

Hormone Replacement Therapy in the Geriatric Patient: Current State of the Evidence and Questions for the Future— Estrogen, Progesterone, Testosterone, and Thyroid Hormone Augmentation in Geriatric Clinical Practice: Part 2*

* Thyroid section

Holtorf, K and Schwartz, E

KEYWORDS

- Thyroid hormone • T₃ • T₄ • TSH • Hypothyroidism
- Reverse T3 • Pituitary dysfunction

THYROID

Hypothyroidism is a common disorder characterized by inadequate amounts of thyroid hormones available to meet the need for thyroid at the cellular level. Typical symptoms of hypothyroidism include fatigue, weight gain/obesity, depression, cold extremities, thin/friable nails, muscle aches, headaches, decreased libido, low basal body temperature (consistently below 98.6°F), weakness, cold intolerance, loss of temporal eyebrow hair, water retention, and dry skin.

The incidence of thyroid dysfunction with its attendant cellular thyroid deficiency increases significantly with age.^{63–66} Because many of the symptoms attributable to subclinical hypothyroidism are often seen with normal aging, significant cellular hypothyroidism often goes undetected and subsequently untreated.

The authors have nothing to disclose.

© Holtorf Medical Group, Torrance, CA, USA

Clin Geriatr Med 27 (2011) 561–575

doi:10.1016/j.cger.2011.07.004

geriatric.theclinics.com

0749-0690/11/\$ – see front matter © 2011 Elsevier Inc. All rights reserved.

Historically, elevated thyroid-stimulating hormone (TSH) with normal T4 and T3 levels was considered compensated hypothyroidism and thus euthyroid in need of no treatment. Studies have demonstrated that, despite the normal T3 and T4 levels, subclinical hypothyroidism is often associated with significant symptoms and an increased risk of morbidity and mortality. Compensated hypothyroidism and subclinical hypothyroidism are becoming misnomers, because they present clinically significant signs and symptoms of hypothyroidism that do benefit from correct treatment.⁶⁷ The symptoms studied and directly connected to hypothyroidism include neuromuscular dysfunction,⁶⁸ depression,^{69,70} memory loss and cognitive impairment,^{66,71} high cholesterol levels,⁷² deteriorating general function,⁶⁵ skeletal muscle abnormalities,⁷³ decreased exercise tolerance and myocardial dysfunction.^{74–77} Significant improvement in symptoms occurs when thyroid hormone supplementation is instituted (note increased use of T3 in addition to T4).^{78–80} In aging patients, low thyroid mimics normal aging and other conditions as noted.^{81–93}

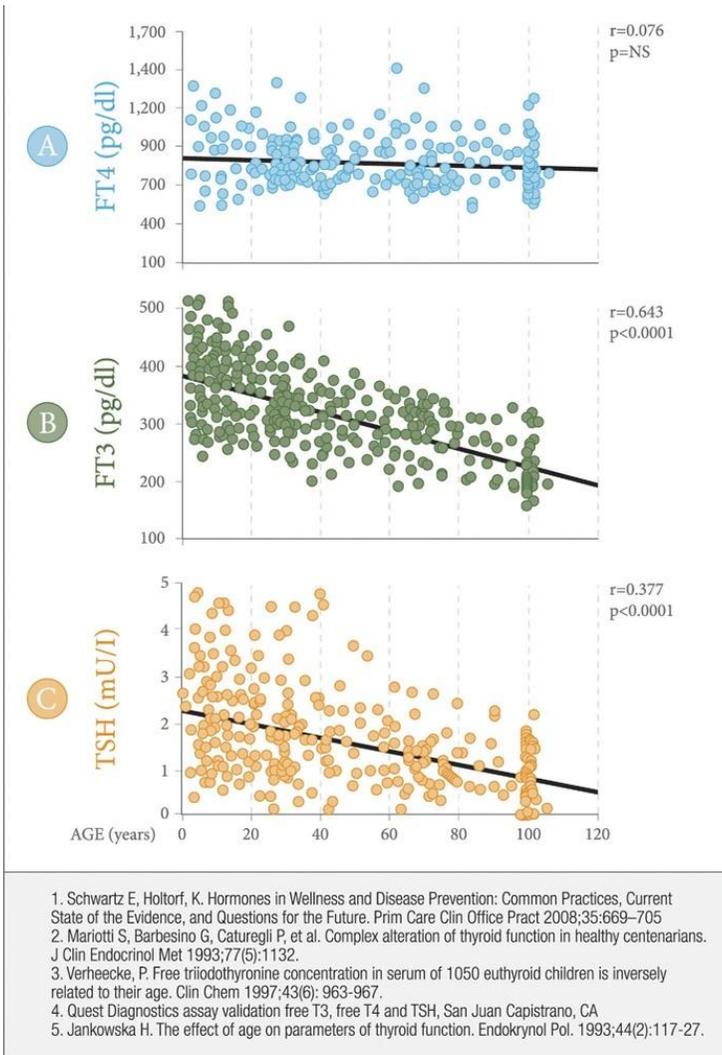
Diagnosis

TSH, a pituitary hormone whose function is to stimulate thyroid hormone production by the thyroid gland, is considered the only diagnostic test for hypothyroidism and the most sensitive marker of peripheral tissue availability of thyroid hormones. We have been trained to implicitly assume that TSH levels within the normal range indicate a euthyroid condition necessitating no further testing or clinical substantiation for the condition. To date, in most clinical practices in the United States, hypothyroidism is diagnosed solely when the TSH level is consistently above the upper limit of normal of 4.0 to 5.0 ng/dL. Unfortunately, this assumption no longer holds true when we delve into the domain of thyroid function in the aging population. With significant physiologic stress, illness, or inflammation there is demonstrable suppression of TSH, making the TSH test unreliable because it stays within normal range failing to reflect true thyroid status.^{82,94} Under these conditions, tissue T3 levels are diminished owing to a reduction in uptake of T4, leading to decreasing T4 to T3 conversion.^{82,83,95} Consequently, serum measurements reflect increased serum T4 levels and reduced TSH levels despite the absence of sufficient thyroid hormone in the peripheral tissues.

As a result, when relying on serum tests only, clinicians do not treat patients presenting with this thyroid picture assuming they are euthyroid (normal T3, low T4, and normal TSH). Unfortunately, this situation limits our understanding of the physiologic changes occurring at the cellular level leaving a gaping hole and missing the opportunity to help the patients' condition.^{83,84}

Aging and chronic illness also affect the hypothalamic–pituitary–thyroid–cellular axis. Both states tend to present with decreased TSH, decreased conversion of T4 to T3 in the cell, and increased reverse T3 levels.^{84,85} In these cases, serum reverse T3 levels may be a useful indicator of low tissue T3 levels because diminished cellular uptake of T4, diminished T4 to T3 conversion and diminished cellular T3 levels correlate inversely with serum reverse T3 levels.⁸⁵

Another finding in the aging patient is a reduction in TSH response to thyrotropin-releasing hormone from the pituitary, resulting in depressed levels of TSH. This suppression is similar to the TSH suppression found in severely ill patients with documented nonthyroidal illness (**Fig. 1**).^{94,96}



©2009 Kent Holtorf, M.D. and the National Academy of Hypothyroidism

Fig. 1. Age dependent variations in mean serum levels of Free T4 (A), Free T3 (B) and TSH (C) in healthy individuals—a combined analysis of the literature. Demonstrates that TSH is not a reliable marker of active thyroid (T3) levels (low T3 levels are associated with decreased, not increased, TSH levels). (*Courtesy of Kent Holtorf, MD and the National Academy of Hypothyroidism.*)

TSH failure to respond to thyrotropin-releasing hormone stimulation in the elderly further contributes to confusing information gained from standard thyroid testing in this population. Increased incidence of systemic illness and multiple medications in the elderly also directly affect thyroid function, further reducing the accuracy of the standard thyroid tests (T4 and TSH) as markers of true thyroid status.

In aging patients who present with symptoms consistent with hypothyroidism but have a normal TSH and T4 level, a T3/rT3 ratio may help gain more insight of tissue thyroid status. Optimal tissue levels are associated with a free T3/rT3 ratio greater than 1.8. (free T3 is reported in picograms per deciliter and reverse T3 in picograms per deciliter).⁸¹⁻⁹³

Although there are limitations in all type of testing for this age group, obtaining free triiodothyronine, reverse triiodothyronine, and triiodothyronine/reverse triiodothyronine ratios may be helpful to provide a somewhat accurate evaluation of tissue thyroid status and may predict favorable responders to thyroid supplementation.

Treatment

Thyroid replacement is not reported as beneficial during acute stress. When the stress is chronic or age-related treatment with T3 (liothyronine [Cytomel; Jones Pharma,

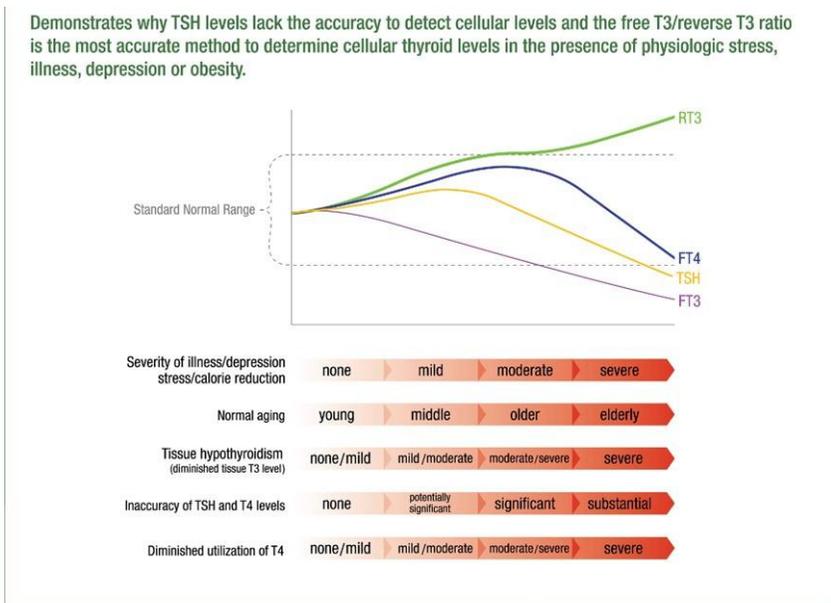


Fig. 2. Associated serum thyroid levels with progressively decreasing tissue thyroid levels due to stress, illness, depression, calorie reduction or aging (Why standard blood tests lack sensitivity to detect low thyroid in the presence of such conditions). (Courtesy of Kent Holtorf, MD and the National Academy of Hypothyroidism.)

Bristol, TN, USA]) containing preparations as opposed to T4 only preparations (levothyroxine [Synthroid, Abbott, Abbott Park, IL, USA]) has been proven to be of significant benefit. Serum testing demonstrating improvement demonstrate reduced free T3/reverse T3 ratio, but clinical improvement is striking (**Fig. 2**).^{81–93,97–99}

Many symptomatic patients with low tissue thyroid levels (as defined by a free T3/reverse T3 ratio of 1.8 and symptoms of hypothyroidism) with normal TSH and T4 levels may benefit from T3 thyroid replacement, often with significant improvement in fatigue, depression,^{100,101} weight gain and obesity,¹⁰² heart failure,⁹⁰ fibromyalgia,^{103,104} cholesterol levels,^{72,105} and numerous other chronic conditions.

In conclusion, the data reviewed herein have shown hormone therapies to improve some conditions associated with aging. Additionally, some of the long-held fears of significant side effects associated with hormone supplementation may be overstated, especially when providing patients with individualized care and optimal monitoring. We encourage clinicians to consider such interventions based on the evidence presented. More long-term studies are needed to further quantify and substantiate the risks and benefits associated with the use of such therapies.

REFERENCES

1. Brown-Séquard CE. The effects produced on man by subcutaneous injection of a liquid obtained from the testicles of animals. *Lancet* 1889;137:105–7.
2. Dickinson P, Zinneman HH, Swaim WR, et al. Effects of testosterone treatment on plasma proteins and amino acids in men. *J Clin Endocrinol Metab* 1969;29:837–41.
3. Sorva R, Kuusi T, Taskinen MR, et al. Testosterone substitution increases the activity of lipoprotein lipase and hepatic lipase in hypogonadal males. *Atherosclerosis* 1988;69:191–7.
4. Kasperk CH, Wergedal JE, Farley JR, et al. Androgens directly stimulate proliferation of bone cells in vitro. *Endocrinology* 1989;124:1576–8.
5. Gardner FH, Nathan DG, Piomelli S, et al. The erythrocythaemic effects of androgens. *Br J Haematol* 1968;14:611–5.
6. Feldman HA, Longcope C, Derby CA, et al. Age trends in the level of serum testosterone and other hormones in middle-aged men: longitudinal results from the Massachusetts Male Aging Study. *J Clin Endocrinol Metab* 2002;87:589–98.
7. Mulligan T, Frick M, Zuraw Q, et al. Prevalence of hypogonadism in males aged at least 45 years: the HIM study. *Int J Clin Pract* 2006;60:762–9.
8. Winters J. Current status of testosterone replacement therapy in men. *Arch Fam Med* 1999;8:257–63.
9. Kaufman JM, Vermeulen A. The decline of androgen levels in elderly men and its clinical and therapeutic implications. *Endocr Rev* 2005;26:833–76.
10. Ding EL, Song Y, Malik VS, Liu S. Sex differences of endogenous sex hormones and risk of type 2 diabetes: a systematic review and meta-analysis. *JAMA* 2006;295:1288–99.
11. Selvin E, Feinleib M, Zhang L, et al. Androgens and diabetes in men: results from the third National Health and Nutrition Examination Survey (NHANES III). *Diabetes Care* 2007;30:234–8.
12. Stellato RK, Feldman HA, Hamdy O, et al. Testosterone, sex hormone-binding globulin, and the development of type 2 diabetes in middle-aged men: prospective results from the Massachusetts Male Aging Study. *Diabetes Care* 2000;23:490–4.
13. Laaksonen DE, Niskanen L, Punnonen K, et al. Testosterone and sex hormone binding globulin predict the metabolic syndrome and diabetes in middle-aged men. *Diabetes Care* 2004;27:1036–41.

14. Shores MM, Matsumoto AM, Sloan KL, et al. Low serum testosterone and mortality in male veterans. *Arch Intern Med* 2006;166:1660–5.
15. Khaw KT, Dowsett M, Folkard E, et al. Endogenous testosterone and mortality due to all causes, cardiovascular disease, and cancer in men: European prospective investigation into cancer in Norfolk (EPIC-Norfolk) Prospective Population Study. *Circulation* 2007;116:2694–701.
16. Wald M, Meacham RB, Ross LS, et al. Testosterone replacement therapy for older men. *J Androl* 2006;27:126–32.
17. Matsumoto AM. Hormonal therapy of male hypogonadism. *Endocrinol Metab Clin North Am* 1994;23:857–75.
18. Gruenewald DA, Matsumoto AM. Testosterone supplementation therapy for older men: potential benefits and risks. *J Am Geriatr Soc* 2003;51:101–15.
19. Blum J, Harris RH. Diagnosis and treatment of hypogonadism with emphasis on erectile dysfunction and osteoporosis. *Prim Care Case Reviews* 2003;6:97–109.
20. Basaria S, Dobs AS. Hypogonadism and androgen replacement therapy in elderly men. *Am J Med* 2001;110: 563–72.
21. Bhasin S, Bagatell CJ, Bremner WJ, et al. Issues in testosterone replacement in older men. *J Clin Endocrinol Metab* 1998;83:3435–48.
22. Carruthers M, Trinick TR, Wheeler MJ. The validity of androgen assays. *The Aging Male* 2007;10:165–72.
23. Wheeler MJ, Barnes SC. Measurement of testosterone in the diagnosis of hypogonadism in the ageing male. *Clin Endocrinol (Oxf)* 2008;69:515–25.
24. Lazarou R, Reyes-Vallejo L, Morgentaler A. Wide variability in laboratory reference values for serum testosterone. *J Sex Med* 2006;3:1085–9.
25. Morgentaler A. Commentary: guidelines for male testosterone therapy: a clinician's perspective. *J Clin Endocrinol Metab* 2007;92:416–7.
26. English KM, Steeds RP, Jones HT, et al. Low-dose transdermal testosterone therapy improves angina threshold in men with chronic stable angina: a randomized, double-blind placebo-controlled study. *Circulation* 2000;102:1906–11.
27. Rosano GM, Leonardo F, Pagnotta P, et al. Acute anti-ischemic effect of testosterone in men with coronary artery disease. *Circulation* 1999;99:1666–70.
28. Webb CM, Adamson DL, de Zeigler D, et al. Effect of acute testosterone on myocardial ischemia in men with coronary artery disease. *Am J Cardiol* 1999;83: 437–9.
29. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci* 2001;56:M146–56.
30. Conroy S. Defining frailty: the holy grail of geriatric medicine. *J Nutr Health Aging* 2009;13:389.
31. Kenny AM, Kleppinger A, Annis K, et al. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels, low bone mass, and physical frailty. *J Am Geriatr Soc* 2010;58:1134–43.
32. Srinivas-Shankar U, Roberts SA, Connolly MJ, et al. Effects of testosterone on muscle strength, physical function, body composition, and quality of life in intermediate-frail and frail elderly men: a randomized, double-blind, placebo-controlled study. *J Clin Endocrinol Metab* 2010;95:639–50.
33. Page ST, Amory JK, Bowman FD, et al. Exogenous testosterone (T) alone or with finasteride increases physical performance, grip strength, and lean body mass in older men with low serum T. *J Clin Endocrinol Metab* 2005;90:1502–10.
34. Snyder PJ, Peachey H, Hannoush P, et al. Effect of testosterone treatment on body composition and muscle strength in men over 65 years of age. *J Clin Endocrinol Metab* 1999;84:2647–53.

35. Clague JE, Wu FC, Horan MA. Difficulties in measuring the effect of testosterone replacement therapy on muscle function in older men. *Int J Androl* 1999;22:261–5.
36. Wittert GA, Chapman IM, Haren MT, et al. Oral testosterone supplementation increases muscle and decreases fat mass in healthy elderly males with low-normal gonadal status. *J Gerontol A Biol Sci Med Sci* 2003;58:618–625.
37. Brill KT, Weltman AL, Gentili A, et al. Single and combined effects of growth hormone and testosterone administration on measures of body composition, physical performance, mood, sexual function, bone turnover, and muscle gene expression in healthy older men. *J Clin Endocrinol Metab* 2002;87:5649–57.
38. Nair KS, Rizza RA, O'Brien P, et al. DHEA in elderly women and DHEA or testosterone in elderly men. *N Engl J Med* 2006;355:1647–59.
39. Basaria S, Coviello AD, Travison TG, et al. Adverse events associated with testosterone administration. *N Engl J Med* 2010;363:109–22.
40. Barrett-Conner E, Von Muhlen DG, Kritz-Silverstein D. Bioavailable testosterone and depressed mood in older men: the Rancho Bernardo Study. *J Clin Endocrinol Metab* 1999;84:573–7.
41. Zarrouf FA, Artz S, Griffith J, et al. Testosterone and depression: systematic review and meta-analysis. *J Psychiatr Pract* 2009;15:289–305.
42. Pope HG Jr, Amiaz R, Brennan BP, et al. Parallel-group placebo-controlled trial of testosterone gel in men with major depressive disorder displaying an incomplete response to standard antidepressant treatment. *J Clin Psychopharmacol* 2010;30:126–34.
43. Barrett-Connor E, Goodman-Gruen D, Patay B. Endogenous sex hormones and cognitive function in older men. *J Clin Endocrinol Metab* 1999;84:3681–5.
44. Cherrier MM, Asthana S, Plymate S, et al. Testosterone supplementation improves spatial and verbal memory in healthy older men. *Neurology* 2001;57:80–8.
45. Haren MT, Wittert GA, Chapman IM, et al. Effects of oral testosterone undecanoate on visuospatial cognition, mood and quality of life in elderly men with low-normal gonadal status. *Maturitas* 2005;50:124–33.
46. Emmelot-Vonk MH, Verhaar HJ, Nakhai Pour HR, et al. Effect of testosterone supplementation on functional mobility, cognition, and other parameters in older men: a randomized controlled trial. *JAMA* 2008;299:39–52.
47. Isidori AM, Giannetta E, Gianfrilli D, et al. Effects of testosterone on sexual function in men: results of a meta-analysis. *Clin Endocrinol (Oxf)* 2005;63:381–94.
48. Boloña ER, Uruga MV, Haddad RM, et al. Testosterone use in men with sexual dysfunction: a systematic review and meta-analysis of randomized placebo-controlled trials. *Mayo Clin Proc* 2007;82:20–8.
49. Emmelot-Vonk MH, Verhaar HJ, Nakhai-Pour HR, et al. Effect of testosterone supplementation on sexual functioning in aging men: a 6-month randomized controlled trial. *Int J Impot Res* 2009;21:129–38.
50. Frankle MA, Eichberg R, Zachariah SB. Anabolic androgenic steroids and a stroke in an athlete: case report. *Arch Phys Med Rehab* 1988;69:632–3.
51. McNutt RA, Ferenchick GS, Kirilin PC, et al. Acute myocardial infarction in a 22-year-old world class weight lifter using anabolic steroids. *Am J Cardiol* 1988;62:164.
52. Meikle AW, Arver S, Dobs AS, et al. Prostate size in hypogonadal men treated with a nonscrotal permeation-enhanced testosterone transdermal system. *Urology* 1997;49:191–6.
53. Behre HM, Bohmeyer J, Nieschlag E. Prostate volume in testosterone-treated and untreated hypogonadal men in comparison to age-matched normal controls. *Clin Endocrinol (Oxf)* 1994;40:341–9.

54. Cooper CS, Perry PJ, Sparks AE, et al. Effect of exogenous testosterone on prostate volume, serum and semen prostate specific antigen levels in healthy young men. *J Urol* 1998;159:441–3.
55. Huggins C, Stevens RE Jr, Hodges CV. Studies on prostatic cancer II: the effects of castration on advanced carcinoma of the prostate gland. *Arch Surg* 1941;43: 209–23.
56. Morgentaler A. Testosterone replacement therapy and prostate cancer. *Urol Clin North Am* 2007;34:555–63.
57. Stattin P, Lumme S, Tenkanen L, et al. High levels of circulating testosterone are not associated with increased prostate cancer risk: a pooled prospective study. *Int J Cancer* 2004;108:418–24.
58. Barrett-Connor E, Garland C, McPhillips JB, et al. A prospective, population-based study of androstenedione, estrogens, and prostatic cancer. *Cancer Res* 1990;50: 169–73.
59. Parsons JK, Carter HB, Platz EA, et al. Serum testosterone and the risk of prostate cancer: potential implications for testosterone therapy. *Cancer Epidemiol Biomark- ers Prev* 2005;14:2257–60.
60. Marks LS, Mazer NA, Mostaghel E, et al. Effect of testosterone replacement therapy on prostate tissue in men with late-onset hypogonadism: a randomized controlled trial. *JAMA* 2006;296:2351–61.
61. Bhasin S, Singh AB, Mac RP, et al. Managing the risks of prostate disease during testosterone replacement therapy in older men. *J Androl* 2003;24:299–311.
62. Liverman CT, Blazer DG. Testosterone and aging: clinical research directions. Institute of Medicine. Washington (DC): National Academies Press; 2004.
63. Canaris GJ, Manowitz NR, Mayor G, et al. The Colorado thyroid disease prevalence study. *Arch Intern Med* 2000;160:526–34.
64. Mariotti S, Barbesino G, Caturegli P, et al. Complex alterations of thyroid function in healthy centenarians. *J Clin Endocrinol Metab* 1993;77:1130–4.
65. Van den Beld AW, Visser TJ, Feelders RA, et al. Thyroid hormone concentrations, disease, physical function and mortality in elderly men. *J Clin Endocrinol Metab* 2005;90:6403–9.
66. Magri F, Fioravanti CM, Vignati G, et al. Thyroid function in old and very old healthy subjects. *J Endocrinol Invest* 2002;25:60–3.
67. McDermott MT, Ridgway C. Subclinical hypothyroidism is mild thyroid failure and should be treated. *J Clin Endocrinol Met* 2001;86:4585–90.
68. Monzani F, Caraccio N, Del Guerra P, et al. Neuromuscular symptoms and dysfunction in subclinical hypothyroid patients: beneficial effect of L-T4 replacement therapy. *Clin Endocrinol* 1999;51:237–42.
69. Joffe RT, Levitt AJ. Major depression and subclinical (grade 2) hypothyroidism. *Psychoneuroendocrinology* 1992;17:215–21.
70. Haggerty JJ Jr, Stern RA, Mason GA, et al. Subclinical hypothyroidism: a modifiable risk factor for depression? *Am J Psychiatry* 1993;150:508–10.
71. Baldini IM, Vita A, Maura MC, et al. 1997 Psychological and cognitive features in subclinical hypothyroidism. *Prog Neuropsychopharmacol Biol Psychiatry* 1997;21: 925–35.
72. Danese MD, Ladenson PW, Meinert CL, et al. Effect of thyroxine therapy on serum lipoproteins in patients with mild thyroid failure: a quantitative review of the literature. *J Clin Endocrinol Metab* 2000;85:2993–3001.
73. Monzani F, Caraccio N, Siciliano G, et al. Clinical and biochemical features of muscle dysfunction in subclinical hypothyroidism. *J Clin Endocrinol Metab* 1997;82:3315–8.
74. Forfar JC, Wathen CG, Todd WT, et al. Left ventricular performance in subclinical hypothyroidism. *QJM* 1985;57:857–65.

75. Foldes J, Istvanfy M, Halmagyi M, et al. Hypothyroidism and the heart. Examination of left ventricular function in subclinical hypothyroidism. *Acta Med Hung* 1987;44:337–47.
76. Kahaly GJ. Cardiovascular and atherogenic aspects of subclinical hypothyroidism. *Thyroid* 2000;10:665–79.
77. Walsh JP, Bremner AP, Bulsara MK, et al. Subclinical thyroid dysfunction as a risk factor for cardiovascular disease. *Arch Intern Med* 2005;165:2467–72.
78. Monzani F, Del Guerra P, Caraccio N, et al. Subclinical hypothyroidism: neurobehavioral features and beneficial effect of l-thyroxine treatment. *Clin Invest* 1993;71:367–71.
79. Ridgway EC, Cooper DS, Walker H, et al. Peripheral responses to thyroid hormone before and after L-thyroxine therapy in patients with subclinical hypothyroidism. *J Clin Endocrinol Metab* 1981;53:1238–42.
80. Nystrom E, Caidahl K, Fager G, et al. A double-blind cross-over 12-month study of L-thyroxine treatment of women with 'subclinical' hypothyroidism. *Clin Endocrinol* 1988;29:63–76.
81. Docter R, Krenning EP, de Jong M, et al. The sick euthyroid syndrome: changes in thyroid hormone serum parameters and hormone metabolism. *Clin Endocrinol (Oxf)* 1993;39:499–518.
82. Peeters RP, Wouters PJ, Kaptein E, et al. Reduced activation and increased inactivation of thyroid hormone in tissues of critically ill patients. *J Clin Endocrinol Metab* 2003;88:3202–11.
83. Iervasi G, Pinitore A, Landi P, et al. Low-T₃ syndrome a strong prognostic predictor of death in patients with heart disease. *Circulation* 2003;107:708–13.
84. Peeters RP, Wouters PJ, van Toor H, et al. Serum 3,3',5'-triiodothyronine (rT₃) and 3,5,3'-triiodothyronine/rT₃ are prognostic markers in critically ill patients and are associated with postmortem tissue deiodinase activities. *J Clin Endocrinol Metab* 2005;90:4559–65.
85. Chopra IJ, Solomon DH, Hepner GW, et al. Misleadingly low free thyroxine index and usefulness of reverse triiodothyronine measurement in nonthyroidal illnesses. *Ann Intern Med* 1979;90:905–12.
86. Carrero JJ, Qureshi AR, Axelsson J, et al. Clinical and biochemical implications of low thyroid hormone levels (total and free forms) in euthyroid patients with chronic kidney disease. *J Intern Med* 2007;262:690–701.
87. Zoccali C, Tripepi G, Cutrupi S, et al. Low triiodothyronine: a new facet of inflammation in end-stage renal disease. *J Am Soc Nephrol* 2005;16:2789–95.
88. Pingitore A, Landi P, Taddei MC, et al. Triiodothyronine levels for risk stratification of patients with chronic heart failure. *Am J Med* 2005;118:132–6.
89. Kozdag G, Ural D, Vural A, et al. Relation between free triiodothyronine/free thyroxine ratio, echocardiographic parameters and mortality in dilated cardiomyopathy. *Eur J Heart Fail* 2005;7:113–8.
90. Pingitore A, Galli E, Barison A, et al. Acute effects of triiodothyronine replacement therapy in patients with chronic heart failure and low T₃ syndrome: a randomized placebo-controlled study. *J Clin Endocrinol Met* 2008;93:1351–8.
91. Dulchavsky SA, Kennedy PR, Geller ER, et al. T₃ preserves respiratory function in sepsis. *J Trauma* 1991;31:753–9.
92. Meyer T, Husch M, van den Berg E, et al. Treatment of dopamine-dependent shock with triiodothyronine: preliminary results. *Deutsch Med Wochenschr* 1979;104:1711–4.
93. Hamilton MA, Stevenson LW, Fonarow GC, et al. Safety and hemodynamic effects of intravenous triiodothyronine in advanced congestive heart failure. *Am J Cardiol* 1998;81:443–7.

94. Van Coevorden A, Laurent E, Decoster C, et al. Decreased basal and stimulated thyrotropin secretion in healthy elderly men. *J Clin Endocrinol Metab* 1989;69:177–85.
95. Hermann J, Heinen E, Kroll HJ, et al. Thyroid function and thyroid hormone metabolism in elderly people low T3–syndrome in old age. *Klin Wochenschr* 1981;59:315–23.
96. Chakraborti S, Chakraborti T, Mandal M, et al. Hypothalamic–pituitary–thyroid axis status of humans during development of ageing process. *Clin Chim Acta* 1999;288:137–45.
97. Hesch RD, Husch M, Kodding R, et al. Treatment of dopamine-dependent shock with triiodothyronine. *Endocr Res Commun* 1981;8:299–301.
98. Klemperer JD, Klein IL, Ojamaa K, et al. Triiodothyronine therapy lowers the incidence of atrial fibrillation after cardiac operations. *Ann Thorac Surg* 1996;61:1323–9.
99. Smidt-Ott UM, Ascheim DD. Thyroid hormone and heart failure. *Curr Heart Fail Rep* 2006;3:114–9.
100. Abraham G, Milev R, Lawson JS. T3 augmentation of SSRI resistant depression. *J Affect Dis* 2006;91:211–5.
101. Posternak M, Novak S, Stern R, Hennessey J, Joffe R, et al. A pilot effectiveness study: placebo-controlled trial of adjunctive L-triiodothyronine (T3) used to accelerate and potentiate the antidepressant response. *Int J Neuropsychopharmacol* 2008;11:15–25.
102. Krotkiewski M, Holm G, Shono N. Small doses of triiodothyronine can change some risk factors associated with abdominal obesity. *Int J Obes* 1997;21:922–9.
103. Lowe J, Garrison R, Reichman A, Yellin J, et al. Effectiveness and safety of T3 (triiodothyronine) therapy for euthyroid fibromyalgia: a double-blind placebo-controlled response-driven crossover study. *Clinical Bulletin of Myofascial Therapy* 1997;2:31–58.
104. Yellin BA, Reichman AJ, Lowe JC, et al. The process of change during T3 treatment for euthyroid fibromyalgia: a double-blind placebo-controlled crossover study. In: *The Metabolic Treatment of Fibromyalgia*. Old Fort (NC): McDowell Publishing; 2000.
105. Tanis BC, Westendorp RGJ, Smelt AHM. Effect of thyroid substitution on hypercholesterolaemia in patients with subclinical hypothyroidism: a re-analysis of intervention studies. *Clin Endocrinol* 1996;44:643–9.

