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Investigation of thyroid function and mortality predictors in patients receiving dialysis: a cross-sectional study

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ABSTRACT

Introduction: Various studies have assessed the link between the thyroid and kidney and concluded that dysfunction in one organ can disrupt the other. Thyroid dysfunction is more prevalent in individuals with end-stage renal disease (ESRD) compared to the general population. Hypothyroid ESRD patients have higher mortality than euthyroid patients. In this study, we evaluated the prevalence of hypothyroidism in dialysis-dependent ESRD patients and assessed the association of possible prognostic factors with mortality.

Methods: Patients who were undergoing dialysis in centers affiliated with the Mashhad University of Medical Sciences were enrolled and followed for a year to obtain survival rates. Lab parameters including thyroid stimulating hormone (TSH), parathyroid hormone (PTH), and magnesium (Mg) were recorded at baseline, and the relationship between these values and mortality was assessed.

Results: The prevalence of hypothyroidism was %23 and %32.5 in hemodialysis and peritoneal dialysis patients, respectively. Blood urea was meaningfully higher in hemodialysis patients, while hypocalcemia and hyponatremia were more common in peritoneal dialysis patients. Higher ages (P=0.006), lower baseline Mg (P=0.044) and PTH (P=0.01), and diabetes (P=0.037) were all linked to a higher risk of mortality.

Conclusion: Hypothyroidism was notably prevalent in our study population. As hypothyroidism is associated with higher mortality, proper screening and intervention in this group are essential. We recommend the prescription of supplementary Mg in dialysis patients as baseline Mg and PTH levels are associated with better outcomes in this group. Diabetes was also associated with higher mortality. Maintaining glycated hemoglobin between %8-%6 is therefore suggested to increase the survival of diabetic patients.

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Introduction

Numerous years of research have been conducted to understand how the thyroid and kidney interact (1). Thyroid hormones play an important role in the development and hemodynamics of the kidney, and kidney disorders can result in thyroid dysfunctions associated with metabolism and catabolism changes (1). Besides having direct detrimental effects on kidney size and structure (e.g., decreasing relative kidney weight and distorting glomerular conformation), hypothyroidism exposes kidneys to ischemic injuries due to decreased cardiac output and alterations in the renin-angiotensin-aldosterone system (2). Patients with renal disease frequently encounter thyroid disorders, particularly those with ESRD receiving hemodialysis or peritoneal

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dialysis. Moreover, hypothyroidism is the most common thyroid disorder reported in ESRD patients (3). Existing evidence on thyroid dysfunction in dialysis patients relates this condition to uremic toxins, protein malnutrition, and inflammation, however; the exact reason behind this association is not fully understood (4).

Rhee et al. investigated the relationship between hypothyroidism and mortality in adult patients receiving dialysis between 2005 and 2011 (5). Their study revealed that patients with chronic kidney disease are more likely to develop hypothyroidism than people with normal renal function (5). This study presents thyroid stimulating hormone (TSH) as a clinical gold standard in correspondence with hypothyroidism development (5).

Another multi-centric study examining thyroid function in 1000 hemodialysis-dependent diabetics with ESRD showed that thyroid dysfunction is associated with higher mortality rates (6). Patients with hypothyroidism and sick euthyroid syndrome had short-term cardiovascular disease mortality risks that were respectively 2.03 and 2.74 times higher than those with normal thyroid function (6).

The suggested association of mortality and hypothyroidism in dialysis patients urged us to assess the prevalence of thyroid dysfunction among ESRD patients receiving dialysis in Mashhad, Iran. We also evaluated and compared the baseline biochemical profile among patients receiving hemodialysis and peritoneal dialysis.

The association of patients' biochemical profile and thyroid function (serum TSH level) with one-year mortality was also assessed. The results of this study are anticipated to aid medical professionals in the early diagnosis of thyroid disorders in these patients through appropriate periodic screening, as well as in the screening of potential prognostic factors in these patients to increase survival.

Materials and Method

Patient selection and data gathering:

A multi-center cross-sectional study was conducted on 313 patients who underwent dialysis (hemodialysis or peritoneal dialysis) at the Mashhad University of Medical Sciences (MUMS), from January 2019 to January 2020. Patients who had ESRD due to different primary causes and underwent dialysis were included. Among these patients, 40 were receiving peritoneal dialysis, while 273 patients were receiving hemodialysis.

Hemodialysis was performed three times a week, four hours per session, and continuous ambulatory peritoneal dialysis was performed three times daily.

Additional inclusion criteria were defined as receiving dialysis for more than a year, ages above 18 years, and having no previous history of thyroid dysfunction. Exclusion criteria included severely ill patients, patients who required hospitalization, and the presence of systemic inflammatory diseases such as lupus.

For all the individuals included in the study, demographic data such as gender, age, and baseline biochemical profile including serum value of phosphorus (P), sodium (Na), potassium (K), calcium (Ca), magnesium (Mg), iron, creatinine, urea, ferritin, hemoglobin (Hb), TSH, free triiodothyronine (FT3), free thyroxine (FT4), parathyroid hormone (PTH), and total iron binding capacity (TIBC) were obtained at baseline using an institutional form.

For those included in the study that underwent dialysis, blood samples were taken prior to hemodialysis sessions to avoid heparin-induced artifactual results. As diabetes mellitus (DM) has been reported to reduce survival in dialysis patients (7), we also recorded a previous history of DM in our patients and included it in our final model assessing mortality in this group.

Mortality assessment

After a year of follow-up, patients' outcomes in terms of mortality were documented. All deceased patients were in the hemodialysis group, and thus, further analysis was conducted on this group exclusively.

Statistical analysis

Biochemical parameters were compared between the two groups using the independent samples t-test, while the prevalence of hypothyroidism and disorders of PTH and electrolyte disturbances (hypo/hypernatremia, hypo/hypercalcemia, hypo/hyperkalemia, and hypo/hyperphosphatemia) between the two groups were compared using the chi-squared test.

Binary logistic regression was employed to investigate the association of patients' demographic data and their obtained biochemical parameters with mortality. All analyses were performed using SPSS software, version 26 (Chicago).

Ethical considerations

The current study was approved by the ethics committee of MUMS (IRMUMSREC.1395.202), and all patients signed written informed consent forms.

Results

The majority of our study population consisted of males (61.6%). The mean age of patients was 52.87 in the hemodialysis group and 49.58 in the peritoneal dialysis group. No significant difference was observed regarding age or gender between the two groups (P=0.179 and P=0.769, respectively).

Table 1 illustrates a comparison of baseline

laboratory markers between patients receiving hemodialysis and peritoneal dialysis. Patients undergoing hemodialysis had significantly higher serum concentrations of urea compared to the ones receiving peritoneal dialysis. However, TIBC levels were higher in the peritoneal dialysis group.

In terms of qualitative comparison, a greater number of hyponatremic and hypocalcemic patients were observed in the peritoneal dialysis group while hyperkalemia was more common in the while hyperkalemia was more common in the hemodialysis group (P=0.026). Regarding the thyroid profile among the two groups, no significant difference was observed, neither in terms of qualitative comparison nor quantitative. Hypothyroidism prevalence was 23% in hemodialysis patients and 32.5% in peritoneal dialysis patients. FT3 and FT4 were higher in peritoneal dialysis than in the hemodialysis groups (P<0.001).

Table 1. Comparison of the biochemical profile and thyroid function between hemodialysis patients and peritoneal dialysis patients

Parameters		Hemodialysis Group	Peritoneal Dialysis Group	P-value
TSH		4.1	4.72	0.14
FT3		2.59	3.73	<0.001
FT4		7.15	10.33	<0.001
TSH	Within normal range	72.00%	65.00%	0.37c
	Below normal range	23.30%	32.50%	
	Above normal range	4.70%	2.50%	
Urea		113.57	100.94	0.006
Hemoglobin		11.17	11.04	0.635
Iron (mean)		71.06	60.1	0.46
TIBC		225.19	325.56	<0.001
Ferritin		478.45	437.75	0.385
PTH		525.61	375.93	0.71
Na	Normal	88.40%	73.70%	0.017a
	Hyponatremia	9.70%	26.30%	
	Hypernatremia	1.90%	0%	
K	Normal	80.20%	94.70%	0.026 a
	Hypokalemia	2.70%	2.60%	
	Hyperkalemia	17.10%	2.60%	
Ca	Normal	54.80%	31.60%	0.009 [a]
	Hypocalcemia	44.40%	68.40%	
	Hypercalcemia	0.80%	0%	
P	Normal	30.40%	34.20%	0.704 [a]
	Hypophosphatemia	1.20%	0%	
	Hyperphosphatemia	68.50%	65.8	
PTH	Normal	19.20%	27.30%	0.286 [b]
	Abnormal	80.80%	72.70%	

During one-year follow-up, 41 patients died, wherein all the deceased patients had received hemodialysis. Table 2 compares the demographic information and biochemical profiles of the deceased and surviving patients.

Serum concentration of Mg and PTH significantly differed between the two groups. Older patients showed a remarkably higher mortality rate. The presence of DM was also associated with a poorer outcome as 45% of the deceased patients had DM at initial evaluation, which was significantly higher compared to the survivor group. Death probability was 2.15 times higher in diabetic versus non-diabetic patients Quantitative analysis of the PTH parameter indicates a remarkable correlation between mortality rate and serum PTH levels.

Our data reveal that serum Mg concentrations are inversely related to mortality as odds of mortality are reduced by 0.62 times per each 1 unit increase in Mg concentration.

Table 2. Association of baseline biochemical profile and one-year mortality

Parameters	Survivors in Hemodialysis Group (n=232)	Non-survivors in Hemodialysis Group (n=41)	P-value	Odds Ratio (95% CI)
Age (years-mean)	51.72	59.02	0.006	1.033 (1.01-1.058)
Gender(Male%)	0.625	0.6	0.853	
Diabetes (%)	14	45	0.037	2.15 (1.05-4.44)
Na (meq/dl)	138.93	138.17	0.224	
K (meq/dl)	4.86	4.85	0.927	
Ca (meq/dl)	8.43	8.27	0.371	
Mg (meq/dl)	2.27	1.96	0.044	0.62 (0.39-0.99)
Iron (mcg/dL)	69.01	82.25	0.493	
TIBC (mcg/dL)	221.1	246.75	0.08	
Ferritin (mcg/dL)	487.88	413.24	0.422	
Hb (g/dl)	11.13	11.49	0.376	
Creatinine (mg/dl)	8.88	7.95	0.061	
PTH (pg/mL)	562.18	350.06	0.01	0.998 (0.997-1)
TSH (mU/L)	4.15	3.85	0.793	
FT3 (ng/dL)	2.57	2.71	0.649	
FT4 (µg/dL)	7.17	7.05	0.901	

Discussion

The link between the thyroid and the kidney has been verified in the past (1-3). Inadequate thyroid hormone secretion affects the equilibrium of water and electrolytes as thyroid hormones are essential for the kidneys' efficient operation (2).

Effects of the thyroid gland on kidneys can be either direct, including the alteration of glomerular and tubular function, or indirect through changes in cardiovascular activity (3). Studies on hypothyroidism in humans and rodents have shown that hypothyroidism can cause up to an 18% increase in the glomerular filtration rate (4).

Moreover, patients suffering from renal abnormalities are more susceptible to thyroid disorders in comparison to healthy individuals (8,9). Numerous studies have been performed to investigate the correlations between thyroid disorders and kidney malfunctions. Zeraati et al. studied the effect of inflammation on thyroid gland function and showed T3 levels tend to decline in ESRD patients as an inflammatory condition starts to emerge (10).

In this cross-sectional study that investigated the relationship between T3 levels and the high-sensitivity C-reactive protein (hs-CRP), 30 patients receiving peritoneal dialysis, 30 patients receiving hemodialysis, and 20 normal individuals were included (10). No significant difference was observed in T3, T4, FT3, and FT4 levels of the patients receiving peritoneal dialysis and hemodialysis (10).

However, our study shows significant FT3 and FT4 concentration differences between the hemodialysis and peritoneal dialysis groups. We believe that this difference is not of clinical importance given that TSH levels do not significantly differ between the two groups in either quantitative or qualitative terms. Regarding iron status and utilization, patients receiving peritoneal dialysis had significantly higher TIBC compared to hemodialytic patients.

Even though these patients exhibited slightly lower levels of iron, ferritin, and hemoglobin, these differences did not reach conventional statistical significance. These differences may be due to different treatment strategies of anemia in the two groups as hemodialysis patients usually receive intravenous iron supplementation while patients receiving peritoneal dialysis are treated with oral iron supplements (11,12).

However, it is important to note that the regulation of iron metabolism in dialysis patients is complex and multifactorial, and other factors such as inflammation, erythropoietin use, and dialysate composition can also affect iron metabolism and TIBC levels. Therefore, further research is needed to fully understand the mechanisms underlying the observed differences in TIBC levels between peritoneal dialysis and hemodialysis patients.

Avram et, al. investigated and compared mortality among patients receiving hemodialysis and peritoneal dialysis, and conceived that mortality rates are significantly higher among patients receiving peritoneal dialysis (13).

Their study followed patients for 12 years while ours only followed them for one year This notable difference between the two study results might be due to the much longer follow-up period in their

study. Nonetheless, our findings suggest that one-year survival is much higher in patients receiving peritoneal dialysis. They also concluded that higher baseline levels of PTH are associated with better outcomes, and stated that higher PTH levels reflect better nutritional status. Even though the odds ratio regarding PTH levels is close to one in our analysis, our findings are somewhat similar to theirs.

They also concluded that higher ages are associated with mortality, which was also a finding in our study. In 2017, Pakfekrat et al. assessed the prevalence of hypothyroidism in 86 hemodialysis patients, and reported a prevalence of 18.6 in this group of patients. They also compared the prevalence of hypothyroidism in the hemodialysis group with healthy controls, and concluded that this prevalence was much higher in hemodialysis patients (14).

However, they only adjusted their control group for sex, weight, age, and gender. As hypothyroidism is affected by other important confounders including drugs, and comorbidities other than ESRD, a fair comparison would require a more precise selection of the control group. Delshad et al. evaluated the prevalence of hypothyroidism in a healthy Iranian adult population, and reported a prevalence of 2.1 and 2.8% in men and women respectively (15).

Considering their findings, our study demonstrates a much higher rate of hypothyroidism in dialysis patients. Although the correlation between TSH levels and mortality did not achieve statistical significance, the data supporting this link is compelling enough to warrant further investigation and proper screening and treatment of hypothyroidism in dialysis patients (5). Goodkin et al. have investigated the association of 25 underlying comorbidities, including DM, with mortality and concluded that the presence of this disease is strongly associated with higher mortality rates, which are in line with our findings (16).

The increased risk of mortality in diabetic dialysis patients necessitates appropriate screening and intervention in this group of patients to increase their survival. Maintaining glycated hemoglobin (HbA1c) between 6%-8% has been strongly reported to increase the survival rate in diabetic dialysis patients (17).

Investigating 21534 patients, Lacson Jr. et al concluded that lower serum Mg concentrations are associated with an increased risk of mortality, whereas, hypermagnesemia was associated with either lower or no increased risk of mortality (18).

Our findings also confirm the protective role of Mg. Several mechanisms have been proposed to explain the association between serum magnesium levels and mortality in dialysis patients. One possible mechanism is the role of magnesium in maintaining cardiovascular health.

Higher serum magnesium levels have been associated with a reduced risk of cardiovascular mortality in hemodialysis patients with hyperphosphatemia, possibly by suppressing calcification of blood vessels(19).

Additionally, higher serum magnesium levels may reflect better nutritional status in dialysis patients (20). Magnesium may also play a role in regulating inflammation and maintaining overall health (21). These findings suggest that maintaining appropriate serum magnesium levels may be an important factor in reducing mortality risk in hemodialysis patients.

Conclusion

The prevalence of hypothyroidism was remarkably high in our study population. As hypothyroidism and mortality have been correlated in previous research, we predict routine thyroid function testing and effective hypothyroidism treatment can increase survival in dialysis patients.

Our findings also reveal that higher PTH and Mg baseline levels are associated with better outcomes in hemodialysis patients, while the presence of DM worsens the outcome in this group and thus, controlling HbA1c (6%-8%) seems beneficial to increase survival. Nutritional status should also be given special attention in hemodialysis patients since earlier research has indicated that higher levels of serum Mg and PTH concentrations may be a reflection of a better nutritional status.

Besides, as hypermagnesemia is not associated with an increased risk of mortality in hemodialysis patients (18), we suggest the prescription of supplementary Mg in this group.

Conflict of Interest

No potential conflict of interest relevant to this article was reported

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