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Interleukin-37 and Interleukin-18 as Prognostic Biomarkers for End-Stage Renal Disease

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ABSTRACT

Inflammatory cytokines like IL-18 and anti-inflammatory cytokines like IL-37 are both involved in the etiology of ESRD and comorbidities including hypothyroidism. Despite the fact that Subclinical Hypothyroidism is common in people with chronic kidney disease, little is known regarding the clinical signs and implications of this ailment in patients with end-stage renal disease. The purpose of this study was to assess the role of Interlaken-18 (IL-18) and Interlaken 37 (IL-37) in end-stage renal disease (ESRD) and to establish the prevalence of hypothyroidism (both subclinical and overt hypothyroidism) in patients with ESRD. In the study, 598 hemodialysis patients of both genders were included. This study included 104 male and female hemodialysis patients (82 with subclinical hypothyroidism and 22 with overt hypothyroidism) and 60 healthy people as a control group. All participants' venous blood was drawn in the morning while they were fasting (8 hours) and subjected to clinical evaluation and laboratory testing. The enzyme-linked immunosorbent assay technique was used to quantify serum IL-18 and IL-37 in all of the study participants. When compared to the control group, the prevalence of IL-18 and IL-37 was higher in Subclinical Hypothyroidism and overt hypothyroidism ($p \leq 0.001$). Early diagnosis of Subclinical Hypothyroidism, which was discovered in 23% of patients with ESRD, may reduce the risk of cardiovascular events and the progression of kidney disease, according to the study. In ESRD patients with hypothyroidism, blood levels of both IL-18 and IL-37 are significantly elevated. In overt hypothyroidism, serum IL-18 and IL-37 levels are higher than in subclinical hypothyroidism.

1. Introduction

End-stage renal disease (ESRD) is the most advanced form of chronic kidney disease, and it is associated with a large increase in mobility and mortality due to cardiovascular disease and infections [1]. Chronic kidney disease is caused by the progressive decrease of renal mass (CKD). It's marked by a drop in GFR over months to years [2]. CKD is associated with a variety of hematological, metabolic, and endocrine disorders [3]. Over the last few decades, researchers have paid unprecedented and unequaled attention to

subclinical primary hypothyroidism in order to diagnose minor variations in thyroid function. "Serum free T4 and free T3 levels within their respective reference ranges in the presence of unusually high serum TSH levels" is what subclinical hypothyroid illness is characterized as [4]. The clinical gold standard for determining hypothyroidism is thyrotropin (TSH) values [5], [6]. End-stage renal disease (ESRD) is a common cause of thyroid hormone changes in the absence of an underlying intrinsic thyroid condition. In individuals with chronic kidney disease (CKD), a range of changes in thyroid hormone levels and/or metabolism have been reported [7], [8]. A high serum thyrotropin (TSH) concentration with normal serum free thyroxine (FT4) and T4 concentrations is biochemically classified as subclinical hypothyroidism [9]. Interleukin-18 (IL-18), a potent pro-inflammatory cytokine with a variety of functions, is a member of the IL-1 family of cytokines, which was originally characterized as an interferon (IFN-y) producing factor produced in a variety of cell types. It participates in cellular as well as humeral reactions [10]. In addition to its pro-inflammatory action, IL-18 plays a role in the evolution of nephropathy through its direct effect on renal function [11].

Interleukin-37, a newly discovered member of the IL-1 family, has the ability to suppress inflammation and the immune response by inhibiting the production of pro-inflammatory cytokines, as well as to alleviate inflammation-induced fatigue by inducing metabolic reprogramming and limiting the metabolic effects of inflammation [12]. IL-37 is a cytokine that has both intracellular and extracellular activities. IL-37 is produced and released in the cytosol in its pro-inactive form, which requires cleavage to become active, and maturation and secretion are regulated by inflammatory caspases in response to inflammasome signaling complexes [13]. In the year 2000, IL-37 was discovered in a computer simulation. Prof. Dinarello's lab was the first to discover that IL-37 had anti-inflammatory capabilities, with wide protective effects against inflammatory disorders [14]. Pro-inflammatory stimuli cause immune and non-immune cells to generate the IL-37 precursor. Caspases break and activate IL-37 intracellularly, and their mature form binds to Smad3; this complex translocates into the nucleus, suppressing cytokine synthesis and therefore lowering inflammation. Extracellularly, IL-37 forms a complex with IL-18Rx and IL-1R8 (previously TIR8 or SIGIRR) that suppresses NF-kB and MAPK and activates Mer-PTEN-DOK pathways to transmit anti-inflammatory signals. IL-37 regulates macrophage polarization, lipid metabolism, inflammasome function, TSLP production, and miRNA function during inflammation to limit the expression of various pro-inflammatory cytokines in favor of the expression of anti-inflammatory ones [13]. Furthermore, IL-37 not only modulates innate and acquired immunity, but it also improves immunological senescence associated with aging. Furthermore, tumor angiogenesis, metastasis, and progression are all inhibited by IL-37. Finally, because IL-37 is abnormally expressed in people with inflammatory disorders, autoimmune diseases, and cancer, it may have the capacity to reduce excessive inflammation. As a result, it could be employed as a marker for a variety of diseases [15]. In the current study, we aimed to evaluate the influence of comorbidities like hypothyroid (Subclinical Hypothyroidism and overt hypothyroidism) on the serum levels of IL-18 and IL-37 in patients with ESRD.

2. Materials and Methods

2.1 Study population and selection of patients

This study was approved by the Ethical committee of Chemistry Department, college of Science, Basra University, in cooperation with Hemodialysis Unit in AL-Basrah Teaching Hospital and Kidney Transplant Center, Hemodialysis Unit in Al-Sadr Teaching Hospital during the period from May 2020 to April 2021. Informed consent was obtained from every patient and control. In the clinical study 598 patients undergoing HD have been consecutively and prospectively screened, with(104)patients (48 males and 56 females) completing the study, aged 40 to 70 years. All patients were divided into two groups: group I included 82

Subclinical Hypothyroidism, group II 22 overt hypothyroidism while group III that control group of 60 healthy individuals, matched for age and sex, as illustrated in Figure 1.

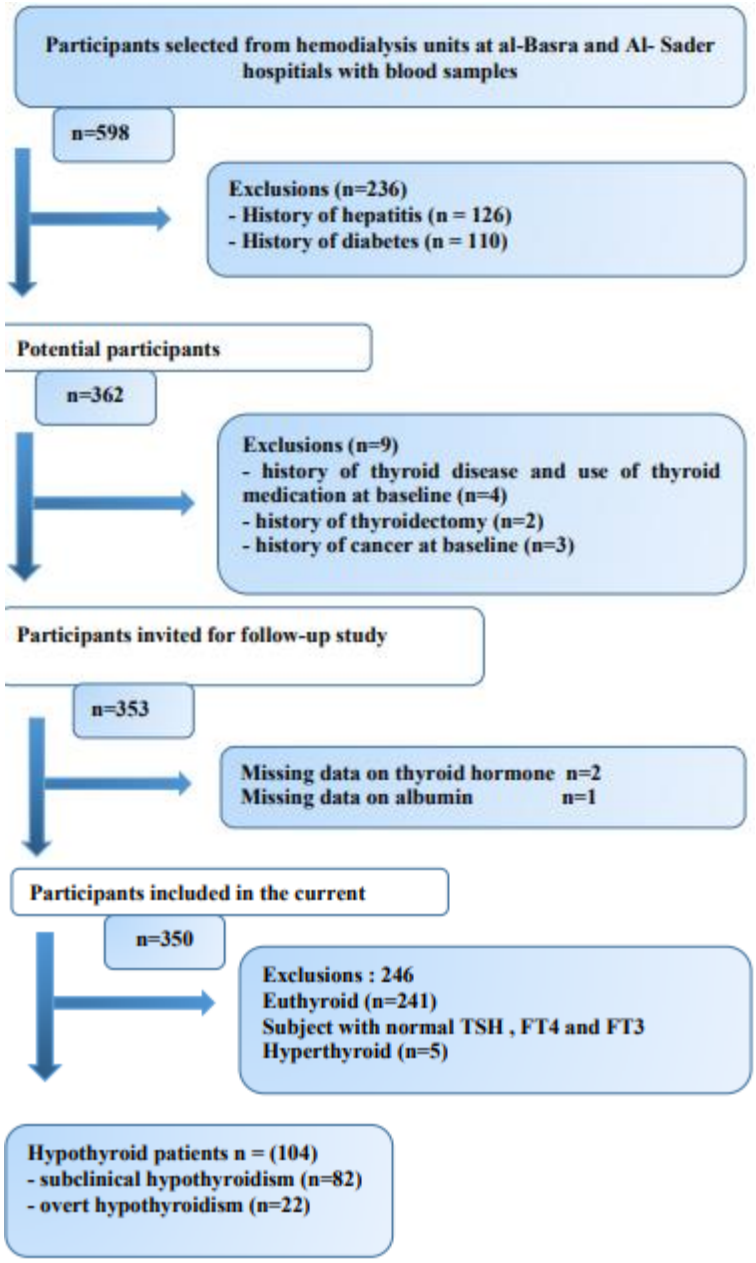

Figure 1: Flow chart of study participants

2.2 Collection of blood samples

After sterilizing the withdrawal site with ethyl alcohol at a 70% concentration, 5 ml of venous blood was withdrawn using sterile medical syringes. Then the serum was transferred to normal tubes at a speed of (5000 rpm) and for a period of (10) minutes, and then the serum was transferred to normal tubes and it was lowered into a deep freeze at a degree of (- 20 C). Repeated freez-thaw cycles were avoided.

2.3 Quantification of serum Interleukin-18 and Interleukin-37

IL-18 and IL-37 serum levels were measured by ELISA kit (pharma Genie, Ireland). The level of Interleukin 18 and interluken-37 are measured by an Enzyme-Linked Immunosorbent Assay (ELISA). The

plate has been pre-coated with human IL-18 antibody Hand IL-37antibody on respectively. IL - 18 and IL-37 are present in the sample are added and binds to antibodies coated on the wells. Then biotinylated human IL-18 and IL-37 Antibody are added and binds to IL-18and IL-37 in the sample. Then Streptavidin-HRP is added and binds to the Biotinylated IL-18 antibody and IL-37 antibody After incubation unbound Streptavidin-HRP is washed away during washing step. Substrate solution is then added and color develops in proportion to the amount of human IL-18 and IL-37 on the reaction is terminated by addition of acidic stop solution and absorbance is measured a 450 nm.

2.4 Statistical analysis

The result of the current study were analyzed using the t-test and chi-square test (X) using the statistical program known as the statistical package for social science (SPSS) under the probability level of $p \leq 0.001$.

3. Results

Table (1) shown the highest mean age in overt hypothyroidism male patients (60.2+_2.35 and the lowest mean age in the control group (54.26±4.42) there was statistically significant differences between overt hypothyroidism and healthy individuals groups regarding the age ($p \leq 0.05$).

The hemodialysis patients were 56% female and 46 % male among the studied groups Among 350 patients meeting eligibility criteria, we observed that 23% (n=82) had Subclinical Hypothyroidism, and 6%(n=22) had overt hypothyroidism were defined by baseline TSH levels. Thyroid status was categorized as Subclinical Hypothyroidism and overt hypothyroidism (TSH 5 - < 10, and ≥ 10 mlu/L, respectively). There was highly statistically significant differences between groups hypothyroid patients and healthy individuals ($p<0.001$), the mean TSH 10.4±1.71 in overt Hypothyroidism patients and lower level FT3, FT4 2.44±0.3, 6.8±0.79 respectively. The mean ± SD of albumin 3.08 ±0.07g/L is lower in comparison with healthy control, low serum Ca (8.34±0.08) and elevated serum phosphate (5.7±0.08). $P<0.001$ On the other hand we observed elevated levels of IL 18 and IL-37 in hemodialysis patients With reduced GFR in both Subclinical Hypothyroidism and overt hypothyroidism (25.20±1.18ml/min per 1.73 m²,17.4±0.68 ml/min per 1.73 m².

Table 1: Characteristics and biochemical of the study groups

Characteristics	Subclinical hypothyroidism Mean ± SD		Overt hypothyroidism Mean ± SD		Healthy Controls Mean ± SD		P value
	Male(38)	Female(44)	Male(10)	Female(12)	Male(30)	Female(30)	
age(years)	56.13±4.42	56.25±3.63	60.20±2.53	57.33±1.49	54.26±5.37	55.10±3.75	>0.05 a,b ≤0.05c,d
GFR (ml/min/1.73m^2)	27.79±1.26**	25.20±1.18**	19.22±1.65**	17.40±0.68**	93.26±12.66	92.80±1.24	<0.001**a,b,c,d
BMI(kg/m^2)	24.69±0.93**	24.21±0.99**	25.90±1.64	25.30±0.40	26.10±1.19	25.82±1.15	<0.001**a,b ‹>0.05 c,d
HD duration(years)	4.8±1.17	6.5±1.21	6.7±1.22	4.6±1.18	0	0	
Creatinine (mg/dL)	9.80±0.99**	10.90±0.95**	11.20±0.69**	11.70±0.63**	0.48±0.15	0.62±0.24	<0.001**a,b,c,d
Urea (mg/dL)	112.37±1.25**	124.50±1.22**	178.80±1.78**	192.30±1.64**	32.70±1.24	28.49±1.24	<0.001**a,b,c,d
Albumin (g/dL)	3.26±0.12**	3.32±0.12**	3.10±0.09**	3.08±0.07**	4.48±0.139	4.56±0.11	<0.001**a,b,c,d
Calcium (mg/dL)	8.61±0.15**	8.53±0.22**	8.24±0.48**	8.34±0.08**	9.51±0.13	9.10±0.20	<0.001**a,b,c,d
Phosphate	5.54±0.12**	5.56±0.12**	5.67±0.08**	5.71±0.08**	3.48±0.139	3.52±0.13	<0.001**a,b,c,d

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(mg/dL)							
T3(nmol/L)	**1.46±1.42**	**1.35±0.13***	**1.26±0.11**	**1.28±0.08***	**1.99±2.23**	**1.47±0.68**	**>0.05 a,c ،<0.05b,d**
T4 (nmol/L)	**84.98±1.83****	**87.30±1.17**	**59.40±3.09****	**61.24±2.05****	**95.20±1.24**	**87.73±0.68**	**<0.001 a,c,d ،>0.05 b**
FT3 (Pmol/L)	**2.67±1.11****	**2.65±0.08****	**2.28±0.10****	**2.44±0.30****	**3.40±0.40**	**3.80±0.68**	**<0.001**a,b,c,d**
FT4 (Pmol/L)	**11.15±1.89****	**11.18±1.36****	**6.10±1.65****	**6.80±0.79****	**16.20±1.24**	**16.60±1.24**	**<0.001**a,b,c,d**
TSH (mLu/L)	**7.10±1.19****	**7.30±1.18****	**10.20±1.79****	**10.40±1.71****	**2.80±1.24**	**2.50±1.24**	**<0.001**a,b,c,d**
IL-18 (pg/ml)	**14.50±1.22****	**14.60±1.21****	**14.31±0.56****	**14.60±0.40****	**9.09±1.17**	**8.99±1.11**	**<0.001**a,b,c,d**
IL-37 (µg/ml)	**127.64±1.21****	**129.75±1.35****	**138.20±1.12****	**140.40±1.15****	**115.40±1.37**	**108.86±18.35**	**<0.001**a,b,c,d**

BMI: Body Mass Index, GFR: Glomerular Filtration Rate, HD: Hemodialysis Duration, IL-18 : Interleukin-18,IL-37 : Interleukin -37, Data are presented as Mean ± SD, SD: Standard Deviation ; a: comparison between male healthy group and Subclinical hypothyroidism male; b:comparison between female healthy group and Subclinical hypothyroidism female; c: comparison between male healthy group and Overt hypothyroidism male; d: comparison between female healthy group and Overt hypothyroidism female.* significant; **highly significant.

The result of laboratory tests showed that median 14.6 of IL 18 in overt Hypothyroidism combustion with healthy control median 2.6and the median for IL-37 140.4 in overt hypothyroidism while control was the median 112.2.as shown in table 2.

Table 2: Levels of IL 18 and IL-37 in pg./ ml of healthy control and patients with Subclinical hypothyroidism and Overt hypothyroidism. The values are the Mean ± SD

		Patients				**Healthy Controls**	
		Subclinical hypothyroidism		**Overt hypothyroidism**			
		Male (23)	**Female (33)**	**Male (01)**	**Female (01)**	**Male (21)**	**Female (21)**
				IL-18 (pg/ml)			
Mean ± SD		**14.50±1.41****	**14.60±1.21****	**14.31±0.56****	**14.60±0.40****	**9.09±1.17**	**8.99±1.11**
Median		**14.5**	**14.55**	**14.45**	**14.6**	**9**	**2.6**
SE		**0.22**	**0.18**	**0.17**	**0.11**	**0.21**	**0.20**
Range		**01.4-05.4**	**01.4-05.1**	**02.4-04.0**	**03.1-04.1**	**1.2-01.1**	**1.2-01.1**
95% CI	**Lower**	**14.03**	**14.24**	**13.90**	**14.34**	**8.65**	**8.57**
	Upper	**14.96**	**14.97**	**14.71**	**14.85**	**9.53**	**9.41**
				IL-37 (µg/ml)			
Mean ± SD		**127.64±1.21****	**129.75±1.35****	**138.20±1.12****	**140.40±1.15****	**115.40±1.37**	**108.86±18.35**
Median		**127.55**	**129.6**	**138.2**	**140.4**	**112.2**	**112.2**
SE		**0.19**	**0.20**	**0.35**	**0.33**	**0.25**	**3.35**
Range		**014.1-011.1**	**011.1-020.1**	**025.2-031.0**	**023.5-031.1**	**002.3-001.3**	**00.1-003.1**
95% CI	**Lower**	**127.24**	**129.33**	**137.39**	**139.6**	**114.88**	**102.01**
	Upper	**128.04**	**130.16**	**139.01**	**141.1**	**115.91**	**115.72**

Data are presented as Mean ± SD, SD: Standard Deviation, SE: Standard Error, Range: is the difference between the highest and lowest values in the set, 95% CI: Confidence Intervals (lower and Upper), p-value Non- significant (p>0.05), A* significant (p<0.05), A** High significant (p<0.01), the level of significance in comparison with the corresponding control value.

Table 3: Correlation between the serum level of IL-18 and IL-37 in (pg/ml) and laboratory investigations in Subclinical hypothyrodsim

	Subclinical hypothyrodsim N= 82			
	Serum Level of IL-18		Serum Level of IL-37	
Characteristics	Correlation Coefficient	*P*	Correlation Coefficient	*P*
age(years)	0.053	0.637	0.265	0.016
GFR (ml/min/1.73m^2)	0.330	0.002**	-0.092	0.414
BMI(kg/m^2)	-0.079	0.481	-0.146	0.192
HD duration(years)	-0.09	0.423	0.644	0.001**
Creatinine (mg/dL)	0.510	0.001**	0.793	0.001**
Urea (mg/dL)	0.101	0.365	0.634	0.001**
Albumin (g/dL)	0.505	0.001**	0.644	0.001**
Calcium (mg/dL)	0.472	0.001**	0.264	0.016*
Phosphate (mg/dL)	0.524	0.001**	0.573	0.001**
T3(nmol/L)	-0.245	0.027*	-0.165	0.137
T4 (nmol/L)	0.424	0.001**	0.741	0.001**
FT3 (Pmol/L)	-0.746	0.001**	-0.454	0.001**
FT4 (Pmol/L)	0.332	0.002**	0.164	0.140
TSH (mLu/L)	0.591	0.001**	0.572	0.001**
IL-18 (pg/ml)	1.000	--	0.479	0.001**
IL-37 (µg/ml)	0.479	0.001**	1.000	--

BMI: Body Mass Index, GFR: Glomerular Filtration Rate, HD: Hemodialysis Duration, IL-18: Interleukin-18,IL-37: Interleukin -37, Data are presented as Mean ± SD, SD: Standard Deviation.* significant; **highly significant.

IL 37 positively corelated with, urea, creatinine, phosphate, TSH and IL-18(P<0.001) 0n the contrary, significant negative correlation was detected in albumin (p=0.001). A significant positive correlation was detected urea, creatinine, Ca, phosphate, FT3, TSH and IL37 and serum level of IL-18 (p=0.001). Whereas a significant negative correlation was in FT3(p=0.005), T3(P=0.032) and albumin(p=0.002). On the contrary, there was no relation between age, BMI, GFR and T4 (Table 4).

Table 4: Correlation between the serum level of IL-18 and IL-37 in (pg/ml) and laboratory investigations in Overt hypothyrodsim

	Overt hypothyrodsim N= 22			
	Serum Level of IL-18		Serum Level of IL-37	
Characteristics	Correlation Coefficient	*P*	Correlation Coefficient	*P*
age(years)	-0.025	0.914	-0.355	0.105
GFR (ml/min/1.73m^2)	0.523	0.013	0.053	0.816
BMI(kg/m^2)	-0.129	0.568	-0.061	0.789
HD duration(years)	0.067	0.768	-0.040	0.859
Creatinine (mg/dL)	0.810	0.001**	0.767	0.001**
Urea (mg/dL)	0.481	0.023*	0.840	0.001**
Albumin (g/dL)	-0.624	0.002**	-0.675	0.001**
Calcium (mg/dL)	0.714	0.001**	0.576	0.005**
Phosphate (mg/dL)	0.780	0.001**	0.758	0.001**
T3(nmol/L)	-0.458	0.032*	-.0118	0.600
T4 (nmol/L)	0.363	0.097	0.135	0.549
FT3 (Pmol/L)	-0.576	0.005**	-0.345	0.116
FT4 (Pmol/L)	0.183	0.416	0.238	0.286
TSH (mLu/L)	0.841	0.001**	0.608	0.003**
IL-18(pg/ml)	1.000	--	0.674	0.001**

IL-37 (pg/ml)	**0.674**	**0.001****	**1.000**	**--**

BMI: Body Mass Index, GFR: Glomerular Filtration Rate, HD: Hemodialysis Duration, IL-18: Interleukin-18,IL-37: Interleukin -37, Data are presented as Mean ± SD, SD: Standard Deviation.* significant; **highly significant.

In our study, the ROC curve was used to find out the best cutoff points of IL 18 and IL-37 in cases of ESRD. IL __18 level a cutoff of 11.70 pg/ml had the sensitivity of 97 % the specificity of 100% positive predictive value (PPV) of 100%, negative predictive value (NPV) of 90%, and accuracy of 96% in the detection. IL-37 level at a cutoff value of 121.55 pg./ml had the sensitivity of 98% the specificity of 100,%, PPV of 100% NPV 92% and accuracy of 97% in detection (Table 5).

Table 5: Diagnostic validity of Interleukin 37 and Interleukin 18

	Cutoff points	**Sensitivity %**	**Specificity %**	**Positive predictive value %**	**Negative predictive value %**	**Diagnostic accuracy %**
IL-18	**11.70**	**97**	**100**	**100**	**90**	**96**
IL-37	**121.55**	**98**	**100**	**100**	**92**	**97**

IL-18: Interleukin-18,IL-37: Interleukin -37.

4. DISCUSSION

In this study, we found a link between hypothyroidism and inflammation in dialysis patients, as measured by TSH levels (the clinical gold standard). We discovered that hypothyroidism was connected with inflammation in a significant and independent way, and that subcategories of hypothyroidism (subclinical and overt) were likewise associated with greater inflammatory levels. Previous research has found an increased prevalence of hypothyroidism and goiter in patients with ESRD who require maintenance dialysis. While many possible causes have been proposed, such as altered iodine metabolism and autoimmune thyroiditis, the specific pathways are yet unknown [16], [17]. Recent studies have discovered a higher prevalence of hypothyroidism in people with a lower estimated GFR, regardless of age, gender, or race/ethnicity. There was also hypothyroidism, which was associated with a gradually increasing risk of a decreased GFR. Many ESRD patients have hypothyroidism, either subclinical or overt. Hormonal abnormalities become more severe as renal failure progresses, according to various studies [18], [19]. The above-mentioned illnesses are influenced by a variety of elements, each of which must be identified in order to fully comprehend the etiology of hormonal imbalances. The researchers looked at how concomitant hypothyroidism and substitution medication affected conversion ratios and the rT3 / T3 ratio in patients with renal failure, where thyroid hormone concentrations, both total and free fractions, are usually low [20], [21]. Abnormalities occurring from thyroid hormone production, hormone breakdown, conversion, and transport with the participation of proteins are the cause of thyroid hormone concentration reductions. The hypothalamus- pituitary-thyroid axis' control is also disrupted [24]. T4 and fT4 concentrations may be normal or slightly lowered in RF, while dialysis patients may have higher fT4 and lower T4 concentrations, which is likely due to T4-protein binding problems caused by heparin during HD [22], [22], [26]. In the current investigation, lower T4, fT4, T3, and fT3 readings were also found in HD patients with newly diagnosed hypothyroidism, which could be due to the patients' poor general health (Table 1). Total T4 concentrations showed similar, but less significant, tendencies. The hypothyroidism group of HD patients had the worst laboratory results (highest IL-37, IL-18, lowest albumin), which can disrupt thyroid hormone metabolism (Table 1). Other researchers found similar correlations for thyroid hormones, linking lower T4 concentrations to acidosis, lower albumin concentrations, and anemia [20], [24], [25], [27]. Furthermore, there was a negative connection between total T4 content and urea in the literature [26].

Low total T3 levels in CKD patients appear to be one of the leading causes of death in euthyroid patients, affecting up to 39% of those with the disease [18], [19], [28], [29]. In comparison to the control group, all analyzed groups of HD patients had statistically significant reduced T3 and fT3 concentrations (Table 1). Other researchers have verified our findings [28- 31]. T3 concentration is reduced due to a drop in 5'-deiodinase (D1) activity and an increase in 5'-deiodinase (D3) activity, but not due to a reduction in T4 availability [28- 31]. Low total T3 concentrations in ESRD patients could be attributed to HD eliminating the free hormone, decreased T3 binds, increased hormone catabolism, decreased T3 secretion by the thyroid gland, and lastly, reduced T4 to T3 non-thyroidal conversion [29- 32].

We discovered higher levels of Interlaken-18 and Interlaken-37 in the groups of ESRD patients treated with hemodialysis in the current investigation, particularly in individuals with subclinical hypothyroidism and overt hypothyroidism (Table 1). Other researchers have found a link between total T3 and increased levels of pro-inflammatory and anti-inflammatory cytokines, as well as decreased albumin levels [20], [33], [34].

Subclinical hypothyroidism is defined as a high serum TSH concentration combined with normal fT4 and T3 concentrations [9]. The cause of CAPD patients' increased TSH levels was unknown. Increased prevalence of ID hypothyroidism in ESRD patients may be related to iodide excess due to poor renal excretion [35]. According to the findings, all of the tested groups had significantly higher IL- 18 serum levels than the control group. Furthermore, some research suggests that cytokines can be used as markers for the advancement of micro inflammation and the occurrence of hypothyroidism. Hemodialysis patients have higher levels of IL-18, a pro-inflammatory cytokine. When compared to a healthy control group, the study found a highly significant rise in IL-37 serum [36].

5. Conclusion

We can conclude from this study that IL-18 serum levels increased considerably in individuals with Subclinical Hypothyroidism and overt hypothyroidism, suggesting that it may have a role in the onset, development, and progression of nephropathy in hypothyroid and ESRD patients. Because of its positive correlation with some renal functions, IL-37 may be regarded a predictive factor for the advancement of the renal disease associated with hypothyroidism.

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