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Thyroid Hormone Abnormalities and Frailty in Elderly Patients with Chronic Kidney Disease: A Hypothesis

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ABSTRACT

Thyroid hormones play a crucial role in the metabolic activities of adults, affecting almost every organ system. All types of thyroid diseases are encountered in the elderly. As symptoms and signs of thyroid diseases may overlap with what is considered to be "normal aging," the presence of a thyroid disorder may go undiagnosed in the elderly. This potential problem is further compounded in elderly patients with chronic kidney disease (CKD), where the presence of an underlying hormonal problem such as hypothyroidism may be erroneously attributed to multiple comorbidities, the aging process, or the kidney disease. Frailty is being recognized as a contributing factor to the poor outcomes (hospitalization and high mortality) in elderly patients with CKD. Predisposing factors leading to frailty in elderly with CKD such as increased inflammatory markers, anemia, low testosterone, sarcopenia, and depression are associated with thyroid hormonal abnormalities. These associations are remarkable and raise the question of whether routine monitoring and screening for thyroid hormone changes in elderly CKD patients might be helpful in identifying reversible causes of frailty. In this review, we will focus on the associations between thyroid hormone abnormalities and the predisposing factors of frailty in elderly patients with CKD. If a cause–effect relationship of thyroid hormone abnormalities and factors predisposing to frailty in CKD patients is established, identification and treatment of thyroid abnormalities in this population would assume increased importance.

Globally, the number of elderly is expected almost to triple, from 743 million in 2009 to 2 billion in 2050. With every passing month, another 870,000 people turn 65 years, and this figure is projected to grow almost 2 million a month (1). Although the total US population increased threefold during the 20th century, the elderly population increased more than 10-fold. (2,3). The prevalence of chronic kidney disease (CKD) stages 1 through 4 increased from 10.0% in 1988–1994 to 13.1% in 1999–2004 (4). In fact, 75% of the CKD population in the US is 65 years of age or older (5). This growth trend is mirrored in end-stage renal disease (ESRD); compared with 1994, the overall incidence for ESRD in the elderly in 2004 increased 24% for those aged 65–74, and 67% for those 75 years and older (6).

Frailty is a term that has been used for some time with varying definitions. Earlier definitions were vague and described an elderly patient who is lacking general strength and is susceptible to diseases. Fried et al. (7) suggested a more precise and standard definition in which three or more of five components would define frailty; unintentional weight loss (10 pounds or more in a year), self-reported exhaustion, weakness (measured by grip strength), slow walking speed, and low physical activity. Shlipak et al. (8) demonstrated that CKD is associated with a greater prevalence of both frailty and disability in the elderly population with the prevalence of frailty and disability being 15% and 12%, respectively, in elderly with CKD, versus only 6% and 7%, respectively, in elderly with normal kidney function.

Similarly, frailty is highly prevalent in patients with ESRD on hemodialysis (HD) (9) and increases as a function of aging: 44.4% in patients younger than 40 years, 66.4% in patients aged 50–60 years, and 78.8% in ESRD patients older than 80 years (9). Furthermore, frailty is independently associated with high risks of death and hospitalization (9). Several other studies confirmed that the frailty is associated with several adverse health outcomes such as functional decline (worsening mobility, activities of daily living disability, recurrent falls, hip and nonspine fractures), hospitalization, and death (7,10–12).

Several factors have been suggested as predisposing to frailty in elderly patients in general and more so in elderly patients with CKD, as shown in Table 1 (13).

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TABLE 1. Predisposing factors to frailty

Increased inflammatory markers
Anemia
Anorexia and nausea leading to poor nutrition, weight loss, and sarcopenia
Hormonal changes
Depression
Decreased muscle strength

One of these factors is thyroid hormone abnormalities, both directly and indirectly through effects on other hormone systems.

Thyroid hormone changes are prevalent in elderly patients with CKD/ESRD (14–16) and are associated with many of the components contributing to frailty. Based on the multiple associations noted between changes in thyroid function and the various components that constitute frailty, we postulate that thyroid function changes contribute to the frailty syndrome seen in elderly patients with CKD. In this review, we will discuss the various associations that were described between thyroid hormonal changes and frailty in elderly with CKD/ESRD.

Thyroid Hormone Physiology

There are primarily two biologically active thyroid hormones: thyroxine (T4) and 3, 5, 3′-tri-iodothyronine (T3). Although T4 is solely a product of the thyroid gland, T3 is a product of the thyroid as well as many other tissues. For the thyroid gland to function normally, iodine is required. Iodine obtained from food is transported as iodide into thyroid follicular cells where it rapidly diffuses to the apical surface of the cells and is subsequently transported to exocytotic vesicles fused with the apical cell membrane (17). In these vesicles, the iodide is rapidly oxidized and covalently bound to a few of the tyrosyl residues of thyroglobulin. Thyroglobulin is a 660-kD (kilo Dalton) glycoprotein found mostly in the lumen of thyroid follicles (18). T4 is formed by coupling of two di-iodotyrosine residues and T3 is formed by coupling of one mono-iodotyrosine and one di-iodotyrosine residues. More than 99.95% of the T4 and 99.5% of the T3 in serum are bound to several serum proteins (19). Because nearly all of the T4 and T3 in serum are bound, changes in the serum concentrations of the binding proteins have a major effect on serum total T4 and T3 concentrations.

Thyroid Hormone in the Elderly

The thyroid gland plays an important and specific role in the relationships between the endocrine system and aging (20–23). Thyroid diseases are common in the elderly and include clinical and subclinical hypo- and hyperthyroidism, nontoxic nodular goiter, and thyroid cancer. The frequency of overt hypothyroidism in the elderly ranges from 0.5% to 5%. Subclinical hypothyroidism, defined as an increase in thyroid-stimulating hormone (TSH) accompanied by a normal T4 ranges with few or no symptoms of hypothyroidism (24), is even more frequently noted in the elderly (25,26). Subclinical hypothyroidism prevalence increases with age, affecting approximately 6% of persons aged 70–79 years and 10% of those 80 years or older (27).

Symptoms of hypothyroidism can be easily confused with symptoms of aging or other disorders. An insidious onset of fatigue, weakness, cold intolerance, constipation, depression and/or mental deterioration, hearing loss, cardiomegaly, and congestive heart failure may occur with hypothyroidism. Hyperthyroidism, on the contrary, occurs less frequently in the elderly (0.5–3%) (28–30). Elderly hyperthyroid patients display fewer signs and symptoms when compared with younger people (22,31) and may have atypical presentations as osteoporosis (32) or symptoms related to heart failure (33).

Thyroid Hormone in CKD

The kidney normally plays an important role in the metabolism, degradation, and excretion of several thyroid hormones. Thus, any impairment in kidney function can disturb thyroid physiology. Thyroid hormones also play an important role in kidney growth and function (34,35). The kidney normally contributes to the clearance of iodide, primarily by glomerular filtration. Thus, iodide excretion is diminished in patients with advanced CKD; leading to an elevated plasma inorganic iodide concentration. Increases in total body inorganic iodide can potentially block thyroid hormone production that may explain the slightly higher frequency of goiter and hypothyroidism in patients with CKD (36).

Several changes in thyroid hormonal levels are noted in patients with CKD/ESRD. Two recent studies found an increased prevalence of hypothyroidism in patients with CKD. Lo et al. (14) analyzed data from the Third National Health and Nutritional Examination Survey (NHANES), finding that, among 14,623 adult participants, hypothyroidism was present in 5.4% of subjects with glomerular filtration rate (GFR) >90 ml/min per 1.73 m^2 with incremental increases to 10.9%, 20.4%, and 23% of subjects with GFR 60–89, 45–59, and <45 ml/min per 1.73 m^2, respectively. Subclinical hypothyroidism was observed in 56% of hypothyroidism cases in patients with CKD (14). More recently, Chonchol et al. (15) showed the prevalence of subclinical hypothyroidism to increase from 7% at an estimated GFR $\geq$90 ml/min per 1.73 m^2 to 17.9% at an estimated GFR <60 ml/min per 1.73 m^2.

Most patients with ESRD have reduced plasma levels of free T3, reflecting diminished conversion of T4 to T3 in the periphery (37). Although these changes affect the total T3 concentration, the circulating levels of serum T3 may be increased in patients with ESRD, possibly due to reduced renal clearance (38). The plasma concentration of TSH is usually normal in CKD (36,37) as well as in patients on HD, peritoneal dialysis (PD), and after kidney transplantation (39). However, the TSH response to exogenous thyroid-releasing hormone (TRH) is often blunted or delayed, with a prolonged time required to return to baseline levels (40). This delay in recovery may

be explained by reduced renal clearance of TSH and TRH.

Thyroid in Elderly Patients with CKD

Thyroid disorders seem to increase with age in patients with CKD. Lin et al. (16) investigated the prevalence of thyroid dysfunction and nodular goiter in patients undergoing HD and PD. Dialysis patients had a higher prevalence of thyroid dysfunction, including reduced serum total T3, total T4 and fT4, and increased serum TSH. Both hypothyroidism and nodular goiter were more frequent in dialysis patients than in controls. The frequency of goiter in dialysis patients incrementally increased with age from 40% in patients younger than 40 years to 43.4% and 58.5%, respectively, in patients 40–49 years and 50–59 years to 65.2% in patients older than 60 (16).

Subclinical hypothyroidism is also more common with increasing age (41) and is also highly prevalent in patients with renal impairment (14). Although elderly patients with subclinical hypothyroidism have no clinical features of thyroid disorder, they tend to have poorer outcomes (42,43).

Predisposing Factors of Frailty and Thyroid Hormones Abnormalities

Although there are no published data linking frailty directly to thyroid abnormalities in elderly patients with CKD, the increased prevalence of frailty in these patients and the poor outcome associated with this problem highlight the importance of investigating any potential reversible causes that may contribute to frailty. The available literature suggests an association between thyroid hormonal abnormalities first, and some of the symptoms (Fig. 1) associated with frailty. We will focus on some of these associations in the following section.

Increased Inflammatory and Procoagulant Factors

Walston et al. showed that frailty in the elderly was associated with increased inflammatory and procoagulant markers and that this increase was independent of the disease status (44). High IL-6 levels in older adults are associated with disability and impaired mobility (45). The InChianti study showed that high levels of IL-6 and C-reactive protein (CRP) were associated with poor physical activity, decreased muscle strength, and central obesity in adults older than 65 years (46). Similar results were found in elderly patients with CKD, where kidney disease was independently associated with elevations in inflammatory and procoagulant biomarkers (47). Similarly, a pilot study conducted by Swidler et al. (48) on 26 elderly CKD patients demonstrated a high prevalence of frailty in association with elevated inflammatory markers.

Several investigators have studied the association of disturbed thyroid hormone levels and inflammatory

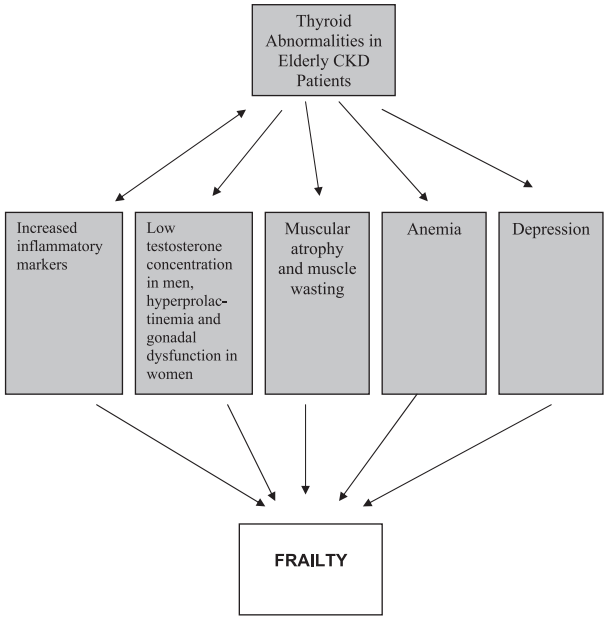

FIG. 1. Association between thyroid abnormalities and frailty in elderly patients with CKD.

markers in nondialysis CKD patients. Inflammation was associated with low Free T3 (fT3) serum levels in CKD patients (49). Markers for oxidative stress in undialyzed CKD patients are associated with altered thyroid status (50). Zoccali et al. (51) showed that intercurrent acute inflammatory processes correlated with diminished plasma fT3 in a group of 17 patients with CKD not on dialysis. They noted lower circulating fT3 levels at the zenith of inflammation than after its resolution.

FT3 was also strongly and inversely associated with inflammatory markers in a study of 200 patients with ESRD on HD; plasma fT3 was also lower in the HD patients compared to healthy controls (50).

These findings were confirmed in another study of the relationship between thyroid hormones and markers of endothelial damage as well as markers of inflammation and other homeostatic parameters in 96 ESRD patients on HD (52). In this study, thyroid dysfunction in uremic patients was independently associated with endothelial damage and inflammatory status (52). Furthermore, in a cohort of PD patients, inflammatory markers (IL6, albumin, CRP) were independently correlated with fT3 levels (42). Plasma fT3 levels were low in those PD patients with elevated IL6, CRP, and low albumin (42). Even in a cohort of euthyroid stage 5 CKD patients, low total T3 levels were associated with increase in IL6, hs-CRP, and VCAM1 inflammatory markers (53), and predicted all cause mortality.

Whether thyroid hormonal changes were a cause or effect of the inflammatory status remains to be further elucidated. Regardless of the "chicken or the egg dilemma," subjects on dialysis with low fT3 levels have higher levels of inflammatory markers and a worse all-cause mortality when compared to those with higher fT3 levels (42,49,51). One rationale suggested to explain the interactions between thyroid hormone abnormalities and the presence of increased inflammatory markers is

that proinflammatory cytokines may inhibit T3 production or increase tissue turnover (54–58). A proposed mechanistic rationale for this effect is that cytokine induced competition for limited amounts of coactivators, decreases hepatic type I iodothyronine 5-deiodinase expression, resulting in decrease T3 production (59). This is relevant because persistent inflammation and wasting are common among CKD patients and probably contribute to cardiovascular diseases and hence mortality (60,61).

All these studies confirm that disturbed thyroid hormone levels in patients with CKD/ESRD are associated with increased inflammatory markers, one of the hallmarks of frailty. Whether the thyroid hormonal level abnormalities play a direct role in the CKD-associated frailty by its association with the increased inflammatory markers remains to be proven.

Hormonal Changes

Both aging and CKD are associated with several changes in hormonal levels and activities. These changes may contribute to the pathophysiology of frailty in elderly patients with CKD (62). A role for growth hormone has been suggested in the pathogenesis of frailty in elderly CKD patients (63). The decrease in testosterone hormone levels with aging and with CKD (64) may decrease muscle mass and strength, as well as impair function in older patients (65). Primary hypothyroidism is associated with low testosterone concentration in men, and replacing the thyroid hormone improves the free and total testosterone concentrations (66). In women, hypothyroidism is also associated with gonadal dysfunction mediated primarily by hyperprolactinemia (66). There is also a disruption in the hypothalamic–pituitary–gonadal axis in patients with CKD leading to low testosterone levels. The exact mechanism is still unknown, but the lack of appropriate cyclic GnRH and cyclic LH hormone releases causes low testosterone levels in men with CKD and ovarian cyclic disruption in women with CKD (67,68).

Hypothyroidism seems to correlate strongly with hypotestosteronism. This is an important relationship because the latter has been implicated in frailty in elderly patients (69,70).

Malnutrition and Sarcopenia

Inadequate food intake is a common finding in elderly persons and more so in ESRD patients. Alterations in taste, smell, and mental status, often found in patients with CKD, can contribute to malnutrition. This age-related reduction in food intake, accelerated further in CKD, can lead to further weight loss complicated by an increased loss of muscle mass and strength causing sarcopenia (71). Advanced sarcopenia, associated with malnutrition, is synonymous with physical frailty and is estimated to affect 30% of people older than 60 years and may affect $>50\%$ of those older than 80 years (72). The published data from the NHANES database have shown that $>60\%$ of community dwelling elderly adults with GFR < 60 ml/min/1.73 m^2 have moderate-to-severe sarcopenia (73). Malnutrition, inflammation, comorbid diseases (diabetes, cardiovascular diseases, infections), and endocrine disorders (vitamin D deficiency, hyper-parathyroidism, growth hormone deficiency) have all been implicated as causes of sarcopenia in CKD patients (74).

Similarly, thyroid abnormalities in elderly patients with CKD are associated with sarcopenia. Both hypo- and hyperthyroidism in elderly patients with CKD are also associated with alterations in muscle strength and functional decline (65). The muscular atrophy and muscle wasting have been documented in overt primary hypothyroid patients by biopsy and electromyogram (75,76). Muscle energy metabolism (substrate utilization and exercise tolerance) is impaired even in subclinical hypothyroidism (77). Thyroid hormonal changes can also contribute to sarcopenia through the thyroid's effects on testosterone. Hypotestosteronism is associated with hypothyroidism in the elderly (65). Low testosterone levels in the elderly have been implicated in sarcopenia (78) and testosterone supplementation in males has been proven to increase muscle mass (79). Hence, hypothyroidism could be a cause of muscle wasting and sarcopenia in elderly CKD patients either directly or indirectly via hypotestosteronism.

Anemia

Anemia is highly prevalent in elderly persons (80) and in patients with CKD (81). Based on the NHANES III study, 34% of all anemia noted in the elderly are secondary to folate, vitamin B12, and iron deficiency (82). Another 32% of the anemia is due to chronic diseases including CKD (82). Most of the iron deficiency anemia in the elderly is due to gastrointestinal or nutritional deficiencies (82). Iron deficiency plays a role in thyroid hormone production by decreasing the activity of heme-dependent thyroid peroxidase (83). Iron deficiency anemia causes lower oxygen transport and thyroid hypoxia leading to impaired thyroid metabolism (83).

Hypothyroidism is associated with different types of anemia. Several investigators have shown that hypothyroidism may contribute to epoietin resistance in chronic HD patients (84–86). The uncomplicated anemia secondary to hypothyroidism in children and adolescents with hypothyroidism (87), but not in adults and elderly (88), responded to thyroid replacement therapy alone. Hypothyroidism is also one of the causes of macrocytic anemia in the elderly (89–91).

Anemia is associated with frailty and mobility dysfunction, and has been associated with mobility dysfunction, physical limitation, and reduced exercise capacity (92,93). The Women's Health and Aging Studies I and II identified anemia as a risk factor for frailty (94). Thus, we can postulate that thyroid abnormalities through its association with anemia may contribute to the frailty in elderly patient with CKD.

Depression

Depression occurs in 20–30% of patients with CKD (95,96). It correlates with both hospitalization and

mortality rates (97), and has been associated with frailty (98). The association between hypothyroidism and depression is well documented (99,100). Symptoms of depression are present in almost half of hypothyroidism patients (101). Hypothyroidism decreases the threshold for depression (102). Thyroid hormone may decrease norepinephrine and serotonin secretion in the brain, thus potentially causing depression (103).

Clinical depression is associated with subclinical hypothyroidism; its treatment has been used to complement antidepressants (104,105). Because hypothyroidism can produce signs and symptoms of depression and can coexist as a second illness in depressed patients, patients with early hypothyroidism may be candidates for thyroid replacement therapy. Clinical examination and measurement of triiodothyronine resin uptake, thyroxine and baseline TSH levels, and TSH response to TRH are necessary to identify candidates for thyroid replacement among cases diagnosed by descriptive criteria as having either major or minor depression, particularly those that are atypical or treatment resistant (106).

Summary

In summary, elderly patients with CKD face many challenges, among them is the frailty syndrome. With what appears to be a pandemic of CKD in the aging population, research to identify new and reversible frailty risk factors in this population is crucial. Identifying these abnormalities may play a role in improving survival and quality of life in these patients. Hormonal abnormalities in elderly with CKD, especially thyroid hormonal problems, are relatively common and can have deleterious effects. All types of thyroid diseases are encountered in the elderly (107). Many of the thyroid hormone changes are associated with symptoms of frailty in elderly patients with CKD.

To our knowledge, there are no direct trials that evaluated the effects of thyroid replacement on frailty in elderly patients with CKD. Although no solid conclusion could be drawn from these associations between thyroid hormonal changes and frailty, these associations make sufficient grounds to warrant initiating studies evaluating the effects of treating the thyroid abnormalities on frailty symptoms.

Further research is needed to address whether routine screening and monitoring of thyroid function are beneficial and cost effective to these elderly patients with CKD/ESRD, and whether thyroid hormone replacement, especially in patients with subclinical hypothyroidism, is helpful.

References

1. United Nations (UN) Report: Commission on Population and Development Forty-Second Session, 30 March–3 April 2009. Programme implementation and future programme of work of the Secretariat in the field of population World demographic trends. Available at http://www.un.org/esa/population/cpd/cpd2009/comm2009.htm, accessed April 1, 2010
2. U.S. Census Bureau, Current Population Reports, P20-546. Available at www.census.gov, accessed April 1, 2010
3. U.S. Census Bureau, "2008 National Population Projections," released August 2008. Available at http://www.census.gov/population/www/projections/2008projections.html, accessed April 1, 2010
4. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, Eggers P, Van Lente F, Levey AS: Prevalence of CKD in the United States. *JAMA* 298:2038–2047, 2007
5. Hallan SI, Coresh J, Astor BC, Åsberg A, Powe NR, Romundstad S, Hallan HA, Lydersen S, Holmen J: International comparison of the relationship of chronic kidney disease prevalence and ESRD risk. *J Am Soc Nephrol* 17:2275–2284, 2006
6. Hsu C-Y, Vittinghoff E, Lin F, Shlipak M: The incidence of end-stage renal disease is increasing faster than the prevalence of chronic renal insufficiency. *Ann Intern Med* 141:95–101, 2004
7. Fried LP, Tangen CM, Walston J, Newman AB, Hirsch C, Gottdiener J, Seeman T, Tracy R, Kop WJ, Burke G, McBurnie MA: Cardiovascular Health Study Collaborative Research Group: frailty in older adults: evidence for a phenotype. *J Gerontol Med Sci* 56A:M146–M156, 2001
8. Shlipak MG, Stehman-Breen C, Fried LF, Song X, Siscovick D, Fried LP, Psaty BM, Newman AB: The presence of frailty in elderly persons with chronic renal insufficiency. *Am J Kid Dis* 43:861–867, 2004
9. Johansen KL, Chertow GM: Significance of frailty among dialysis patients. *J Am Soc Nephrol* 18:2960–2967, 2007
10. Woods NF, LaCroix AZ, Gray SL, Aragaki A, Cochrane BB, Brunner RL, Masaki K, Murray A, Newman AB: Women's Health Initiative. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. *J Am Geriatr Soc* 53:1321–1330, 2005
11. Walston J, Hadley EC, Ferrucci L, Guralnik JM, Newman AB, Studenski SA, Ershler WB, Harris T, Fried LP: Research agenda for frailty in older adults: toward a better understanding of physiology and etiology: summary from the American Geriatrics Society/National Institute on Aging Research Conference on Frailty in Older Adults. *J Am Geriatr Soc* 54:991–1001, 2006
12. Ensrud KE, Ewing SK, Taylor BC: Frailty and risk of falls, fracture, and mortality in older women: the Study of Osteoporotic Fractures. *J Gerontol Med Sci* 62:744–751, 2007
13. Abdel-Rahman EM: Available at http://www.asn-online.org/education_and_meetings/geriatrics/Chapter34.pdf
14. Lo JC, Chertow GM, Go AS, Hsu CH: Increased prevalence of subclinical and clinical hypothyroidism in persons with chronic kidney disease. *Kidney Int* 67:1047–1052, 2005
15. Chonchol M, Lippi G, Salvagno G, Zoppini G, Muggeo M, Targher G: Prevalence of subclinical hypothyroidism in patients with chronic kidney disease. *Clin J Am Soc Nephrol* 3:1296–1300, 2008
16. Lin CC, Chen TW, Ng YY, Chou YH, Yang WC: Sol. Thyroid dysfunction and nodular goiter in hemodialysis and peritoneal dialysis patients. *Perit Dial Int* 18:516–521, 1998
17. Spitzweg C, Heufelder AE, Morris JC: Thyroid iodine transport. *Thyroid* 10: 321–330, 2000.
18. Van Herle AJ, Vassar Gt, Dumont JE: Control of thyroglobulin synthesis and secretion. *N Engl J Med* 301:239–249, 1979
19. Bartalen L: Recent achievements in studies on thyroid hormone-binding proteins. *Endocr Rev* 11:47–64, 1990
20. Campbell AJ, Reinken J, Allan BC: Thyroid disease in the elderly in the community. *Age Ageing* 10:47–52, 1981
21. Felicetta JV: Thyroid changes with aging: significance and management. *Geriatrics* 42:86–92, 1987
22. Levy EG: Thyroid disease in the elderly. *Med Clin North Am* 75:151–167, 1991
23. Mokshagunda S: Barzel US thyroid disease in the elderly. *JAGS* 41:1361–1369, 1993
24. Helfand M, Redfern CC: Screening for thyroid disease: an update. *Ann Int Med* 129:144–158, 1998
25. Robuschi G, Safran M, Braverman LE, Gnudi A, Roti E: Hypothyroidism in the elderly. *Endocr Rev* 8:142–153, 1987
26. Griffin JE: Review: hypothyroidism in the elderly. *Am J Med Sci* 299:334–345, 1990
27. Surks MI, Hollowell JG: Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. *J Clin Endocrinol Metab* 92:4575–4582, 2007
28. Kabadi UM: Thyroid disorders and the elderly. *Compr Ther* 15:53–65, 1989
29. Bagchi N, Brown TR, Parish RF: Thyroid dysfunction in adults over age 55 years: a study in an urban US community. *Arch Intern Med* 150:785–787, 1990
30. Federman DD: Hyperthyroidism in the geriatric population. *Hosp Pract* 26: 61–64, 69, 73–76, 1991
31. Nordyke RA, Gilbert FI, Harada ASM: Graves' disease influence of age on clinical findings. *Arch Intern Med* 148:626–631, 1988
32. Baran DT, Braverman LE: Thyroid hormones and bone mass. *J Clin Endocrinol Metab* 72:1182–1183, 1991

33. Woeber KA: Thyrotoxicosis and the heart. *N Engl J Med* 327:94–98, 1992
34. Katz A, Emmanouel DS, Lindheimer MD: Thyroid hormone and the kidney. *Nephron* 15:223–249, 1975
35. Algun E, Topal C, Ozturk M, Sekerolu MR, Durmus A: Urinary beta-2 microglobulin in renal dysfunction associated with hypothyroidism. *Int J clin Pract* 58:240–245, 2004
36. Kaptein EM: Thyroid hormone metabolism and thyroid diseases in chronic renal failure. *Endocr Rev* 17:45, 1996
37. Medri G, Carella C, Padmanabhan V, Rossi CM, Amato G, De Santo NG, Beitins IZ, Beck-Peccoz P: Pituitary glycoprotein hormones in chronic renal failure: evidence for an uncontrolled alpha-subunit release. *J Endocr Invest* 16:169–174, 1993
38. Santini F, Chiovato L, Bartalena L, Lapi P, Palla R, Panichi V, Velluzzi F, Grasso L, Chopra IJ, Martino E, Pinchera A: Study of serum 3,5,3'-triiodothyronine sulfate concentration in patients with systemic non-thyroidal illness. *Eur J endocr* 134:45–49, 1996
39. Lebkowska U, Malyszko J, Mysliwiec M: Thyroid function and morphology in kidney transplant recipients, hemodialyzed, and peritoneally dialyzed patients. *Transplant Proc* 35:2945–2948, 2003
40. Duntas L, Wolf CF, Keck FS, Rosenthal J: Thyrotropin-releasing hormone: pharmacokinetic and pharmacodynamic properties in chronic renal failure. *Clin Nephrol* 38:214, 1992
41. Wilson S, Parle JV, Roberts LM, Roalfe AK, Hobbs FDR, Clark P, Sheppard MC, Gammage MD, Pattison HM, Franklyn JA: Prevalence of subclinical thyroid dysfunction in the elderly in England—the Birmingham Elderly Thyroid Study (BETS): a community based cross-sectional survey. *J Clin Endocrinol Metab* 91:4809–4816, 2006
42. Enia G, Panuccio V, Cutrupi S, Pizzini P, Tripepi G, Mallamaci F, Zoccali C: Subclinical hypothyroidism is linked to micro-inflammation and predicts death in continuous ambulatory peritoneal dialysis. *Nephrol Dial Transplant* 22:538–544, 2007
43. Chen HS, Wu TEJ, Lu RA, Wang ML, Chen RL, Lin HD: Subclinical hypothyroidism is a risk factor for nephropathy and cardiovascular diseases in Type 2 diabetic patients. *Diabet Med* 24:1336–1344, 2007
44. Walston J, McBurnie MA, Newman A: Frailty and activation of the inflammation and coagulation systems with and without clinical comorbidities results from the cardiovascular health study. *Arch Intern Med* 162:2333–2341, 2002
45. Ferrucci L, Harris TB, Guralnik JM, Tracy RP, Corti MC, Cohen HJ, Penninx B, Pahor M, Wallace R, Havlik RJ: Serum IL-6 level and the development of disability in older persons. *J Am Geriatr Soc* 47:639–646, 1999
46. Cesari M, Penninx BW, Pahor M, Lauretani F, Corsi AM, Guralnik JM, Ferrucci L: Inflammatory markers and physical performance in older persons: the InCHIANTI study. *J Gerontol A Biol Sci Med Sci* 59:242–248, 2004
47. Shlipak MG, Fried LF, Crump C, Bleyer AJ, Manolio TA, Tracy RP, Furberg CD, Psaty BM: Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. *Circulation* 107:87–92, 2003
48. Swidler MA, Uribarri J, Siu A, Viassara H: Characterization of frailty in older adults with chronic kidney disease (CKD): correlations with biomarkers of inflammation. *J Am Soc Nephrol* 16:F-PO 813, 2005
49. Zoccali C, Mallamaci F, Tripepi G, Cutrupi S, Pizzini P: Low triiodothyronine and survival in end-stage renal disease. *Kidney Int* 70:523–528, 2006
50. Singh PA: Indian. *J Physiol Pharmacol* 50:279–284, 2006
51. Zoccali C, Tripepi G, Cutrupi S, Pizzini P, Mallamaci F: Low triiodothyronine: a new facet of inflammation in end-stage renal disease. *J Am Soc of Nephrol* 16:2789–2795, 2005
52. Malyszko J, Malyszko JS, Pawlak K, Mysliwiec M: Thyroid function, endothelium, and inflammation in hemodialyzed patients: possible relations? *J Renal Nutr* 17:30–37, 2007
53. Carrero JJ, Qureshi AR, Axelsson J, Yilmaz MI, Rehnmark S, Witt MR, Bárány P, Heimbürger O, Suliman ME, Alvestrand A, Lindholm B, Stenvinkel P: Clinical and biochemical implications of low thyroid hormone levels (total and free forms) in euthyroid patients with chronic kidney disease. *J Int Med* 262:690–701, 2007
54. Ozawa M, Sato K, Han DC, Kawakami M, Tsushima T, Shizume K: Effects of tumor necrosis factor-alpha/cachectin on thyroid hormone metabolism in mice. *Endocrinology* 123:1461–1467, 1988
55. Torpy DJ, Tsigos C, Lotsikas AJ, Defensor R, Chrousos GP, Papanicolaou DA: Acute and delayed effects of a single-dose injection of interleukin-6 on thyroid function in healthy humans. *Metabolism* 47:1289–1293, 1998
56. Bartalena L, Brogioni S, Grasso L, Velluzzi F, Martino E: Relationship of the increased serum interleukin-6 concentration to changes of thyroid function in nonthyroidal illness. *J Endocrinol Invest* 17:269–274, 1994
57. Van der Poll T, Romijn JA, Wiersinga WM, Sauerwein HP: Tumor necrosis factor: a putative mediator of the sick euthyroid syndrome in man. *J Clin Endocrinol Metab* 71:1567–1572, 1990
58. Boelen A, Platvoet-Ter Schiphorst MC, Wiersinga WM: Association between serum interleukin-6 and serum 3,5,3′-triiodothyronine in non-thyroidal illness. *J Clin Endocrinol Metab* 77:1695–1699, 1993
59. Yu J, Koenig RJ: Regulation of hepatocyte thyroxine 5¢-deiodinase by T3 and nuclear receptor coactivators as a model of the sick euthyroid syndrome. *J Biol Chem* 275:38296–38301, 2000
60. Stenvinkel P, Heimburger O, Paultre F, et al.: Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney Int* 55:1899–1911, 1999
61. Qureshi AR, Alvestrand A, Divino-Filho JC, et al.: Inflammation, malnutrition, and cardiac disease as predictors of mortality in hemodialysis patients. *J Am Soc Nephrol* 13(Suppl. 1):S28–S36, 2002
62. Gupta D, Bundschu HD: Testosterone and its binding in the plasma of male subjects with chronic renal failure. *Clin Chim Acta* 36:479–484, 1972
63. Abdel-Rahman EM: Holley: a review of the effects of growth hormone changes on symptoms of frailty in the elderly with chronic kidney disease. *Semin Dial* 22:532–538, 2009
64. Morley JE, Kim MJ, Haren MT: Frailty and hormones. *Rev Endo Met Dis* 6:101–108, 2005
65. Valenti G: Frailty as a dysruption of steroid "syncrinology" in elderly man. *Acta Biomed* 78(S1):222–224, 2007
66. Meikle AW: The interrelationships between thyroid dysfunction and hypogonadism in men and boys. *Thyroid* 14:S17–S25, 2004
67. Holley JL: The hypothalamic-pituitary axis in men and women with chronic kidney disease. *Adv Chronic Kidney Dis* 11:337–341, 2004
68. Anantharaman P, Schmidt RJ: Sexual function in chronic kidney disease. *Adv Chronic Kidney Dis* 14:119–125, 2007
69. Cappola AR, Xue QL, Fried LP: Multiple hormonal deficiencies in anabolic hormones are found in frail older women: the Women's Health and Aging Studies. *J Gerontol A Biol Sci Med Sci* 64:243–248, 2009
70. Cawthon PM, Ensrud KE, Laughlin GA, Cauley JA, Dam TT, Barrett-Connor E, Fink HA, Hoffman AR, Lau E, Lane NE, Stefanick ML, Cummings SR, Orwoll ES: Sex hormones and frailty in older men: the osteoporotic fractures in men (MrOS) study. *J Clin Endocrinol Metab* 94:3806–3815, 2009
71. Bales CW, Ritchie CS: Sarcopenia, weight loss, and nutritional frailty in the elderly. *Annu Rev Nutr* 22:309–323, 2002
72. Baumgartner R, Koehler K, Gallagher D, Romero L, Heymsfield SB, Ross RR, Garry FJ, Lindeman RDl: Epidemiology of sarcopenia among the elderly in New Mexico. *Am J Epidemiol* 147:755–763, 1998
73. Foley RN, Wang C, Ishani A, Collins AJ, Murray AM: Kidney function and sarcopenia in the United States general population: NHANES III. *Am J Nephrol* 27:279–286, 2007
74. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, Franch H, Guarnieri G, Ikizler TA, Kayser G, Lindholm B, Massy Z, Mitch W, Pineda E, Stenvinkel P, Trevinho-Becerra A, Wanner C: A proposed nomenclature and diagnostic criteria for protein–energy wasting in acute and chronic kidney disease. *Kidney Int* 73:391–398, 2008
75. Khaleeli AA, Gohil K, McPhail G, Round JM, Edwards RH: Muscle morphology and metabolism in hypothyroid myopathy: effect of treatment. *J Clin Pathol* 36:519–526, 1983
76. Taylor DJ, Rajagopalan B, Radda GK: Cellular energetics in hypothyroid muscle. *Eur J Clin Invest* 22:358–365, 1992
77. Monzani F, Caraccio N, Siciliano G, Manca L, Murri L, Ferrannini E: Clinical and biochemical features of muscle dysfunction in subclinical hypothyroidism. *J Clin Endocrinol Metab* 82:3315–3318, 1997
78. Baumgartner RN, Waters DL, Gallagher D, Morley JE, Garry PJ: Predictors of skeletal muscle mass in elderly men and women. *Mech Ageing Dev* 107:123–136, 1999
79. Wittert GA, Chapman IM, Haren MT, Mackintosh S, Coates P, Morley JE: Oral testosterone supplementation increases muscle and decreases fat mass in healthy elderly males with low-normal gonadal status. *J Gerontol Med Sci* 58A:618–625, 2003
80. Balducci L: Epidemiology of anemia in the elderly: information on diagnostic evaluation. *J Am Geriatr Soc* 51(3 Suppl.):S2–S9, 2003
81. McClellan W, Aronoff SL, Bolton WK, Hood S, Lorber DL, Tang KL, Tse TF, Wasserman B, Leiserowitz M: The prevalence of anemia in patients with chronic kidney disease. *Curr Med Res Opin* 20:1501–1510, 2004
82. Andres E, Federici L, Serraj K, Kalthenbach G: Update of nutrient-deficiency anemia in elderly patients. *Eur J Intern Med* 19:488–493, 2008
83. Zimmermann MB, Kohrle J: The impact of iron and selenium deficiencies on iodine and thyroid metabolism: biochemistry and relevance to public health. *Thyroid* 12:867–878, 2002
84. Tuam M, Guery B, Goupy C, Menoyo V, Drueke T: Hypothyroidism and resistance to human recombinant erythropoietin. *Nephrol Dial Transplant* 19:1020–1021, 2004
85. Dilek M, Akpolat T, Cengiz K: Hypothyroidism as a cause of resistance to erythropoietin. *Nephron* 92:248, 2002

86. Sungur C, Erbas T, Akpolat T: Resistance to human recombinant erythropoiten in hypothyroidism. *Acta Haematol* 88:162, 1992
87. Chu JY, Monteleone JA, Peden VH, Graviss ER, Vernava AM: Anemia in children and adolescents with hypothyroidism. *Clin Pediatr* 20:696–699, 1981
88. Christ-Crain M, Meier C, Huber P, Zulewski H, Staub J, Müller B: Effect of restoration of euthyroidism on peripheral blood cells and erythropoietin in women with subclinical hypothyroidism. *Hormones* 2:237–242, 2003
89. Kaferle J, Strzoda CE: Evaluation of macrocytosis. *Am Fam Physician* 79:203–208, 2009
90. Oh RC, Holt SN: How do you evaluate macrocytosis without anemia? *J Fam Psychol* 57:548–550, 2008
91. Mahmoud MY, Lugon M, Anderson CC: Unexplained macrocytosis in elderly patients. *Age Ageing* 25:310–312, 1996
92. Chaves PHM, Ashar B, Fried LP: Looking at the relationship between hemoglobin concentration and prevalent mobility difficulty in older women: should the criteria currently used to define anemia in older women in the elderly be evaluated? *J Am Geriatr Soc* 50:1257–1264, 2002
93. Odden MC, Whooley MA, Shlipak MG: Association of chronic kidney disease and anemia with physical capacity: the Heart and Soul Study. *J Am Soc Nephrol* 15:2908–2915, 2004
94. Chaves PH, Semba RD, Leng SX, Woodman RC, Ferrucci L, Guralnik JM, Fried LP: Impact of anemia and cardiovascular disease on frailty status of community dwelling older women: the Women's Health and Aging Studies I and II. *J Gerontol A Biol Sci Med Sci* 60:729–735, 2005
95. Hedayati SS, Jiang W, O'Connor CM, Kuchibhatla M, Krishnan KR, Cuffe MS, Blazing MA, Szczech LAl: The association between depression and chronic kidney disease and mortality among patients hospitalized with congestive heart failure. *Am J Kidney Dis* 44:207–215, 2004
96. Cohen S, Norris L, Acquaviva K, Peterson R, Kimmel Pl: Screening, diagnosis, and treatment of depression in patients with end-stage renal disease. *Clin J Am Soc Nephrol* 2:1332–1342, 2007
97. Lopes AA, Albert JM, Young EW, Satayathum S, Pisoni RL, Andreucci VE, Mapes DL, Mason NA, Fukuhara S, Wikstrom B, Saito A, Port FK: Depression as a predictor of mortality and hospitalization among hemodialysis patients in the United States and Europe in Dialysis Outcomes and Practice Patterns Study (DOPPS). *Kidney Int* 66:2047–2053, 2004
98. Andrew MK, Rockwood K: Psychiatric illness in relation to frailty in community-dwelling elderly people without dementia: a report from the Canadian Study of Health and Aging. *Can J Aging* 26:33–38, 2007
99. Marangell LB: Current issues: women and bipolar disorder. *Dialogues Clin Neurosci* 10:229–238, 2008
100. Guimaraes JM, deSouza LC, Baima J, Sichieri R: Depression symptoms and hypothyroidism in a population-based study of middle-aged Brazilian women. *J Affect Disord* 117:120–123, 2009
101. Boswell EB, Anfinson TH, Nemeroff CB: Depression associated with endocrine disorders. In: MM Robertson, CLE Katona (eds). *Depression and Physical Illness*. Chichester, UK: Wiley, 1997:256–292.
102. Iga J, Taniguchi T, Ohmori T: Mood swing from severe depression to mania following acute alteration of thyroid status. *Gen Hosp Psychiatry* 27:451–453, 2005
103. Whybrow PC, Prange AJ: A hypothesis of thyroid-catecholamine-receptor interaction. Its relevance to effective illness. *Arch Gen Psychiatry* 38:106–113, 1981
104. Haggerty JJ, Stern RA, Mason GA, Beckwith J, Morey CE, Prange AJ: Subclinical hypothyroidism: a modifiable risk factor for depression? *Am J Psychiatry* 150:508–510, 1993
105. Alessi C, Cassel C: Medical evaluation and common medical problems of the geriatric psychiatry patient. In: J Sadavoy (ed.). *Comprehensive Textbook of Geriatric Psychiatry*, 3rd edn. New York: WW Norton and Co., 2004:281–313
106. Gold MS, Pottash AL, Extein I: Hypothyroidism and depression. Evidence from complete thyroid function evaluation. *JAMA* 245:1919–1922, 1981
107. Chiovato L, Mariotti S, Pinchera A: Thyroid diseases in the elderly: Balliere's. *Clin Endocr Metab* 11:251–270, 1997