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Editorial

Abnormal thyroid function in peritoneal dialysis patients: Lots of smoke but no fire

Thyroid disorders are the second most common endocrine condition following diabetes mellitus. It is not difficult for physicians to diagnose and treat patients with overt hypothyroidism or hyperthyroidism presenting significant biochemical derangements and clinical symptoms. In the spectrum of subclinical thyroid dysfunction and nonthyroidal illness syndrome (i.e., alterations in thyroid hormones without any underlying intrinsic thyroid disorder), however, it is not always an easy task. The interpretation of thyroid functions in patients with chronic kidney disease (CKD) or end-stage renal disease (ESRD) is even more complicated by the declination in glomerular filtration rate (GFR), the difference in dialysis modalities, and comorbidities.

CKD is a well-known cause of nonthyroidal illness syndrome and affects all levels of the hypothalamus-pituitary-thyroid axis. Serum TSH levels are usually normal or elevated in CKD patients with normal or low free and total T3 and T4 levels.[1] Low T3 syndrome is the most frequently observed thyroid alteration in CKD patients.[1] An epidemiological study using data from NHANES III, indicated a higher prevalence of hypothyroidism in predialysis CKD patients; it is mainly subclinical among these patients.[2] Furthermore, there was a graded and increased likelihood of hypothyroidism with progressively lower GFR.[2] These disarrangements are similar in ESRD patients after the commencement of peritoneal dialysis (PD) treatment. The major thyroid dysfunctions in PD patients include subclinical hypothyroidism and low T3 syndrome.[3] The clearance of iodide is primarily by glomerular filtration. Thus, iodide excretion is diminished in advanced CKD, with subsequent elevation in plasma inorganic iodide concentration. Increases in total body inorganic iodide can block thyroid hormone production (the Wolff-Chaikoff effect), which may explain the high incidence of subclinical hypothyroidism in CKD patients.[4] Low T3 levels reflect a diminished conversion of T4 to T3 in the periphery. Its physiological significance has been interpreted as an adaptive compensatory attempt to conserve energy stores by reducing metabolic rate in diseased states.

Increasing evidence supports the association of subclinical hypothyroidism with cardiovascular diseases (CVD) and mortality. Because of the known effects of thyroid hormone, including modulating heart rate, cardiac contractility, arterial peripheral resistance and cholesterol metabolism, it is reasonable to predict adverse cardiovascular effects in subclinical hypothyroidism. Recent large, prospective, cohort and meta-analysis studies have demonstrated that subclinical hypothyroidism is associated with an increased risk for CVD, cardiovascular and all-cause mortality.[5,6] Moreover, patients with low T3 levels also had a high risk for acute myocardial infarction, heart failure and mortality.[7,8]

CVD is the major cause of mortality among CKD patients. In line with previous studies in unselected populations, there is an association between T3 levels and inflammatory markers including C-reactive protein (CRP), and interleukin 6(IL-6), nutritional marker (albumin), and cardiac function in CKD patients.[9] Furthermore, the reduction in total T3, but not in free T3 levels, was associated with increased all-cause and cardiovascular mortality in euthyroid CKD patients.[9] In PD patients, subclinical hypothyroidism displayed a lower left ventricular ejection fraction (LVEF) compared to those with normal TSH levels. Elevated TSH levels were associated with decreased LVEF[10] and low serum free T3 levels were associated with arterial stiffness.[11] Further investigations showed an inverse relationship between free T3 levels and CRP and IL-6, as well as serum albumin levels, in PD patients.[12] During a 2.8-year follow-up, the lower free T3 levels were associated with a survival disadvantage.[12] Several factors, including malnutrition and intercurrent processes, may be involved in the reduction of serum T3 in PD patients. The presence of malnutrition, associated with a reduction of binding protein synthesis, could reduce plasma total T3 concentration. The elevated IL-1, IL-6 and TNF-α in PD patients, can mediate down-regulation of deiodinase, an enzyme responsible for T4-to-T3 conversion in peripheral tissues.[13] It would explain how chronic inflammation associated with CKD interferes with the normal process of T3 synthesis from T4.

In this issue of the *Journal*, Lin et al examined the relationship between thyroid function and mortality in PD patients with long dialysis duration.[14] The major finding of this study was the presence of a mild thyroid dysfunction linked to an increased risk of mortality in long-term PD patients. The result confirmed previous findings. Why can abnormal thyroid function predict mortality in long-term PD patients? Abnormal thyroid function may be part of the pathologic processes leading to a progressive deterioration of the cardiovascular system. On the contrary, the hypothesis of an adaptive and

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protective effect of abnormal thyroid function in PD patients has become questionable. Another possible interpretation is that abnormal thyroid function is a marker of poor health, which is not causally related to cardiovascular disease. Indeed, there are more noncardiac deaths among long-term PD patients. Unlike T3, the relationship between inflammation and T4 in CKD or PD patients is less defined. The authors first demonstrated free T4 levels inversely correlated with CRP in PD patients. It is a tempting idea to replace thyroxine in PD patients with abnormal thyroid function; however, we still need to understand the clinical and biochemical implications of these derangements, before the intervention.

There are some points to be clarified in this study.[14] Firstly, all PD patients were classed as having either an abnormal or normal thyroid function status based on one blood test; there was a lack of information about follow-up thyroid function tests. In a study on hemodialysis patients,[4] the multiple regression analysis showed that total T3 and free T3 were independently associated with dialysis duration. The authors should tone down their conclusion regarding the relationship between thyroid dysfunction and mortality over a relatively long period using tests obtained at a single point of time. Moreover, Tang et al[15] stated that the diagnosis of hypothyroidism in uremic patients cannot be made by clinical or routine laboratory values and rests on the presence of an overtly elevated serum TSH concentration. Secondly, laboratory data overlap between hypothyroidism and nonthyroidal illness syndrome, and it is difficult to differentiate them exactly in PD patients. The term "abnormal thyroid function" in this article,[14] which may include the two different conditions, is nonspecific and heterogonous. It is not biologically plausible to further explore the possible underlying mechanisms between thyroid hormone and mortality in PD patients. Although the authors tried to account for variables affecting mortality in a multivariate analysis, they may not have accounted for currently known risk factors, like serum albumin, systolic blood pressure, and smoking status. Finally, this is a retrospective study on a highly selective PD patient group, with long dialysis duration. The potential bias inherent in the study would render the conclusion premature. Therefore, until further mechanistic studies have been performed, abnormal thyroid function should be considered as a marker for survival disadvantage and not an etiological factor in PD patients. Just as the authors stated, we should be alerted to the alteration of thyroid function tests in PD patients, and search for the possible causes of the derangement.

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