correlation between anthropometric value, body mass composition indices and OS. Furthermore, OS might be promoted by fat tissue in HD patients and also could have negative influence on lean tissue mass.

In addition, we also measured antioxidant defence in serum of our HD population by measuring plasma THIOLS. Significant seasonal variations in THIOLS level was found with the peak value in October. Similar pattern of seasonal difference was found for THIOLS and serum albumin and prealbumin level. In multivariate analysis results showed that serum prealbumin level was most significant predictor for THIOLS level.

Our results did not show statistically significant seasonal difference in level of TBARS. Previous findings suggested that TBARS levels are increased in the subcutaneous fat tissue of patients with ESRD (71). In contrast to previous study, in our study fat tissue indices (FTI, FTM, ATM) significantly changed over season but TBARS level did not change significantly. But, it is important to note that those HD patients with longer dialysis duration had significantly higher TBARS which might reflect higher level of OS. The inflammatory status and duration of dialysis treatment are the most important factors relating to oxidative stress in HD patients (72). In line with those findings our HD patients with longer dialysis duration had significantly higher level of TBARS.

Also, total antioxidant capacity expressed as FRAP did not show significant seasonal differences. It is well known that fruits and vegetables supply the organism with low-molecular exogenous antioxidants and may contribute to the overall antioxidant capacity of plasma. Furthermore, maintenance HD patients are subject to a number of dietary restrictions and their overall diet frequently does not meet daily caloric and protein requirements (73). Also, the risk of elevated potassium and fluid overload may lie behind decreased fruit and vegetable consumption in this group of patients (74). Malnutrition and hypoalbuminemia reduce antioxidant defence (75) and albumin and prealbumin, commonly used nutritional markers, possess antioxidant properties and can account for significantly lower FRAP values in HD patients when compared with the healthy controls (67). Despite significant seasonal variation in serum albumin, prealbumin and uric acid level our results did not show seasonal variations in FRAP and vitamin C. These findings suggest that many other components contribute to total antioxidants capacity of plasma in HD patients.

During HD therapy, a significant amount of vitamin C is lost and also ascorbic free radicals are formed contributing thus to enhanced OS. Our data did not show significant seasonal variation in vitamin C level. Possible explanation for this findings might be supplementation of vitamin C as regular treatment in our HD unit for every HD patient.

There was not statistically significant difference between season in the DMS and MIS score. These result is in line with result from our previous study (26) were we did not find seasonal difference in DMS score nor difference between cold and mild months (26). But is important to note that in multivariate analysis MIS was most significant positive predictor for FTI and negative predictor for LTI and BCM. Wang WL showed that a high MIS was significantly correlated with a low LTI and low FTI (76). The difference may be due to older HD patients, more women and different region and season in our study.

Several limitations need to be acknowledged. One limitation of this study is that the influence of the dietary habits on nutritional status was not considered. Furthermore, this is single centre observational study with few cases. Also, the study period was nine months and we did not show data for spring season so in this condition a lot of biases such is selection and measured bias might occur. Future multicentre studies on seasonal variation of nutritional status and oxidative stress in maintenance HD patients are needed, with larger number of participants in a different climate region and in a prospective search model and for a longer study period.

Conclusion

We confirmed that seasonal variation in clinical, body mass composition and laboratory parameters that reflect nutritional status are common among maintenance HD patients. Also, to our knowledge this is the first study that showed seasonal variation in OS parameters. Therefore, our results suggest possible bidirectional correlation between OS and body mass composition parameters, especially those parameters of body composition that reflect fat tissue. It is well known from previous studies that MIS, DMS, serum albumin and inflammatory markers are commonly used predictor of mortality of HD patients. Also, there is a growing body of evidence suggesting that OS predict all- cause and/or CV mortality and adverse CV events in HD patients. These results indicate a need of more regular and systemic approach to careful examination of nutritional status in HD patients with special attention to body mass composition. It is important to note that these seasonal variations might lead to biases in the interpretation of results in clinical studies in which measurement schedules for clinical, biochemical, body mass composition and OS parameters vary during the year.

Based on the results from our previous study (26) as well as the results from this study conducted in a mild Mediterranean climate in Dalmatia, South Croatia, we concluded that clinician should pay more attention to seasonal factors when interpreting nutritional status and oxidative stress and planning nutritive intervention for this population of maintenance HD patients.

Abbreviations

ESRD: End stage renal disease

CKD: Chronic kidney disease

OS: Oxidative stress

HD: Haemodialysis

PEW: Protein energy wasting

LTM: lean tissue mass

CRP: C-reactive protein

hsCRP: high sensitivity C-reactive protein

MIS: Malnutrition inflammation score

DMS: Dialysis malnutrition score

WC: Waist circumference

HC: Hip circumference

MUAC: Mid-upper arm circumference

WHtr: waist-to-height ratio

BMI: body mass index

OH: overhydration volume

LTI: lean tissue index

FTM: fat tissue mass

FTI: fat tissue index

ATM: adipose tissue mass

BCM: body cell mass

d-ROMs: derivatives of reactive oxygen metabolites

TBARS: thiobarbituric reactive substances

THIOLS: plasma protein reduced thiol content

FRAP: ferric reducing ability of plasma

CARR U: Caratelli units

FRASC: ferric reducing/antioxidant and ascorbic acid assay

TPTZ: tripyridyltriazine

EDTA: ethylene-diamine-tetraacetic acid

DTNB: 2-nitrobenzoic acid

MDA: malondialdehyde

TBA: thiobarbituric acid

Declarations

Availability of data and materials

BackgroundThe data obtained in the current study will be available from the corresponding author upon reasonable request after publication of the results on the main research questions.

Conflict of interest

The authors declare that they have no conflict of interest.

Funding

None.

Ethical approval

All procedures performed in this study were in accordance with the ethical standards of University Hospital Center Split and with the 1964 Helsinki declaration and its later amendments. The study protocol was accepted by the Hospital Ethics Committee of the University Hospital Centre Split (class 500-03/14-01/40, number: 2181-147-01/06/J.B.-14-2).

Informed consent

Informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Acknowledgements

Not applicable

Contributions

T.I.B., JR and M.R.: study concept and design, analysis and interpretation of data. T.I.B., JR and ASP: acquisition of data. J.R. and M.R.: drafting of the manuscript. D.M., L.T. and J.R.: discussion and critical revision of the manuscript.

References

1.Foley RN.Clinical epidemiology of cardiac disease in dialysis patients: left ventricular hypertrophy, ischemic heart disease, and cardiac failure.Semin Dial. 2003 Mar-Apr;16(2):111-7.

2. Parfrey PS, Foley RN. The clinical epidemiology of cardiac disease in chronic renal failure. J Am Soc Nephrol.1999 Jul;10(7):1606-15.

3. Usvyat LA, Carter M, Thijssen S, et al. Seasonal variations in mortality, clinical, and laboratory parameters in hemodialysis patients: a 5-year cohort study. Clin J Am Soc Nephrol. 2012;7:108–15.

4. Duni A, Liakopoulos V, Rapsomanikis KP, et al. Chronic kidney disease and disproportionally increased cardiovascular damage: does oxidative stress explain the burden? Oxid Med Cell Longev. 2017;9036450

5.Annuk M, Fellstrom B, Akerblom O, et al.. Oxidative stress markers in pre-uremic patients. Clin Nephrol. 2001;56(4):308-14.

6. Dounousi E, Papavasiliou E, Makedou A, et al. Oxidative stress is progressively enhanced with advancing stages of CKD. Am J Kidney Dis. 2006;48(5):752-60.

7. Boudouris G, Verginadis II, Simos YV, et al. Oxidative stress in patients treated with continuous ambulatory peritoneal dialysis (CAPD) and the significant role of vitamin C and E supplementation. Int Urol Nephrol. 2013;45(4):1137-1144

8. Liakopoulos V, Roumeliotis S, Gorny X, et al. Oxidative stress in patients undergoing peritoneal dialysis: a current review of the literature. Oxid Med Cell Longev. 2017:3494867.

9. Sangeetha LakshmiB, Harini Devi N, SuchitraMM et al. Changes in the inflammatory and oxidative stress markers during a single hemodialysis session in patients with chronic kidney disease. Ren Fail. 2018;40(1):534-40.

10. Handelman GJ, Walter MF, Adhikarla R, et al. Elevated plasma F2- isoprostanes in patients on long-term hemodialysis. Kidney Int. 2001;59(5):1960-66.

11. Locatelli F, Canaud B, Eckardt KU, et al. Oxidative stress in end-stage renal disease: an emerging threat to patient outcome. Nephrol Dial Transplant. 2003;18(7):1272-80.

12. Morena M, Cristol JP, Bosc JY, et al. Convective and diffusive losses of vitamin C during haemodiafiltration session: a contributive factor to oxidative stress in haemodialysis patients.

Nephrol Dial Transplant. 2002;17(3):422-27

13. Canaud B, Cristol J, Morena M, et al. Imbalance of oxidants and antioxidants in haemodialysis patients. Blood Purif. 1999;17(2−3):99-106.

14. Fouque D, Kalantar-Zadeh K, Kopple J et al. A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease. Kidney Int. 2008;73(4):391-8.

15. Ikizler TA. A Patient with CKD and Poor Nutritional Status. Clin J Am Soc Nephrol 2013; 8: 2174−82.

16. Qureshi AR, Alvestrand A, Divino-Filho JC et al. Inflammation, malnutrition,

and cardiac disease as predictors of mortality in hemodialysis patients. J Am Soc Nephrol. 2002;13:28-36.

17. Kovesdy CP, Kalantar-Zadeh K. Why is protein-energy wasting associated with mortality in chronic kidney disease? Semin Nephrol. 2009; 29(1):3−14.

18. Lacson E Jr, Ikizler TA, Lazarus JM, et al. Potential impact of nutritional intervention on end-stage renal disease hospitalization, death, and treatment costs. J Ren Nutr. 2007; 17:363−71.

19. Chertow GM, Ackert K, Lew NL et al. Prealbumin is as important as albumin in the nutritional assessment of hemodialysis patients. Kidney Int 2000; 58:2512−7.

20. Shinaberger CS, Kilpatrick RD, Regidor DL et al. Longitudinal associations between dietary protein intake and survival in hemodialysis patients. Am J Kidney Dis 2006;48:37−49.

21. Duranton F, Kramer A , Szwarc I et al. Geographical Variations in Blood Pressure Level and Seasonality in Hemodialysis Patients. Hypertension 2018;71:289-96.

22. Broers NJH, Usvyat LA, Marcelli D et al. Season affects body composition and estimation of fluid overload in haemodialysis patients: variations in body composition; a survey from the European MONDO database. Nephrol Dial Transplant (2015) 30: 676−681

23. Cheung AK, Yan G, Greene T et al. Seasonal variations in clinical and laboratory variables among chronic hemodialysis patients. J Am Soc Nephrol 2002;13:2345−52.

24. Tozawa M, Iseki K, Iseki C, et al. Seasonal blood pressure and body weight variation in patients on chronic hemodialysis. Am J Nephrol 1999;19:660−7.

25. Strózecki P, Doroszewski W, Kretowicz M, et al. Seasonal profile of calcium phosphate metabolism in hemodialysis patients with secondary hyperparathyroidism. Pol Arch Med Wewn 2002;108:867−71.

26. Ilić Begović T,Radić J, Radić M et al. Seasonal Variations of Nutritional Status in Maintenance Hemodialysis Patients. Ther Apher Dial.2016;20(5):468-75.

27. Afsar B, Kirkpantur A. Are there any seasonal changes of cognitive impairment, depression, sleep disorders and quality of life in hemodialysis patients? Gen Hosp Psychiatry 2013;35:28–32

28. Kalantar-Zadeh K, Kopple JD, Block G et al. A Malnutrition Inflammation Score is correlated with morbidity and mortality in maintenance hemodialysis subjects. Am J Kidney Dis 2001;38(6):1251-63.

29. Radić J, Bašić-Jukić N, Vujičić B, et al. Anemia Is Correlated with Malnutrition and Inflammation in Croatian Peritoneal Dialysis Patients: A Multicenter Nationwide Study. Peritoneal dialysis international. 2017; 37(4):472-75.

31. Kalantar-Zadeh K, Kleiner M, Dunne E et al. A Modified quantitative subjective global assessment of nutrition for dialysis patients. Nephrol Dial Transplant.1999;14(7):173

32. bcm-fresenius.com [Internet]. Bad Homburg: BCM – Body Composition Monitor, Fresenius Medical Care; [cited 2018 July 10]. Available from: http://www.bcm-fresenius.com/.

33. Van Biesen W, Williams JD, Covic AC et al. Fluid status in peritoneal dialysis patients: the European Body Composition Monitoring (EuroBCM) study cohort. PLoS One 2011; 6(2): e17148.

34. Alberti A, Bolognini L, Macciantelli D et al. The radical cation of N,N-diethl-para-phenylendiamine: a possible indicator of oxidative stress in biological samples. Res Chem Intermed 2000;26(3):253–67.

35. Verde V, Fogliano V, Ritieni A et al. Use of N,N-dimethyl-p-phenylenediamine to evaluate the oxidative status of human plasma. Free Radic Res 2002;36(8):869–73.

36. Benzie IFF, Strain JJ. Simultaneous automated measurement of total 'antioxidant' (reducing) capacity and ascorbic acid concentration. Redox Rep 1997;3:233–38.

37. Chung WY, Chung JK, Szeto YT et al. Plasma ascorbic acid: measurement, stability and clinical utility revisited.Clin Biochem.2001 Nov;34(8):623-7.

38. Ellman GL: Tissue sulfhydryl groups.Archives of Biochemistry and Biophysics; 1959;82:70–7

39. Hu ML, Louie S, Cross CE et al. Antioxidant protection against hypochlorous acid in human plasma. J Lab Clin Med 1993;121:257–62.

40. Himmelfarb J, McMonagle E, McMneamin. Plasma protein thiol oxidation and carbonyl formation in chronic renal failure.Kidney Int 2000;58:2571–78.

41. Esterbauer H, Cheeseman KH. Determination of aldehydic lipid peroxidation products: malonaldehyde and 4-hydroxynonenal. Methods Enzymol. 1990;186:407-21.

42. Lapenna D, Ciofani G, Pierdomenico SD, et al. Reaction conditions affecting the relationship between thiobarbituric acid reactivity and lipid peroxides in human plasma. Free Radic Biol Med.2001; 1;31(3):331-5.

43. Marcelli D, Brand K, Ponce P, et al. Longitudinal changes in body composition in patients after initiation of hemodialysis therapy: results from an international cohort. J Ren Nutr. 2016;26:72–80.

44. Rymarz A, Bartoszewicz Z, Szamotulska K. The Associations Between Body Cell Mass and Nutritional and Inflammatory Markers in Patients With Chronic Kidney Disease and in Subjects Without Kidney Disease. J Ren Nutr. 2016;26(2):87-92.

45. Pommer W. Preventive nephrology:The Role of Obesity in Different Stages of Chronic Kidney Disease. Kidney Dis 2018;4:199–204.

46. Evans PD, McIntyre NJ, Fluck RJ et al. Anthropomorphic measurements that include central fat distribution are more closely related with key risk factors than BMI in CKD stage 3. PLoS One 2012, 7(4):e34699.

47. Postorino M, Marino C, Tripepi G et al. Abdominal obesity and all-cause and cardiovascular mortality in end-stage renal disease. J Am Coll Cardio. 2009;53(15): 1265–72.

48. Taylor AE, Ebrahim S, Ben-Shlomo Y et al. Comparison of the associations of body mass index and measures of central adiposity and fat mass with coronary heart disease, diabetes, and all-cause mortality: a study using data from 4 UK cohorts. Am J Clin Nutr 2010; 91(3):547–56.

49. Taylor RW, Keil D, Gold EJ et al. Body mass index, waist girth, and waist-to-hip ratio as indexes of total and regional adiposity in women: evaluation using receiver operating characteristic curves. Am J Clin Nutr 1998; 67(1):44–9.

50. Lamacchia O, Pinnelli S, Camarchio D et al. Waist-to-height ratio is the best anthropometric index in association with adverse cardiorenal outcomes in type 2 diabetes mellitus patients. Am J Nephrol 2009; 29(6):615–19.

51. Kittiskulnam P, Chertow GM, Kaysen GA et al. Misclassification of obesity by body mass index among patients receiving hemodialysis. Am J Kidney Dis 2016;67(4):709-11.

52. Ishimura E, Okuno S, Kim M et al. Increasing Body Fat Mass in the First Year of Hemodialysis J Am Soc Nephrol 2001;12:1921–26.

53. Avesani CM, Trolonge S, Deleaval P et al: Physical activity and energy expenditure in haemodialysis patients: an international survey. Nephrol Dial Transplant 2012; 27: 2430–34.

54. Stack AG, Molony DA, Rives T, et al. Association of physical activity with mortality in the US dialysis population. Am J Kidney Dis. 2005; 45: 690–01.

55. Tentori F, Elder SJ, Thumma J et al: Physical exercise among participants in the Dialysis Outcomes and Practice Patterns Study (DOPPS): correlates and associated outcomes. Nephrol Dial Transplant

2010; 25: 3050–62.

56. van den Ham EC, Kooman JP, Schols AM et al. Similarities in skeletal muscle strength and exercise capacity between renal transplant and hemodialysis patients. Am J Transplant 2005; 5: 1957–65.

57. Kaysen GA, Greene T, Daugirdas JT et al. Longitudinal and cross-sectional effects of C-reactive protein, equilibrated normalized protein catabolic rate, and serum bicarbonate on creatinine and albumin levels in dialysis patients. Am J Kidney Dis 2003;42(6):1200–11.

58. Kaysen GA, Dubin JA, Muller HG et al. The acute-phase response varies with time and predicts serum albumin levels in hemodialysis patients. The HEMO Study Group. Kidney Int; 2000; 58(1):346–52.

59. Rambod M, Kovesdy CP, Bross R et al. Association of serum prealbumin and its changes over time with clinical outcomes and survival in patients receiving hemodialysis. Am J Clin Nutr. 2008;88:1485–94.

60. Kalantar-Zadeh K, Kilpatrick RD, Kuwae N et al. Revisiting mortality predictability of serum albumin in the dialysis population: time dependency, longitudinal changes and population-attributable fraction. Nephrol Dial Transplant; 2005:20(9):1880–8.

61. Dalrymple LS, Johansen KL, Chertow GM, et al. Longitudinal measures of serum albumin and prealbumin concentrations in incident dialysis patients: the comprehensive dialysis study. J Ren Nutr. 2013;23(2):91-97.

62. Guinsburg AM, Usvyat LA, Etter M et al. Monitoring Dialysis Seasonal Variations in Mortality and Clinical Indicators in International Hemodialysis Populations From the MONDO Registry. BMC Nephrol .2015;14:16:139.

63. Myron Johnson A, Merlini G, Sheldon J et al. Clinical indications for plasma protein assays: transthyretin (prealbumin) in inflammation and malnutrition. Clin Chem Lab Med 2007; 45:419–26.

64. Chertow GM, Goldstein-Fuchs DJ, Lazarus JM et al. Prealbumin, mortality, and cause-specific hospitalization in hemodialysis patients. Kidney Int 2005; 68:2794–800.

65. Sreedhara R, Avram MM, Blanco M et al. Prealbumin is the best nutritional predictor of survival in hemodialysis and peritoneal dialysis. Am J Kidney Dis. 1996; 28:937–42.

66. Yanai M, Satomura A, Uehara Y et al. Circannual rhythm of laboratory test parameters among chronic haemodialysis patients. Blood Purif 2008;26:196–203.

67. Maraj M, Kuśnierz-Cabala B, Dumnicka P et al. Redox Balance Correlates With Nutritional Status Among Patients With End-Stage Renal Disease Treated With Maintenance Hemodialysis Oxid Med Cell Longev. 2019; 5:6309465.

68. Hsu WL, Li SY, Liu JS et al. High Uric Acid AmelioratesIndoxyl Sulfate Induced Endothelial Dysfunction and Is Associated with Lower Mortalityamong Hemodialysis Patients. Toxins 2017; 9 (1): 20.

69. Beberashvili I, Erlich A, Azar A et al. Longitudinal Studyof Serum Uric Acid, Nutritional Status, and Mortalityin Maintenance Hemodialysis Patients. Clin J Am Soc Nephrol. 2016 6;11(6):1015-23.

70. Martinez Cantarin MP, Whitaker-Menezes D, Lin Z et al. Uremia induces adipose tissue inflammation and muscle mitochondrial dysfunction. Nephrol Dial Transplant 2017;1;32(6):943-51.

71. Gotoh M, Nagase S, Aoyagi K et al. Thiobarbituric Acid Reactive Substances Are Increased in the Subcutaneous Fat Tissue of Patients With End-Stage Renal Disease. Nephrol Dial Transplant 1997;12(4):713-7.

72. Nguyen-Khoa T, Massy ZA, De Bandt JP et al.Oxidative stress and haemodialysis: role of inflammationand duration of dialysis treatment. Nephrol Dial Transplant.2001:16(2):335-40.

73. Stark S, Snetselaar L, Hall B et al. Nutritional intake in adult hemodialysis patients. Top Clin Nutr 2011;26(1): 45–56.

74. Kalantar-Zadeh K, Tortorici AR, Chen JL et al. Dietary restrictions in dialysis patients: is there anything left to eat? Semin Dial.2015; 28(2):159-68.

75. Mirończuk-Chodakowska I, Witkowska AM, Zujko ME. Endogenousnon-enzymatic antioxidants in the human body. Adv Med Sci.2018;63(1):68-78.

76. Wang WL, Liang S, Zhu FL et al. Association of the malnutrition-inflammation score with anthropometry and body composition measurements in patients with chronic kidney disease. Ann Palliat Med. 2019;8(5):596-603.

Tables

Table 1. Characteristics of the study sample (N=45)

Parameters	Median* (interquartile range)
	All patients
	(N=45)
Age (mean; years)	70 (60.5-76.5)
Female/Male (number)	15/30
Dialysis vintage (mean; months)	27 (16-53.5)
Dialysis malnutrition score	10 (9-12)
Malnutrition inflammation score	8 (6-9)
Dry weight (kg)	27 (16-53.5)
BMI (kg/m^2)	24.63 (22.3-27.43)
MUAC (cm)	27.5 (26-29.75)
Triceps skin fold (mm)	6 (4-10)
Waist circumference (cm)	100 (88.25-107)
WHtR	0.56 (0.52 − 0.62)
Hip circumference (cm)	102 (97-105.5)
Leukocytes (x10^9/L)	6.1 (4.85-7.35)
Haemoglobin (g/L)	109 (103.5-117)
TIBC (µmol/L)	41 (38-46)
Uric acid (µmol/L)	354 (314.5-398.5)
Pre HD urea (mmol/L)	21.7 (18.8-24.05)
Creatinine (µmol/L)	854 (763-1012.5)
Albumin (g/L)	37 (35-40)
Prealbumin (g/L)	0.29 (0.25-0.33)
Phosphates (mmol/L)	1.64 (1.32-1.8)
C-reactive protein (mg/L)	5.6 (1.95-11.1)
hs-CRP (mg/L)	3.67 (1.63-8.68)
Overhydration (L)	2.65 (2.1 - 4)
Lean tissue index (kg/m^2)	16.2 (13.6 - 17.8)
Fat tissue index (kg/m^2)	6.4 (4.3 - 10.1)

Fat tissue mass (kg)	13.7 (9.3 − 23.5)
Lean tissue mass (kg)	47.7 (39.7 - 56.2)
Adipose tissue mass (kg)	18.65 (12.5 - 31.9)
Body cell mass (kg)	27.7 (22.7 - 32.3)
d-ROMs (Caratelli units (Carr U))	467.15 (407.25 - 494.07)
FRAP (AVG µmol/L vitamin C equivalent)	588.04 (495.8 - 636.76)
THIOLS (AVG GSH µmol/L)	7.2 (6.03-7.71)
TBARS (AVG mda nmol/L)	438.35 (395.82 − 480.67)
VITAMIN C (AVG µmol/L)	24.65 (17.49 − 32.6)

BMI, body mass index; MUAC, mid upper arm circumeference; WHtR, Waist to height ratio; HD, haemodialysis; TIBC, total iron binding capacity; hs, CRP, high sensitivity C-reactive protein; d-ROMs, Derivatives of reactive oxygen metabolites; FRAP,Ferric reducing ability of plasma; THIOLS, plasma reduced thiol content; TBARS, thiobarbituric acid reactive substances;

Table 2. Seasonal variations in anthropometric and body composition parameters in 135 haemodialysis sessions performed on 45 maintenance haemodialysis patients.

	Median (interquartile range)			P*
	Initial measurement	After 3 months	After 6 months	
	July	October	January	
Dry weight (kg)	78.4 (63,5-85)	78 (62.5 - 86)	78 (63.5-86.75)	0.61
BMI (kg/m^2)	24.63 (22.3-27.43)	24.52 (22 - 27.4)	25.14 (21.99-27.4)	0.61
MUAC (cm)	27.5 (26-29.75)	27.5 (25.8 - 30)	26.5 (26-30)	0.46
Triceps skin fold (mm)	6 (4-10)	8 (4 - 10)	10 (4-13)	0.01[†]
Waist circumference (cm)	100 (88.25-107)	103 (88.5-108.8)	102 (89.5-108)	0.03[†]
WHtR	0.55 (0.52 - 0.62)	0.56 (0.52- 0.62)	0.57 (0.53 - 0.63)	0.02[‡]
Hip circumference (cm)	102 (97-105.5)	102 (98 - 106.5)	101 (97.5-107)	0.05
Overhydration (L)	2.65 (2.1 - 4)	1.95 (1.1 - 3.6)	1.85 (1.1 - 2.6)	0.004[‡]
Lean tissue index (kg/m^2)	16.2 (13.6 - 17.8)	14.65 (12.5-17.9)	12.5 (10.1 - 14.2)	<0.001[]
Fat tissue index (kg/m^2)	6.4 (4.3 - 10.1)	7.9 (5.8 - 10)	11.5 (7.8 - 14.7)	<0.001[]
Fat tissue mass (kg)	13.7 (9.3- 23.5)	16.7 (11.1 -24.9)	26.0 (17.2 - 32.2)	<0.001[]
Lean tissue mass (kg)	47.7 (39.7 - 56.2)	41.35 (37.9-57.9)	36.1 (29.5 - 44.2)	<0.001[]
Adipose tissue mass (kg)	18.65 (12.5 - 31.9)	22.7 (15.1 -33.9)	35 (23.3 - 43.8)	<0.001[]
Body cell mass (kg)	27.7 (22.7 - 32.3)	23.95 (21 - 35.6)	19.4 (14.5 - 24.8)	<0.001[]

*Friedmanov test (Post-hoc Conover)

[†] At P < 0.05 level significant differences are between initial measurement vs. after 3 months, initial measurement vs. after 6 months. after 3 months vs. after 6 months

[‡] At P < 0,05 level significant differences are between initial measurement vs. after 3 months, initial measurement vs. after 6 months

[] At P < 0,05 level significant differences are between initial measurement vs. after 6 months, after 3 months vs. after 6 months

BMI, body mass index; MUAC, Mid upper arm circumference; WHtR,Waist to height ratio

Table 3. Seasonal variations in biochemical parameters and nutritional scores in 135 haemodialysis sessions performed on 45 maintenance haemodialysis patients.

	Median (interquartile range)			P*
	Initial measurement	After 3 months	After 6 months	
	July	October	January	
Leukocytes (x10^9/L)	6.1 (4.85-7.35)	6.1 (5 - 7.6)	6.9 (5.7-8.3)	0.33
Haemoglobin (g/L)	109 (103.5-117)	115 (107 - 121)	115 (107-122)	0.14
Uric acid (µmol/L)	354 (314.5-398,5)	333 (288 - 370)	330 (301-384)	0,03§
Pre HD urea (mmol/L)	21.7 (18.8-24.05)	23.9 (21.4 - 26.7)	25.2 (22-28.1)	0.002‡
Creatinine (µmol/L)	854 (763-1012.5)	840 (791.5 - 981.5)	898 (777-970)	0.66
Albumin (g/L)	37 (35-40)	33 (30 - 35.5)	35 (32-38)	0.001⌂
Prealbumin (g/L)	0.29 (0.25-0.33)	0.26 (0.2 - 0.3)	0.31 (0.25-0.35)	0.001‡
Phosphates (mmol/L)	1.64 (1.32-1.8)	1.65 (1.4 - 2)	1.67 (1.35-1.92)	0.49
C-reactive protein (mg/L)	5.6 (1.95-11.1)	5.8 (2.2 - 10.8)	8.3 (2.6-15.9)	0.13
hs-CRP (mg/L)	3.67 (1.63-8.68)	3.39 (1.3 - 9.3)	4.56 (1.86-9.87)	0.78
Dialysis Malnutrition Score	10 (9-12)	11 (8.5-14)	10 (8-10)	0.07
Malnutrition Inflammation Score	8 (6-9)	8 (5.5-10)	8 (6-9.5)	0.85

*Friedmanov test (Post-hoc Conover)

‡At P < 0.05 level significant differences are between initial measurement vs.after 3 months. initial measurement vs. after 6 months

⌂At P < 0.05 level significant differences are between initial measurement vs.after 6 months. after 3 months vs. after 6 months

- At P < 0.05 level significant differences are between initial measurement vs. after 3 months

HD, haemodialysis; hs-CRP, high sensitivity C-reactive protein;

Table 4. Seasonal variations in oxidative parameters in 135 haemodialysis sessions performed on 45 maintenance haemodialysis patients

	Median (interquartile range)			P*
	Initial measurement	After 3 months	After 6 months	
	July	October	January	
d-ROMs (Caratelli units (Carr)	467.15 (407.25-494.07)	484.86 (442.8 - 527.1)	499.56 (459.36-517.97)	0.02¶
FRAP (AVG µmol/L vitamin C equivalent)	588.04 (495.8-636.76)	564.74 (493.9 – 634.9)	575.69 (517.86-632.54)	0.83
THIOLS (AVG GSH µmol/L)	7.2 (6.03-7.71)	8.21 (7 - 9.8)	7.98 (6.31-8.81)	0.02‡
TBARS (AVG mda nmol/L)	438.35 (395.82-480.67)	440.85 (420 – 477.5)	424.17 (385.81-478.38)	0.16
VITAMIN C (AVG µmol/L)	24.65 (17.49-32.6)	28.06 (23.7 – 34.2)	24.52 (16.7-31.35)	0.09

*Friedmanov test (Post-hoc Conover)

‡ At P < 0.05 level significant differences are between initial measurement vs.after 3 months. initial measurement vs. after 6 months

¶At P < 0.05 level significant differences are between initial measurement vs.after 6 months

d-ROMs, Derivatives of reactive oxygen metabolites; FRAP, ferric reducing ability of plasma; THIOLS, Plasma protein reduced thiol content; TBARS, thiobarbituric acid reactive substances;

Table 5. Correlations of body composition parameters with nutritional parameters in January among all study participants (N=45).

		Spearman's rank correlation ρ*(p-value)						
		OH	FTI	FTM	LTI	LTM	ATM	BCM
Leukocytes (x10⁹/L)	Rho	-0.056	0.017	0.096	0.130	0.095	0.099	0.095
	P	0.75	0.92	0.59	0.47	0.60	0.58	0.60
Creatinin (μmol/L)	Rho	0.109	-0.048	0.074	0.137	0.315	0.066	0.253
	P	0.54	0.79	0.68	0.45	0.07	0.72	0.16
CRP (mg/L)	Rho	-0.072	0.136	0.181	-0.109	-0.009	0.189	-0.063
	P	0.69	0.45	0.31	0.55	0.96	0.29	0.73
hs-CRP (mg/L)	Rho	-0.032	0.235	0.243	-0.178	-0.155	0.251	-0.186
	P	0.86	0.19	0.17	0.32	0.39	0.16	0.30
Albumin (g/L)	Rho	-0.244	0.103	-0.054	0.036	-0.119	-0.054	-0.067
	P	0.16	0.57	0.77	0.84	0.51	0.77	0.71
Prealbumin (g/L)	Rho	**-0.369**	-0.323	-0.285	**0.434**	**0.467**	-0.287	**0.475**
	P	**0.03**	0.07	0.11	**0.01**	**0.01**	0.11	**0.01**
MUAC (cm)	Rho	-0.089	**0.455**	**0.503**	0.039	0.085	**0.503**	0.053
	P	0.62	**0.01**	**<0.001**	0.83	0.64	**<0.001**	0.77
Waist circumference (cm)	Rho	0.016	**0.571**	**0.657**	0.015	0.149	**0.649**	0.095
	P	0.93	**<0.001**	**<0.001**	0.94	0.41	**<0.001**	0.60
Triceps skin fold (mm)	Rho	-0.165	0.287	0.258	-0.265	-0.329	0.266	-0.297
	P	0.35	0.11	0.15	0.14	0.06	0.13	0.09
WHtR	Rho	-0.088	**0.641**	**0.631**	-0.070	-0.044	**0.624**	-0.066
	P	0.62	**<0.001**	**<0.001**	0.70	0.81	**<0.001**	0.72
Hip circumference (cm)	Rho	-0.133	**0.648**	**0.758**	-0.079	0.045	**0.752**	-0.009
	P	0.45	**<0.001**	**<0.001**	0.66	0.80	**<0.001**	0.96
BMI (kg/m²)	Rho	-0.106	**0.711**	**0.738**	-0.054	-0.019	**0.728**	-0.046
	P	0.55	**<0.001**	**<0.001**	0.77	0.91	**<0.001**	0.80
Dialysis malnutrition score	Rho	0.128	-0.017	-0.074	-0.181	-0.198	-0.076	-0.212
	P	0.48	0.92	0.69	0.32	0.28	0.68	0.24
Malnutrition	Rho	0.053	0.021	0.025	-0.215	-0.136	0.034	-0.174

inflammation score	P	0.77	0.91	0.89	0.23	0.45	0.85	0.33

* Spearman's rank correlation ρ; p value

OH, overhydration, FTI, fat tissue index, FTM ,fat tissue mass, LTI, lean tissue index, LTM, lean tissue mass, ATM, adispose tissue mass, BCM, body cell mass; CRP, C-reactive protein. hs CRP, high sensitivity C-reactive protein; MUAC, mid upper arm circumference; WHtR, Waist to height ratio; BMI, body mass index
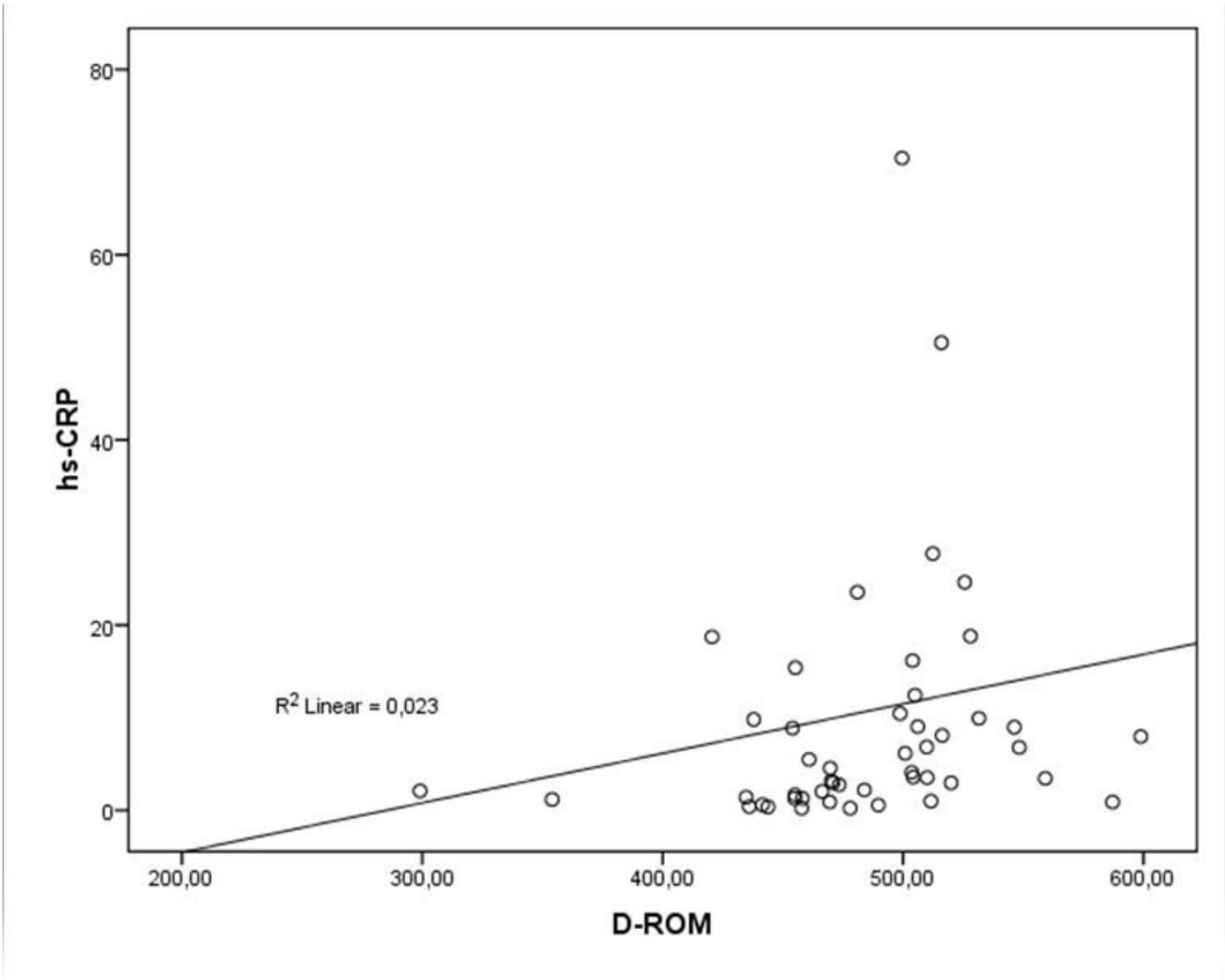
Figures

Figure 1

Correlations between hs C-reactive protein (hs CRP) and derivatives of reactive oxygen metabolites (d-ROMs).
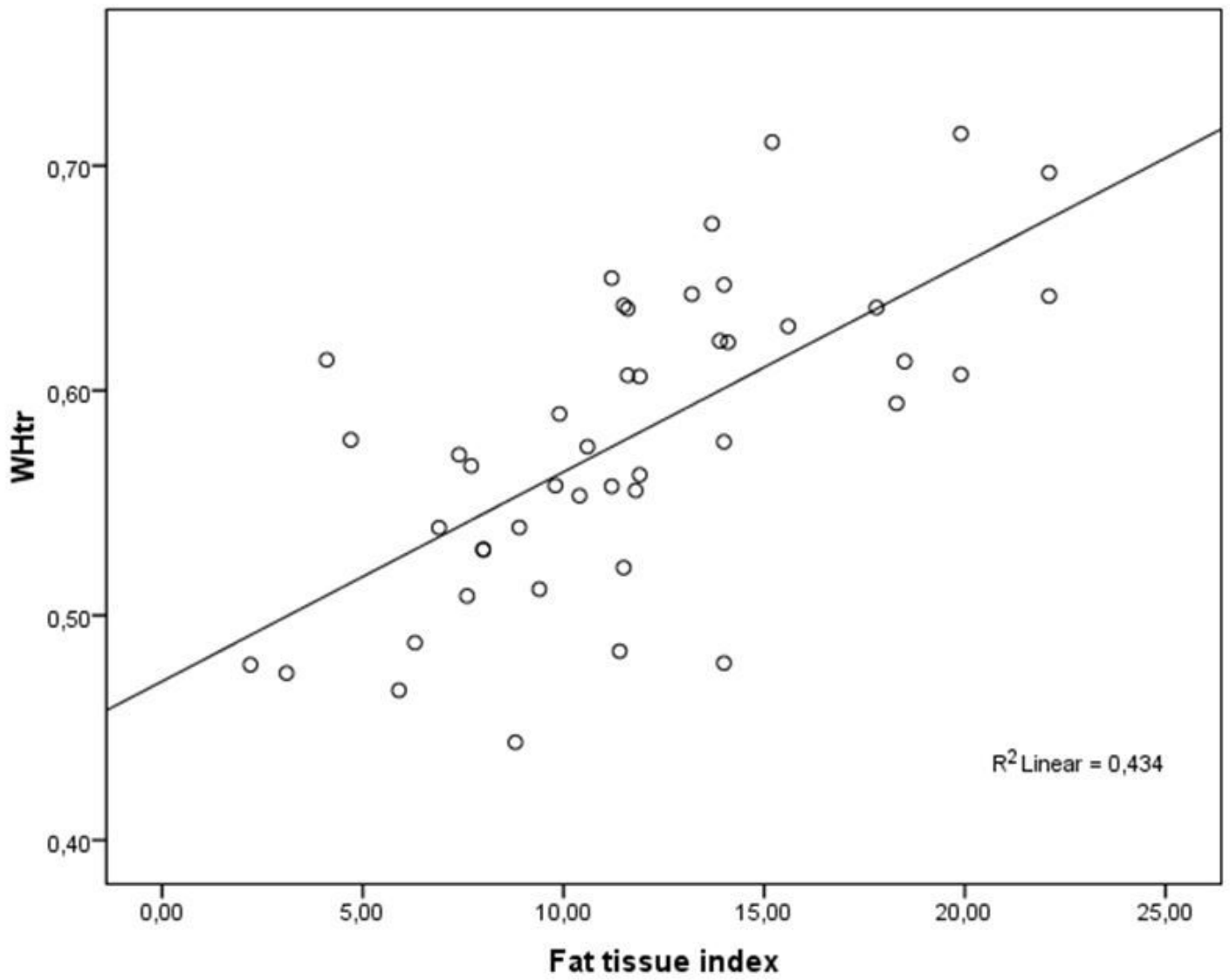
R^2 Linear $= 0,434$

Figure 2

Correlations between waist to height ratio (WHtR) and fat tissue index (FTI).