

Original Article

Evaluation of Oxidative Stress and Thyroid Hormone Status in Hemodialysis Patients in Gorgan

Abdoljalal Marjani^{1*}, Javad Velayeti², Azad Reza Mansourian¹ and Nahid Dahmardeh³

¹Metabolic Disorders Research Center,
Department of Biochemistry and Biophysics,
Gorgan Faculty of Medicine, Golestan University of Medical Sciences,
Gorgan, Golestan Province, Iran

²Student Research Committee,
Gorgan Faculty of Medicine, Golestan University of Medical Sciences,
Gorgan, Golestan province, Iran

³Department of Biology,
University of Sistan and Baluchestan,
Zahedan, Iran

Abstract

The aim of this study focused on serum malondialdehyde levels and erythrocyte superoxide dismutase and catalase activities in haemodialysis patients and compared with control groups. Forty-five hemodialysed patients and forty-five control groups recruited in this study. Serum creatinine and urea, thyroid hormones levels and erythrocyte antioxidant enzyme activities were determined. Hemodialysis patients showed higher levels of MDA than control groups ($P < 0.01$), but the levels of T3, fT3 and fT4, SOD and CAT were low in hemodialysis patients ($P < 0.01$). Serum T3, fT3 and fT4 levels were significantly negative correlated with MDA ($P < 0.01$). It is concluded that serum lipid peroxidation is markedly increased in hemodialysis patients. This means that elevated reactive oxygen species may interact with the lipid molecules in hemodialysis patients. Hemodialysis may cause significant changes in thyroid hormone levels. TSH level in hemodialysis patients is slightly similar to that of control groups. This suggests that thyroid is able to re-synthesize for hormonal urinary losses.

Introduction

Thyroid hormones (THs) are necessary for metabolic

function of the kidneys. The kidney is an organ for metabolism and elimination of thyroid hormones and a target of some of the iodothyronines' actions. Thyroid dysfunction may affect on glomerular and tubular functions and electrolyte and water homeostasis. It may cause a reduction in glomerular filtration, hyponatremia and water excretion alteration (1-3). Many studies have shown that patients on regular hemodialysis (HD) tolerate a chronic illness which was not involved the thyroid, but these patients indicated low serum thyroxin (T4) and triiodothyronine

***Corresponding author :**

Prof. Dr. Abdoljalal Marjani, Department of Biochemistry and Biophysics, Metabolic Disorders Research Center, Gorgan Faculty of Medicine, Golestan University of Medical Sciences, Gorgan, Golestan Province, Iran; Tel. & Fax : +98(171)4421651 & 4440225; E-mail:abdoljalal@yahoo.com

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(T3) levels (4-5). Some studies revealed decreased T3 and T4 levels while the thyroid-stimulating hormone (TSH) levels are not elevated (6). There may be an association between thyroid hormones and the oxidative and antioxidative status in the body. It has been reported that thyroid dysfunction such as hypothyroidism reduce oxidant production which may not protect organism against oxidant damage (7-8). There are limited and controversial studies on the oxidative status of hypothyroidism (9-11). Different antioxidant enzymes may protect oxidative effects of free radicals on lipids, proteins, and DNA. These enzymes consist of superoxide dismutase (SOD) and catalase (CAT) (12). Superoxide dismutase catalyzes the alteration of the superoxide anion into hydrogen peroxide (H₂O₂). Hydrogen peroxide then changed to water (H₂O) by catalase or glutathione peroxidase (GPx) (13-14). Lipid peroxidation which express as malondialdehyde (MDA) may change in different age and ethnic groups, gender and different kinds of diseases (15-21). Hemodialysis is the most effective method in balancing the metabolic abnormalities related to renal oxidative stress that causes to morbidity in hemodialysis patients (22). Chronic renal failure patients who are on hemodialysis therapy show a high percentage of goiter and thyroid dysfunction and cardiovascular disorders (23-25). Free radicals have been revealed to change the activity of some membrane bound tissue enzymes (26). End-stage renal disease can only be overcome by haemodialysis which can be considered as crucial therapeutic regiments for such kidney diseases and for those subjects which are candidate for kidney transplantation (27). The production of reactive oxygen species (ROS) which are the byproducts of haemodialysis therapy is the main obstacle and complications in haemodialysis application for the end stage renal failure (28-30). Thyroid hormones can be altered due to haemodialysis. The thyroid hormones abnormality may accompany with various disorders, including systemic acidosis, the haemodialysis duration, and endothelial injuries and inflammation (31). The aim of this study focused on serum malondialdehyde levels which is an indicator of lipid peroxidation and erythrocyte superoxide dismutase and catalase activities in haemodialysis patients and compared with age matched control groups in Gorgan.

Materials and Methods

Forty-five hemodialysed patients with mean age 51.88±15.90 years who were referred to the hemodialysis unit at 5th Azar Education Hospital of Gorgan Faculty of Medicine, Golestan University of Medical Sciences in Gorgan, Iran in 2015. Patients were compared with forty five age matched control groups (mean age 48.68±15.60). This study was approved by the Research Deputy Ethics Committee of the Golestan University of Medical Sciences. An informed consent from all subjects had been carried out. Hemodialysis patients were being treated three times a week. Clinical history test was performed from all patients. Patients with diabetes mellitus, liver disease, endocrinal diseases, acute or chronic illness, thyroid disorders and any drug that affect TH were excluded from the study. A ten ml blood samples were provided after an overnight fast of 12 hour. Biochemical tests including serum creatinine and urea, thyroid hormones (TSH, T3, T4, free triiodothyronine (fT3) and free thyroxin (fT4)) and erythrocyte antioxidant enzymes (Superoxide dismutase (Code number:706002, Cayman Chemical Commercial kit, Colorimetric method, USA) and catalase (Code number:707002, Cayman Chemical Commercial kit, Colorimetric method, USA)) were determined. The hormonal analysis was done by Monobind kit (Code number:1225-300, Lake Forest CA: 92630, USA) and enzyme immunoassay (ELISA) method. Serum creatinine and urea levels were determined with commercial kits by spectrophotometer techniques (Model JENWAY 6105 UV/VIS) in the Metabolic Disorders Research Center (Gorgan Faculty of Medicine). Serum malondialdehyde was determined with Kei Satoh method (32). Weight was measured, while subjects were minimally clothed without shoes, using digital scales. Height was measured in standing position using tape meter while the shoulder was in a normal position. Body mass index (BMI) was defined as weight in kilograms divided by height in meters squared. Overweight was defined as BMI 25.0-29.9 Kg/m² and obese as BMI ≥30 Kg/m² (33).

The results are shown as means and standard deviations. SPSS- 16 version software was used to calculate the statistical analysis. The evaluation of

data was done by using independent sample t and Pearson correlation tests. A $P < 0.05$ was considered statistically significant.

Results

Table I shows clinical and anthropometric characteristics of the hemodialysis patients and control groups. There was no difference in serum TSH, age and body mass index among the studied groups. There were well significant differences in serum T3, T4, fT3 and fT4, MDA, SOD and CAT compared with control groups. Hemodialysis patients showed higher levels of MDA than those control groups ($P < 0.01$), but the levels of T3, fT3 and fT4, SOD and CAT were low in hemodialysis patients ($P < 0.01$). Table II shows relationship between MDA, SOD and CAT and thyroid hormones in hemodialysis patients. Spearman correlation analysis showed that

the serum T3, fT3 and fT4 levels were significantly negative correlated with MDA (Table II). There was no correlation between thyroid hormones and SOD and CAT.

Discussion

In our present study, we revealed that the thyroid function differed among the hemodialysis group compared to the healthy controls. Serum T3, fT3 and fT4 levels were lower; TSH was slightly higher and T4 was unchanged among those with hemodialysis. Serum lipid peroxidation and antioxidant enzyme activities were significantly high and low among the hemodialysis group compared to the healthy controls, respectively. Some studies have shown a low serum level of T3 in patients with ESRD (34-41). Lim et al. (35) reported a reduced T3 level and decreased conversion of T4 to T3 in uremic patients (35). It is also revealed low serum T4 or fT4 levels in patients undergoing maintenance hemodialysis (36-37, 39-40, 5). The serum TSH level in patients with CRF (34-37, 41-42) had been reported to be almost normal. Our study showed that the serum TSH level in the hemodialysis patients slightly increased and serum fT3 and fT4 level significantly decreased which is in agreement with other studies (43-44, 39-40, 5, 45-51). In our study, slightly increase of TSH level in hemodialysed patients in comparison to control groups was not in accordance with others studies (52). Increase in the serum TSH level was not obvious in hemodialysis patients. The low serum fT4 and fT3 levels may be responsible for low metabolism of the body. Studies on a uremic rat model have shown that there may be a difference in the thyroid hormone metabolism or action in the peripheral system and in the central nervous system in the ESRD patients (53-54). Xess et al showed that CRF patients revealed a significant decrease in T3 (in accordance with our study) and T4 (not in accordance with our study) levels in comparison to control groups (6, 41), but serum TSH levels indicated no significant difference in patients and control groups which was in agreement with other findings (55). The movement of thyroid hormone into and out of the extravascular space may be a possible mechanism of thyroid hormone changes related to hemodialysis (6). There are different findings on

Table I: Clinical data of study subjects.

Parameters	Healthy subjects	Hemodialysis patients	P
n	45	45	-
Age (years)	48.68±15.6	51.88±15.9	0.330
BMI (kg/m ²)	26.41±2.81	25.92±6.67	0.653
TSH (mIU/ml)	2.13±0.84	2.76±2.21	0.079
T3 (ng/ml)	1.25±0.25	0.83±0.32	0.001
T4 (µg/dl)	7.97±1.17	7.53±2.12	0.222
fT3 (pg/ml)	2.78±0.43	2.51±0.59	0.013
fT4 (ng/dl)	1.35±0.18	0.92±0.31	0.001
Creatinine (mg/dl)	0.91±0.77	10.03±1.92	0.001
Urea (mg/dL)	24.72±2.65	103.86±25.9	0.001
SOD (U/ml)	0.15±0.04	0.08±0.13	0.002
CAT (nmol/min/ml)	16.43±7.04	12.31±6.80	0.001
MDA (nmol/ml)	0.45±1.14	2.98±0.89	0.001

Table II: Correlation analyses between oxidative stress biomarkers and thyroid hormones in hemodialysis subjects.

Parameters	CAT	SOD	MDA
TSH	r=-0.016 p=0.883	r=-0.071 p=0.506	r=0.037 p=0.730
T3	r=0.153 p=0.150	r=0.186 p=0.08	r=-0.499* p=0.001
fT3	r=-0.145 p=0.173	r=0.057 p=0.593	r=-0.321* p=0.002
T4	r=-0.039 p=0.716	r=-0.167 p=0.125	r=-0.161 p=0.129
fT4	r=0.172 p=0.104	r=0.239 p=0.053	r=-0.521* p=0.001

variations in serum lipid peroxidation level and erythrocyte antioxidant enzyme activities due to hemodialysis. Some studies indicated an increase, while some show a decrease in the levels. In our study, we determined the level of serum malondialdehyde of hemodialysis patients. Malondialdehyde uses as a specific and sensitive biomarker for the estimation of the lipid peroxidation status in different diseases (56), including in patients under chronic hemodialysis treatment (57). Our results show a significant increase of serum malondialdehyde in the hemodialysis group when compared with the control group. Oxidative damage may depend on different risk factors, but it can be caused by the imbalance between the productions of free radicals and different antioxidant enzymes (58). Lipid peroxidation disrupts the structural integrity of the lipid bilayer, leading to elevated membrane permeability (the release of hydrolytic enzymes and increasing cell damage) and subsequent impaired electron transport for oxidative phosphorylation in mitochondria and increased lysosomal permeability (59). The results of present study indicates that significant difference of antioxidant enzyme activities between hemodialysis and control group may be related with the loss of antioxidant enzymes and the reduction of antioxidant enzymes may be related to elevation of lipid peroxidation in hemodialysed patients which is in agreement with findings of other studies (58, 60, 61). These results show that oxidants and antioxidants imbalance may play an important role in the pathogenesis of some diseases. Some findings showed that the elevated MDA level may act as a metabolic signal for kidney damage and protein leakage including thyroid hormones (62). It is reported that there are a significant increase of the blood SOD and CAT activity in plasma and red blood cells of patients undergoing haemodialysis (61). Some other studies also indicated that the activity of erythrocyte SOD and CAT increased significantly (63-68) while another finding showed a decrease of antioxidant enzymes in erythrocyte of CRF patients (69-75). Study on hemodialyzed patients showed that significantly lower plasma catalase activity was found (64). Study on animal model kidney of the cytoplasmic superoxide dismutase has revealed the decrease of the superoxide dismutase protein

abundance in the kidney tissues of the CRF animals which is in accordance with findings that reported the decrease of superoxide dismutase enzymatic activity in the erythrocytes of patients with chronic renal failure (76-78) and in our results. We found significantly positive correlation between T3, fT3 and fT4 and malondialdehyde which is not in agreement with other studies (42). This correlation between malondialdehyde and above mentioned thyroid hormone levels indicate that the alteration of these hormone levels in hemodialysed patients may depend on variations of lipid peroxidation in these patients. Reduced serum fT3 and T3 may also relate to impaired extrathyroidal changing of T4 to T3. The alteration of T4 and fT4 are less considered in these patients (79). The exact mechanisms for the decrease of T3 are not well known, but some studies have shown that the decreased T3 level correlates with poor cardiac prognosis and a strong predictor of death in cardiac patients (80). Decreased fT3 is not only important in chronic renal failure patients but also in acute and chronic infections; diabetes; and different cardiovascular (CV) diseases (80). Studies have shown that T3 and fT3 are as survival markers in patients with CKD and in HD patients (81). Some researchers have suggested that there is a relationship between T3 levels and thyroid dysfunction and risk of mortality in these patients (82).

It is concluded that thyroid dysfunction in hemodialysis patients are more common than in general population. Hemodialysis may influences thyroid function in various ways. Serum lipid peroxidation is markedly increased in hemodialysis patients. This means that elevated reactive oxygen species may interact with the lipid molecules in hemodialysis patients. Our results suggest that hemodialysis may cause significant changes in thyroid hormone levels. TSH level in hemodialysis patients is slightly similar to that of control groups. This suggests that thyroid is able to re-synthesize for hormonal urinary losses. Because of the high prevalence of thyroid dysfunction in hemodialysis patients, it suggests that screening of thyroid function should be needed.

No conflict of interest

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