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## The association between thyroid function and nutritional status in patients with end-stage renal disease on hemodialysis

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### ABSTRACT

**Introduction:** Malnutrition is common in patients with End-Stage Renal Disease (ESRD) on hemodialysis (HD) which significantly affects their quality of life. ESRD is associated with thyroid dysfunction which may affect morbidity and mortality. Changes in thyroid function in this population could be a marker of malnutrition. Our aim was the assessment of the nutritional status of patients with ESRD on HD and its association with thyroid function.

**Methods:** A cross-sectional study was conducted on 84 patients with ESRD on HD. Nutritional status was assessed by anthropometric measurements and Subjective Global Assessment (SGA) Score. Serum FT3, FT4, and TSH concentrations were determined. CBC, kidney function tests, serum albumin, serum iron, total iron-binding capacity, serum cholesterol, and CRP were measured. Patients' comorbidity status was determined using the Charlson Comorbidity Index (CCI).

**Results:** The mean SGA score for studied patients was  $13.73 \pm 4.4$ , mean values of thyroid functions were: TSH  $2.99 \pm 2.93$  uIU/ml; FT4  $1.08 \pm 0.21$  ng/dl and FT3  $2.55 \pm 0.52$  pg/ml. According to SGA score, 26.2% of patients had normal nutritional status, 69% had mild to moderate malnutrition and 4.8% had severe malnutrition. SGA had significant negative correlation with FT3, while there was no significant correlation between it and FT4 or TSH. Serum FT3 concentration inversely correlated with age ( $r = -0.25$ ,  $P = 0.02$ ), CCI ( $r = -0.48$ ,  $P = 0.0001$ ), CRP ( $r = -0.46$ ,  $P = 0.0001$ ), and SGA ( $r = -0.49$ ,  $P = 0.0001$ ), and positively correlated with serum albumin ( $r = 0.47$ ,  $P = 0.0001$ ). In multivariate regression analysis, SGA was independently associated with FT3 ( $\beta$ ,  $-1.36$ ; 95% confidence interval,  $-2.5$  to  $-0.2$ ,  $P = 0.02$ )

**Conclusions:** Malnutrition is prevalent among patients with ESRD on HD. FT3 is a marker of malnutrition and could be used as an accessible and reproducible periodical method to detect such states.

### ARTICLE HISTORY

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### KEYWORDS

Humans; nutritional Status; thyroid Gland; renal Dialysis; kidney Failure; chronic

## 1. Introduction

End-stage renal disease (ESRD) leads to a lot of hormonal and metabolic disorders [1]. There is a strong cross relationship between the thyroid function and kidney diseases such that the kidney plays a role in the regulation, metabolism, and elimination of thyroid hormones. The thyroid hormones, on the other hand, are involved in the kidney growth, development, and maintenance of water and electrolyte homeostasis [2,3]. Dialysis is also associated with changes in the levels of circulating thyroid hormones which, in turn, may have prognostic implications. Moreover, drugs used to treat thyroid dysfunction may affect kidney function and drugs treating kidney diseases may affect thyroid function [4]. It has been reported that patients with ESRD have reduced levels of tri-iodothyronine (T3) and thyroxine (T4) with elevated thyroid-stimulating hormone (TSH) in absence of overt hypothyroidism. Subclinical hypothyroidism was reported in 21.82% of patients with ESRD on HD [5]. ESRD affects thyroid functions in several ways

through low blood hormone level, reducing the binding to transport proteins, disturbing the peripheral hormone metabolism and inducing the uptake of iodine by the thyroid gland decreasing the tissue hormone quantity [6].

Poor nutritional status and protein energy wasting (PEW) are common among ESRD patients on HD and are considered strong predictors of poor outcome in this population [7]. Many factors are implicated in protein malnutrition and wasting in these patients, including an inadequate nutrient intake, metabolic acidosis, hormonal dysregulation, changes in bowel flora and sustained inflammation. All these factors can result in increased rates of morbidity and mortality [8].

Although thyroid dysfunction is a well-known complication of ESRD, yet, its association with the nutritional status of ESRD patients on HD is not well understood.

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Our aim was to assess the nutritional status of ESRD patients on HD and its association with thyroid function.

## 2. Subjects and methods

From May 2018 till October 2018, a cross-sectional study was conducted on 84 patients with ESRD undergoing HD aged from 30 years to 80 years. They were enrolled from Mit-Khakan Dialysis Unit, Egypt.

### 2.1. Selection criteria for the patients

The subjects included in this study were selected according to inclusion and exclusion criteria.

#### 2.1.1. Inclusion criteria

Adult patients (Age  $\geq 18$  years) with ESRD on maintenance HD for more than 3 months.

#### 2.1.2. Exclusion criteria

Patients with previously identified thyroid illness, patients on medications that might interfere with the thyroid function, patients with acute infection, patient exposed to hospitalization, major surgeries or recent trauma less than 6 months and patients known to have malignancy.

## 2.2. All cases were subjected to

Detailed medical history, full clinical examination, and laboratory investigations that included: complete blood count (CBC); kidney function tests (serum urea, serum creatinine); serum albumin, serum iron, total iron-binding capacity, serum cholesterol, C-reactive protein (CRP) and serum thyroid hormones (TSH, Free T3 (FT3), and Free T4 (FT4)). The samples were drawn immediately before dialysis session and divided into two tubes. One tube had been centrifuged and plasma separated and kept at  $-20^{\circ}\text{C}$  until time of hormonal assay. The other one was used immediately for detecting the biochemical measurements. Thyroid hormones (TSH, FT3, and FT4) were measured by chemiluminescence with Immulite (1000) using kit (Diagnostic Products Corporation; Los Angeles, CA, USA).

Anthropometric measures included: weight, height, body mass index (calculated by dividing weight (kg) to height squared ( $\text{m}^2$ )), midarm circumference (measured using a flexible tape in the halfway point between the acromion of the scapula and the olecranon of the ulna).

Comorbidity was estimated using modified Charlson comorbidity index (mCCI) (excluding age-factor), which is a composite score of multiple comorbid conditions. It is a popular tool of assessing comorbidity and is a strong predictor of outcome in patients with ESRD [9]. Testing the adequacy of dialysis kt/v was done using single pool equation.

Nutritional status was assessed by subjective global assessment score (SGA score): The SGA is an integrated tool that utilizes the clinical judgment of a practitioner to identify patients at risk of or with malnutrition. It consists of seven items, two components related to physical examination (indicator of fat and muscle loss and nutritional status-associated with changes in fluid balance) and five components of medical history (weight change, diet, gastrointestinal symptoms, functional capacity, disease, and nutrition relationship needs). Each component has a score between one (normal) to five (very severe). Thus, malnutrition score has a total score between 7 and 35. Patients having score between 7 and 10 are considered as well-nourished patients. Score between 11 and 22 are considered as having mild to moderate malnutrition. Likewise score between 23 and 35 are considered as severely malnourished [10].

### 2.2.1. Statistical analysis

Results were tabulated and statistically analyzed by using a personal computer using MICROSOFT EXCEL 2016 and SPSS v. 21 (SPSS Inc., Chicago, IL, USA). Statistical analysis was done using: Descriptive: e.g. percentage (%), mean and standard deviation. Analytical: that includes: Chi-Squared ( $\chi^2$ ), t-test, and Pearson's correlation coefficient (r). A value of P less than 0.05 was considered statistically significant.

## 3. Results

The study included 84 hemodialysis patients, 45 (53.6%) males and 39 (46.4%) females with the mean age of  $57.42 \pm 11.09$  years (range, 30 to 80 years). The duration of hemodialysis ranged from 4 months to 11 years with a mean duration of  $38.23 \pm 24.37$  months. 41.7% of patients had hypertension, 8.3% had diabetes mellitus, 19% had both hypertension and diabetes while 31% of the studied group hadn't neither hypertension nor diabetes.

Anthropometric and biochemical parameters are shown in Table 1. The mean weight for studied patients was 75.3 kg, the mean height was 170.19 cm, the mean BMI was  $25.94 \text{ kg/m}^2$ , the mean MAC was 28.43 cm, the mean KT/V for studied patients was 1.2 and the mean CCI for studied patients was 5.54. The mean hemoglobin for studied patients was 9.7 g/dl, the mean creatinine was 8.4 mg/dl, the mean serum iron was 0.7 mg/l, the mean TIBC was 2.35 mg/l, the mean albumin was 3.55 g/dl, the mean urea was 172.42 mg/dl, the mean cholesterol was 178.29 mg/dl and the mean CRP was 10.14 mg/l.

The mean hormonal values of thyroid function were: TSH  $2.99 \pm 2.93$   $\mu\text{IU/ml}$  (range: 0.01–17.1); FT4  $1.08 \pm 0.21$  ng/dl (range: 0.65–1.62) and FT3  $2.55 \pm 0.52$  pg/ml (range: 1.18–3.64).

The mean SGA score for studied patients was  $13.73 \pm 4.4$  (range: 7–25). According to SGA score, 26.2% of patients had normal nutritional status while

**Table 1.** Anthropometric and biochemical characteristics of the patients (N = 84).

	Mean	Standard deviation	Range
Weight (kg)	75.3	15.83	(48–142)
Height (cm)	170.19	8.43	(155–186)
BMI (kg/m <sup>2</sup> )	25.94	5.27	(17–42)
MAC (cm)	28.43	4.63	(19–44)
SGA score	13.73	4.4	(7–25)
CCI	5.54	2.137	(2–11)
Free T3 (pg/mL)	2.55	0.52	(1.18–3.64)
Free T4 (ng/dl)	1.08	0.206	(0.65–1.62)
TSH (uIU/ml)	2.99	2.93	(0.01–17.1)
Hemoglobin (g/dl)	9.7	1.42	(6.9–13.7)
Creatinine (mg/dl)	8.4	1.9	(3.7–13.3)
Serum iron (mg/l)	0.7	0.36	(0.23–2.78)
TIBC (mg/l)	2.35	0.41	(1.6–3.6)
Albumin (g/dl)	3.55	0.52	(2.36–4.9)
KT/V	1.2	0.23	(0.55–1.67)
Urea (mg/dl)	172.42	53.12	(80–300)
Cholesterol (mg/dl)	178.29	29.04	(134–256)
CRP (mg/l)	10.14	8.9	(0.4–36.5)

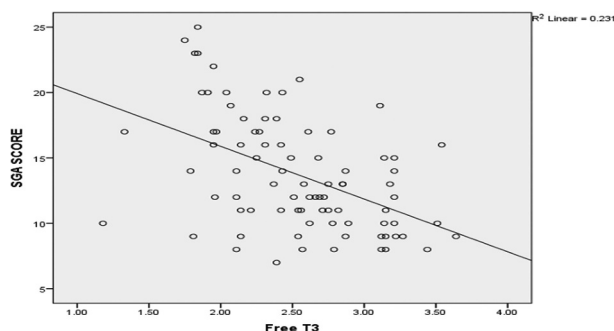
**BMI:** Body mass index **MAC:** Mid arm circumference **SGA score:** Subjective global assessment score. **CCI:** Charlson comorbidity index **Free T3:** Free Triiodothyronine **Free T4:** Free Thyroxine **CRP:** C reactive protein **TSH:** Thyroid Stimulating Hormone **TIBC:** Total iron-binding capacity

69% of them had mild to moderate malnutrition and 4.8% had severe malnutrition.

SGA had significant negative correlation with FT3 (Figure 1), while there was no significant correlation between it and FT4 or TSH. There was also a significant negative correlation between SGA and weight, BMI, MAC, serum albumin, hemoglobin, creatinine, cholesterol, and significant positive correlation between it and duration of dialysis, CRP, and CCI (P-value <0.05), while there was no statistically significant correlation between SGA and age, TIBC, serum iron, urea, or KT/V (P-value >0.05) (Table 2).

The multivariate regression analysis, including variables with P values <0.05 in the univariate analysis, demonstrated that FT3, BMI, albumin, cholesterol, CRP, and CCI were significant independent determinants of SGA among hemodialysis patients (Tables 3 & 4).

Serum FT3 concentration inversely correlated with age ( $r = -0.25$ ,  $P = 0.02$ ), CCI ( $r = -0.48$ ,  $P = 0.0001$ ), CRP ( $r = -0.46$ ,  $P = 0.0001$ ), and SGA ( $r = -0.49$ ,  $P = 0.0001$ ), and positively correlated with serum albumin ( $r = 0.47$ ,  $P = 0.0001$ ) and KT/V ( $r = 0.25$ ,  $P = 0.02$ ) (Table 5).

**Figure 1.** Correlation between free T3 and SGA score.**Table 2.** Correlation between SGA and other variables (N = 84).

Variable	SGA	
	R	P
Free T3 (pg/mL)	-0.51	0.001
Free T4 (ng/dl)	-0.01	0.9
TSH (uIU/ml)	+0.047	0.6
Age (years)	+0.09	0.3
Weight (kg)	-0.48	0.001
BMI (kg/m <sup>2</sup> )	-0.58	0.001
MAC (cm)	-0.58	0.001
Hb (g/dl)	-0.24	0.02
Creatinine (mg/dl)	-0.21	0.05
Serum iron (mg/l)	-0.07	0.5
TIBC (mg/l)	-0.1	0.3
Serum albumin (g/dl)	-0.54	0.001
KT/V	+0.05	0.6
Urea (mg/dl)	-0.03	0.7
Cholesterol (mg/dl)	-0.53	0.001
Duration of dialysis (years)	+0.36	0.001
CRP (mg/l)	+0.67	0.001
CCI	+0.63	0.001

**BMI:** Body mass index **MAC:** Mid arm circumference **Free T3:** Free Triiodothyronine **CRP:** C reactive protein **TIBC:** Total iron-binding capacity **Hb:** Hemoglobin **CCI:** Charlson comorbidity index **Free T4:** Free Thyroxine **TSH:** Thyroid Stimulating Hormone

**Table 3.** Univariate regression analysis for SGA (N = 84).

Variable	B	95%Confidence interval	P value
Free T3 (pg/mL)	-4.03	-5.65 to -2.41	0.001
Age (years)	0.076	-0.009 to 0.16	0.07
Weight (kg)	-0.07	-0.13 to -0.013	0.017
BMI (kg/m <sup>2</sup> )	-0.2	-0.38 to -0.03	0.023
MAC (cm)	-0.32	-0.5 to -0.12	0.002
Hb (g/dl)	-0.8	-1.4 to -0.18	0.012
Creatinine (mg/dl)	-0.5	-0.99 to -0.011	0.045
Albumin (g/dl)	-3.43	-4.9 to -1.9	0.001
Cholesterol (mg/dl)	-0.037	-0.069 to -0.005	0.023
Duration of dialysis	0.053	0.016 to 0.091	0.006
CRP (mg/l)	0.35	0.28 to 0.43	0.001
MIS	0.89	0.82 to 0.96	0.001
CCI	1.52	1.23 to 1.8	0.001

**BMI:** Body mass index **MAC:** Mid arm circumference **Free T3:** Free Triiodothyronine **CRP:** C reactive protein **Hb:** Hemoglobin **MIS:** Malnutrition Inflammation Score **CCI:** Charlson comorbidity index

#### 4. Discussion

One of the most common complications that occur in ESRD patients, with a significant negative impact on life, is malnutrition. Often overlooked or underestimated, malnutrition is clearly associated with increased mortality risk [11].

**Table 4.** Multivariate regression analysis for SGA (N = 84).

Variable	B	95%Confidence interval	P value
Constant	26.11		
Free T3 (pg/mL)	-1.36	-2.5 to -0.2	0.02
Weight (kg)	0.01	-0.05 to 0.07	0.7
BMI (kg/m <sup>2</sup> )	-0.28	-0.5 to 0.05	0.01
MAC (cm)	0.002	-0.18 to 0.18	0.9
Hb (g/dl)	-0.06	-0.42 to 0.29	0.7
Albumin (g/dl)	-1.26	2.3 to 0.22	0.01
Cholesterol (mg/dl)	-0.036	-0.055 to -0.017	0.001
Duration of dialysis (years)	0.006	-0.017 to 0.027	0.6
CRP (mg/l)	0.11	0.036 to 0.19	0.004
CCI	0.4	0.1 to 0.7	0.009

**BMI:** Body mass index **MAC:** Mid arm circumference **Free T3:** Free Triiodothyronine **CRP:** C reactive protein **Hb:** Hemoglobin **CCI:** Charlson comorbidity index



**Table 5.** Correlation between free T3 and other variables (N = 84).

Variable	Free T3	
	R	P
SGA Score	-0.49	0.001
Age (years)	-0.25	0.02
Duration of dialysis (years)	+0.06	0.6
Weight (kg)	+0.07	0.5
BMI (kg/m <sup>2</sup> )	+0.13	0.2
MAC (cm)	+0.16	0.14
CCI	-0.48	0.001
KT/V	+0.25	0.02
Hb (g/dl)	+0.08	0.46
TIBC (mg/l)	-0.05	0.6
Albumin (g/dl)	+0.47	0.001
Urea (mg/dl)	+0.16	0.15
Cholesterol (mg/dl)	-.01	0.35
CRP (mg/l)	-0.46	0.001

**BMI:** Body mass index **MAC:** Mid arm circumference **Free T3:** Free Triiodothyronine **CRP:** C reactive protein **TIBC:** Total iron-binding capacity **Hb:** Hemoglobin **CCI:** Charlson comorbidity index **SGA score:** Subjective global assessment score.

Our results show that the age of the studied group was  $57.42 \pm 11.09$  years. These results agree with another study that reported an increase in prevalence of ESRD with aging particularly after 50 years in both genders [12]. Also, these results go in agreement with an epidemiological study carried out at Menoufia governorate, Egypt which showed that the mean age at the start of dialysis is 52 years [13]. This age is slightly lower than the average worldwide age of ESRD which is more than 60 years in 73% of studies done on 6541 patients with ESRD in a meta-analysis [14]. This may reflect the standard of medical care and early diagnosis of patients with chronic kidney disease. As regarding sex, 53.6% were males, and 46.4% were females in the present study. This is in accordance with other studies which reported the increased incidence of ESRD 50% more in men than in women [15,16] although the incidence of chronic kidney disease is more in women [17].

Results of this study demonstrated that HTN is the commonest cause of ESRD (41.7%) in these patients. These results agree with most of the studies where hypertension and diabetes mellitus are the main causes of renal failure [18].

Based on SGA score about (69%) had mild to moderate malnutrition and (4.8%) had severe malnutrition. This result go in agreement with a Jordanian study which showed that out of 180 patients on regular HD, about 61% were malnourished, 8.5% of them had severe malnutrition [19]. This also agreed with a study done in Cairo Egypt which showed that the prevalence of malnutrition among HD patients was 67% (50% were mild to moderate malnourished and 17% were severe malnourished) [20]. These results were lower than the prevalence reported by another Egyptian study done among HD patients in Assiut city which revealed about 85% malnourished patients (81.6% mild to

moderate malnutrition and 3.6% severe malnutrition) [21]. This difference can be explained by lower educational level, socioeconomic state, and health-care facilities in South Egypt area compared to the capital city. In Saudi Arabia, malnutrition was detected in 79% of ESRD patients on HD according to SGA [22]. These differences in prevalence may be due to environmental diversity and different diet regimens in various regions of the Middle East area.

Our study showed also that SGA score correlated negatively with anthropometric measures (body weight, body mass index, midarm circumference) and laboratory features of malnutrition (serum albumin, hemoglobin level and cholesterol). This goes in agreement with the EQUAL study which reported significant correlations between SGA and nutritional markers such as plasma albumin, creatinine, BMI, and body weight [23]. This also agreed with another study that showed SGA score have a negative correlation with BMI and positive correlation with CRP, and linked it with increased inflammation and mortality [24].

SGA correlated positively with the duration of dialysis. This is in agreement with other studies which stated that the duration of dialysis can be associated with malnutrition [25]. As increased duration of dialysis may lead to loss of nutrients, inflammation and hypercatabolism so, long duration on dialysis may be regarded as one of the main causes of malnutrition.

We also found that SGA had significant positive correlation with CRP as inflammatory marker and associated comorbidities represented by CCI. These findings agreed with a cross-sectional analysis performed in a monocentric study involving 126 patients on maintenance HD. They reported a negative association between the degree of malnutrition evaluated by SGA and serum albumin, and a significant positive correlation with CRP [26]. Chronic inflammation in malnourished patients could be the link through which malnutrition increase the mortality in patients with ESRD [24,27].

Regarding the association between thyroid function and nutritional status, our results showed that SGA, as a marker of nutritional status, had a significant negative correlation with FT3; the FT3 was a significant independent determinant of SGA. While there was no significant correlation between SGA and neither free T4 nor TSH. This goes in agreement with Koo et al., who found that the proportion of malnourished patients assessed by SGA were significantly higher in patients with lower T3 levels [28].

This also agreed with the study done by Fernández-Reyes which showed that half of dialysis patients had decreased levels of serum FT3 without alteration on FT4 or TSH. They also confirmed that low FT3 levels correlate with malnutrition and inflammation parameters and could be considered an early marker for

catabolism or protein energy wasting [29]. In the present work, FT3 had significant positive correlation with serum albumin and negative correlation with CRP. These results go in agreement with the study done by Fan et al., who concluded that low T3 syndrome is closely associated with malnutrition-inflammation complex syndrome [30]. The main source of extrathyroidal FT3 is the peripheral conversion of T4 to T3 by the 5 - deiodinase system [31]. Both protein energy malnutrition and pro-inflammatory stimuli can interfere with the activity of the 5-deiodinase system, resulting in reduced T3 production.

Our results showed also that FT3 had negative correlation with age and CCI which agreed with Koo et al. [28] Similarly, Yavuz D et al, showed that serum FT3 concentration inversely correlated with age, CCI, CRP, and positively correlated with serum albumin. They concluded that plasma FT3 level is one of the earliest surrogate markers of thyroid dysfunction, and this reduction correlates negatively with the severity of illness and associated malnutrition [32].

In 2016, another study stated that plasma FT3 was in positive correlation with serum albumin. It was also observed that FT3 had been highly correlated with inflammatory markers IL-6 and CRP, so FT3 was considered as a good inflammatory marker and strong predictors of mortality [33].

As a result, our findings confirm that the decrease in FT3 in hemodialysis patients is mainly the body's adaptive response to reduced kidney function aiming to reduce baseline metabolism and avoiding catabolism. However, this adaptation may be accompanied by malnutrition, inflammation and increased mortality.

#### 4.1. Limitations of the study

The findings of this study have to be seen in light of some limitations. The small number of the study sample as this study was done at one hemodialysis unit. This was a cross-sectional study; thus, it is not possible to infer a causal relationship between the thyroid dysfunction and malnutrition.

##### 4.1.1. Conclusions

Malnutrition is a common problem among hemodialysis patients. It is associated with decreased levels of FT3, which is associated with poor outcome and increased mortality. For clinicians, periodical measurement of FT3 levels could be an accessible and reproducible method to detect such states.

#### Disclosure statement

No potential conflict of interest was reported by the authors.

#### Notes on contributors

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