Thyroid Function in Physiological Aging and in Centenarians: Possible Relationships With Some Nutritional Markers

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Changes in thyroid function are often described in elderly subjects; however, their pathophysiologic significance and the possible contributory role of both malnutrition and nonthyroidal illness are still debated. The aim of this cross-sectional study was to investigate thyroid function in relationship to some markers of the nutritional status in a group of healthy old subjects and in some centenarians living in nursing homes. Patients included 24 clinically healthy elderly women (age, 71 to 93 years), 24 clinically healthy centenarian women (age, 100 to 106 years), and 20 healthy young subjects (age, 22 to 33 years). Blood samples were drawn from each subject for the evaluation of thyroid-stimulating hormone (TSH), free triiodothyronine (FT_3), free thyroxine ($FT_{4)}$, reverseT_3 (rT3), autoantibodies against thyroglobulin (AbTg) and against thyroid peroxidase (AbTPO), and for the main humoral nutritional markers. TSH and thyroid hormones were assayed by fluoroimmunometric method; rT3 and thyroid autoantibodies by radioimmunoassay (RIA) and enzyme chemiluminescent immunometric assay, respectively. The mean values of TSH, FT_3 and FT_4 fell within the normal range in both groups. However, by comparison to old controls, in centenarian subjects, TSH levels were significantly lower, whereas rT_3 concentrations were slightly, but significantly, increased. Autoantibodies positivity was found in 4.16% of centenarians and in 10.4% and 13.6% of old and young controls. Thus, the incidence of thyroid autoantibodies was lower in centenarians than in old controls. Except for transferrin, lower than the normal range in centenarians, all of the other nutritional markers evaluated fell within the laboratory range of normality. Total cholesterol levels were significantly reduced in centenarians by comparison to old controls. Our results showed an age-related decline of the TSH levels and a significant increase of the rT_3 concentrations in centenarians by comparison to old controls. These findings may be related to an age-dependent reduction of the 5′-deiodinase activity rather than to important changes of nutritional markers.

DURING THE LAST 20 years, many studies have been performed to investigate the role of thyroid function in the aging process. This kind of interest arises particularly from 2 observations: first, the important role played by thyroid hormones in the homeostasis of organism[1] and, second, there are similarities between the signs and symptoms of hypothyroidism and the clinical features of healthy elderly subjects.[2]

The results of these studies, however, are rather discordant both for data concerning the morphologic changes of the thyroid gland[3,4,5-7] and for the results of thyroid hormones metabolism and action.[8,9] These discrepancies may be related to the exclusion in these studies of extreme senescence and to the difficulties in differentiating the true physiologic age-related changes from the drug- and disease-dependent modifications often present in elderly subjects. Furthermore, data interpretation may be limited by the contributory effect of malnutrition and of changes in eating habit. Indeed, the triiodothyronine (T_3) production and the metabolic clearance rate of reverse T_3 (rT_3) decrease in starvation[10] and, moreover, a low-carbohydrate intake may influence T_3 production and metabolism, probably affecting the activity of the hepatic type 1 deiodinase.[1]

An age-related increase of the levels of thyroid autoantibodies has been reported in several studies also in euthyroid subjects,[11-13] suggesting a relationship with aging itself. However, it has recently been suggested that the thyroid autoimmune phenomena in the elderly might be related more to the general status than to aging.[14]

Thus, the aim of our work was the study of thyroid secretion, thyroid autoantibodies, and anthropometrics and biochemical markers of nutrition in healthy old subjects, including a certain number of centenarians, to elucidate the role of age itself and of changes in body composition and nutritional status.

SUBJECTS AND METHODS

Three groups of women were studied: (1) 24 healthy centenarians (age, 100 to 106 years; mean age, 101.69 ± 0.38 SEM); (2) 24 healthy old women (age, 71 to 93 years; mean age, 84.75 ± 1.25 SEM); and (3) 20 healthy young subjects (age, 22 to 33 years; mean age, 27.84 ± 0.66 SEM).

All elderly women, including the centenarians, were free living or living in nursing homes; they were visited by 2 investigators who recorded personal history, number of drugs, smoking habit, blood pressure, heart rate, functional abilities (activity of daily living [ADL], or Barthel index when appropriate), and the cumulative illness rating scale for severity and comorbidity (CIRS). The presence of neoplastic, neurologic, and immunologic diseases were considered as exclusion criteria, as well as the presence of known thyroid diseases or the use of drugs affecting thyroid-stimulating hormone (TSH) or thyroid hormones secretion (ie, thyrostatic treatment, dopamine, and steroids). The most relevant diseases found in aged groups were osteoarthritis, osteoporosis, atherosclerosis, and, particularly in centenarians, visual impairments. The mean number of drugs was 2.1 ± 1.2.

The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethic Committee of the Department of Internal Medicine and Medical Therapy; written informed consent was also obtained from all subjects.

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The clinical evaluation of each subject included: height, weight, body mass index (BMI) = weight divided by the square of height in meters), waist (W) and hip (H) wrist, the waist-to-hip ratio (WHR), and the midarm circumference (MAC); and body composition, after an overnight fast, by a portable body impedance analyzer (STA-BIA Akern, Florence, Italy). With appropriate equations, it was possible to estimate fat mass (FM), fat-free mass (FFM), body cell mass (BCM), and the basal metabolic rate (BMR) using age, height, and weight as variables in addition to resistance.[15]

A blood sample was drawn in the morning after an overnight fast for the assay of serum TSH, free triiodothyronine (FT_3), free thyroxine (FT_4), rT3, autoantibodies against thyroglobulin (AbTG) and against thyroid peroxidase (AbTPO), and some nutritional markers such as hemoglobin, total lymphocyte count, transferrin, total protein, albumin, glycemia, total and high-density lipoprotein (HDL) cholesterol, tryglicerides, azotemia, creatinine, and uric acid.

Serum TSH and thyroid hormones were measured by fluoroimmunometric method (Delphia hTSH Ultra, EG&G Wallac, Italy: intra- and interassay coefficient of variation [CV] = 4.6% and 3.7%, respectively; Delphia FT_3, EG&G: intra- and interassay CV = 7.9% and 6.5%, respectively; Dephia FT_4, EG&G: intra- and interassay CV = 3.3% and 5.7%, respectively). The rT_3 and thyroid autoantibodies were assayed by radioimmunoassay (RIA) and enzyme chemiluminescent assay, respectively (rT_3, BIODATA SpA, Biochem ImmunoSystem, Milan, Italy: intra- and interassay CV= 6.4% and 7.5%; Anti-TG Ab, Immulite 2000; DPC, Los Angeles, CA: intra- and interassay CV = 3.8 % and 5.3%; Anti-TPO Ab, Immulite 2000; DPC: intra- and interassay CV = 5.7% and 5.5%) Humoral biologic and nutritional data were obtained by the conventional methods of the local laboratory.

A nonparametric statistical analysis was performed; data were compared using the Mann-Whitney *U* test, and the relationships between hormonal secretion and clinical data were calculated by the Spearman Rank order correlations. The threshold level of significance was $P < .05$.

RESULTS

Table 1 summarizes the main clinical, anthropometrics and impedenzometric features of old and young women.

The BMI values were significantly lower in centenarians than in healthy old subjects. On the contrary, significantly higher values of waist wrist and WHR were found in centenarians by comparison to young controls; furthermore, centenarians' WHR values were significantly higher than the ones of old women.

Table 1. Clinical and Impedenzometric Features of Young and Old Women (Mean ± SEM)

	Centenarians (N = 24)	Healthy Old Subjects (N = 24)	Young Controls (N = 20)
Age (yr)	1,016 ± 0.3	84.7 ± 1.2	27.8 ± 0.6
BMI (kg/m^2)	19.3 ± 0.6*	22.6 ± 0.8	19.9 ± 0.4
W (cm)	86.0 ± 2.2†	85.3 ± 1.9	68.7 ± 1.2
H (cm)	93.6 ± 2.5	97.5 ± 2.5	90.8 ± 1.3
WHR (cm)	0.92 ± 0.01†‡	0.87 ± 0.01	0.75 ± 0.01
FM%	23.8 ± 2.0*	30.1 ± 1.6	25.8 ± 0.8
FFM%	76.2 ± 5.23‡	69.8 ± 1.6	74.1 ± 0.8
BCM	11.9 ± 1.0*†	20.6 ± 4.4	20.0 ± 0.7
BMR	1,009 ± 65.3†‡	1,240 ± 48.4	1,389 ± 25.8

*$P < .01$ centenarians *v* old subjects.
†$P < .001$ centenarians *v* young controls.
‡$P < .001$ centenarians *v* old subjects.

Table 2. Biochemical Data of Old Women (Mean ± SEM)

	Centenarians (N = 24)	Healthy Old Subjects (N = 24)	Normal Range
Hemoglobin	12.4 ± 0.3	12.6 ± 0.3	12-17 g/dL
Total lymphocyte	1,731.2 ± 178.4	1,781.3 ± 172.1	1.5-3.0 × 10^9/L
Transferrin	169.5 ± 15.9	206.5 ± 15.8	230-430 mg/dL
Total protein	6.69 ± 0.1	6.72 ± 0.1	6.2-8.2 g/dL
Albumin	3.67 ± 0.1	3.78 ± 0.1	3.5-5.5 g/dL
Glycemia	86.21 ± 2.35	83.25 ± 2.12	60-110 mg/dL
Total cholesterol	172.7 ± 6.47*	205.5 ± 11.1	120-200 mg/dL
HDL cholesterol	48.0 ± 3.11	43.5 ± 2.39	30-75 mg/dL
Triglycerides	95.1 ± 5.06	114.8 ± 14.6	40-170 mg/dL
Azotemia	51.2 ± 4.45*	36.5 ± 1.73	10-50 mg/dL
Creatinine	1.00 ± 0.06	0.95 ± 0.05	0.8-1.5 mg/dL
Uric acid	5.14 ± 0.32	5.45 ± 0.41	2.4-6.5 mg/dL

*$P < .05$, centenarians *v* old controls.

A significant increase of the FFM (%) and a parallel reduction of the fat one occurred in centenarians by comparison to old controls, despite the reduction of the total cell mass and of the basal metabolic rate in the former when compared with the latter. Indeed, the ratio of BMR to BCM was progressively increased when going from young to old and centenarian women (70.1 ± 1.5, 73.3 ± 5.8, and 86.0 ± 5.7, respectively) The difference between centenarians and young controls reached statistical significance ($P < .01$).

Except for transferrin, of which levels were below the lower normal limit in centenarians, all of the other nutritional and hematologic parameters evaluated fell within the normal range. Total cholesterol serum levels were significantly lower in centenarians than in old controls (Table 2).

No abnormalities of the thyroid function were found among centenarian women and elderly subjects, whereas 1 of the 20 young controls had subclinical hyperthyroidism (normal FT_3 and FT_4 concentrations and suppressed TSH) and thus was excluded from the study.

The occurrence of AbTG and AbTPO positivity was clearly lower (4.16%) in centenarians than in old and in young controls (10.4% and 13.6%, respectively) even if the Chi square analysis and the Yates correction did not show statistically significant differences.

Figure 1 shows the TSH and thyroid hormones values in the 3 groups of subjects. Serum TSH concentration was not different in young and old controls, whereas it was significantly lower in centenarians than in healthy old subjects.

No significant differences in FT_4 and FT_3 concentrations were found among the 3 groups evaluated. However the FT_3/FT_4 ratio, a marker of the 5'-deiodination activity, was progressively lower when going from young subjects to aged people and, finally, to centenarians (Fig 2). Serum rT_3 was clearly higher in old subjects, particularly in centenarians, by comparison to young controls.

Table 3 shows the regression analysis summary. Positive correlations linked the MAC to TSH and FT_3 levels ($r = .320$, $P < .05$ and $r = .372$, $P < .01$, respectively).

Serum FT_4 and rT_3 were positively correlated with the WHR and negatively with the BCM and the BMR, suggesting the maintenance of the relationship between thyroid hormones and metabolic status.

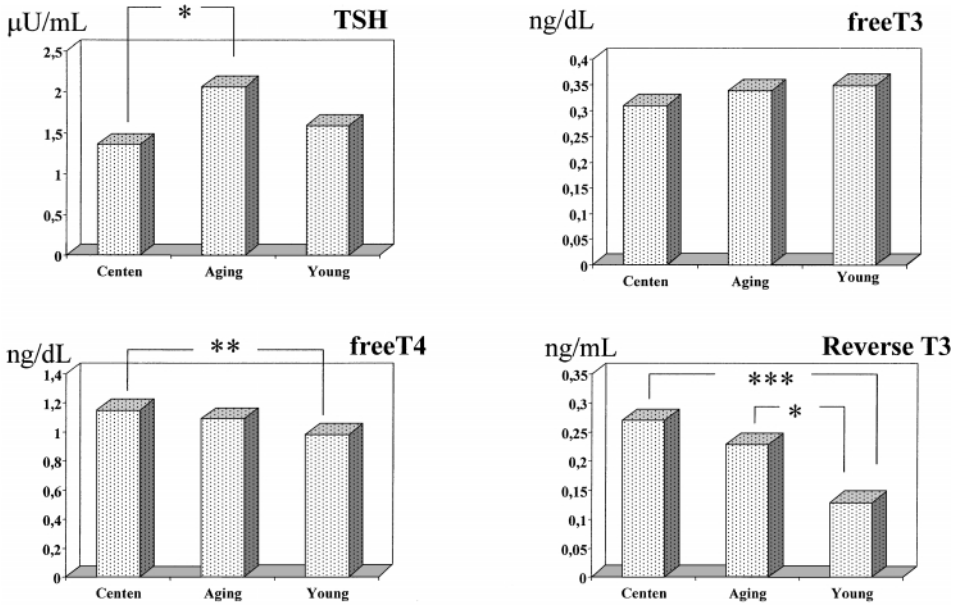

Fig 1. Serum TSH and thyroid hormone values in centenarian, healthy old, and young women (mean ± SEM). Mann-Whitney *U* test: * *P* < .05; ** *P* < .01; * *P* < .001.**

Serum FT_3 was significantly related to hemoglobin, total protein, albumin, and transferrin. On the contrary, serum rT_3 did not show any significant relationship with the biochemical parameters evaluated.

DISCUSSION

Despite the great interest in thyroid function in the aging process, many studies are limited to the 7th to 8th decade of life. Moreover, the results of these studies are often discordant, particularly for TSH secretion, which is reported as unchanged[16,17] or slightly increased in elderly subjects.[18,19] Also, the hypothalamic-pituitary-thyroid axis seems to change with aging, but the TSH response to TRH stimulation is described as normal,[20] increased,[21] or reduced without circadian modulation.[22]

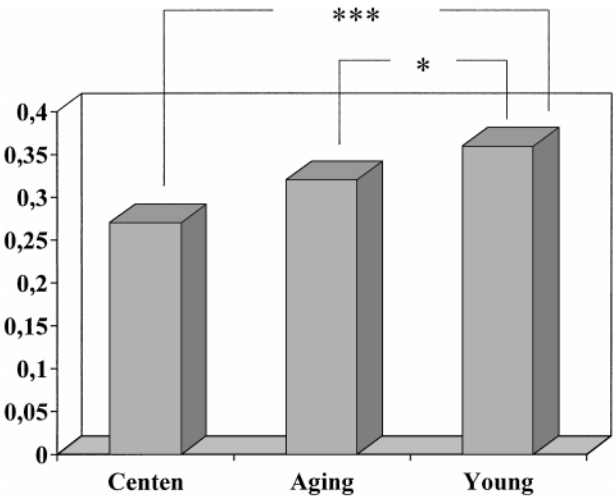

Fig 2. FT_3/FT_4 ratio in centenarian, old, and young women (mean ± SEM). Mann-Whitney *U* test: ** *P* < .01; * *P* < .001.**

Other confounding factors are health and nutritional status of the subjects studied, because they are potentially able to affect the thyroid function. Therefore, in this work, we evaluated the thyroid function and the nutritional pattern in 3 selected groups of healthy subjects, young, old, and very old.

The results of the anthropometrics and impedenzometric evaluations showed that centenarians were generally thinner than healthy old controls, but fat distribution was similar in the 2 groups of elderly subjects, confirming the age-related trend toward the central or intrabdominal localization of fat.[23] It is well known that in the young and adult population, increasing values of WHR, and in particular, of waist wrist[24] is significantly related to a progressive worsening of lipid pattern and of glucose-insulin metabolism. This finding seems to be not true in very elderly subjects, since our centenarians, when compared with old control subjects, had higher WHR values together with lower total cholesterol and higher HDL cholesterol levels.

Our findings are only partially in agreement with other data in the literature concerning aging and centenarians,[25] which found a lower WHR in centenarians than in aged subjects. Obviously, some limitations in the interpretation of these data must be taken into account, such as the difficulty in recruiting

Table 3. Linear Regression Analysis Summary

TSH *v* MAC	($r = .320$, $P < .01$)
FT_3 *v* MAC	($r = .372$, $P < .01$)
Hemoglobin	($r = .512$, $P < .001$)
Total protein	($r = .351$, $P < .01$)
Albumin	($r = .354$, $P < .01$)
FT_4 *v* WHR	($r = .303$, $P < .01$)
BCM	($r = -.469$, $P < .01$)
BMR	($r = -.328$, $P < .01$)
rT_3 *v* WHR	($r = .520$, $P < .001$)
BCM	($r = -.505$, $P < .001$)
BMR	($r = -.493$, $P < .001$)

a wide number of healthy or relatively healthy centenarians, the imbalance between the number of males and females, the postural changes, and the altered compressibility of subcutaneous tissue.

The percentage of FFM was similar in centenarians and in young controls, being in both groups higher than in old controls. Even in this case, some limitations must be considered: today, the available equations to convert electrical resistance and reactance in all the bioimpedance parameters are adjusted for height, weight, gender, and age, but for very elderly subjects, these equations are inaccurate. Within these important limits, our findings suggest that centenarians exhibited a "juvenile" type of body composition.

Few studies have evaluated body composition in healthy centenarians. In 1 study concerning healthy Italian centenarians, the absolute values of FFM were significantly lower in centenarians than in aged and adult subjects,[25] but after appropriate covariates, FFM resulted higher in centenarians than in aged controls.

Regarding the thyroid function, no abnormalities were found in aged subjects, in contrast to other studies reporting a prevalence of overt and subclinical hypothyroidism of 7% and 14% in the US and of 0.9% and 0.6% of aged women in Italy[26] and a prevalence of hyperthyroidism ranging from 0.5% to 2.3%.[27,28]

In hospitalized geriatric patients, positivity for thyroid autoantibodies frequently occurs, being related more to age than to nonthyroidal illness.[29] Previous studies reported an increased prevalence of antithyroid autoantibodies in hundreds of older subjects,[11,12] whereas our study showing a decreased prevalence, concerns only 48 women, half of them being centenarians. The apparent discrepancy may be explained by considering that first, the small number of subjects evaluated could underestimate the antibody positivity, and second, that the results of studies of elderly people are often confounded by their real health status, and finally, by the fact that centenarians are probably a highly selected group of subjects. Thus, selection criteria might strongly influence the results. Our findings show a low antiTG and anti-TPO positivity both in aged subjects and in centenarians, in agreement with other recent observations[14,30] and support the hypothesis that thyroid autoimmunity might be dependent on a peculiar genetic background[14] and on general healthy status.[31]

Only with the inclusion of centenarians, a slight, but significant, age-related decrease of TSH secretion was found in our study, probably due to an increased sensitivity of thyrotrophs to the negative feedback of thyroid hormones or to neuroendocrine changes of the hypothalamic-pituitary-thyroid axis.[32] The presence of goiter affects TSH concentration with time, and goiter is hard to assess in elderly patients. In our study, only a careful clinical evaluation had excluded the presence of goiter, since it seemed not ethically correct to perform a thyroid scintography in healthy free-living centenarians.

Mild and not significant FT_3 and FT_4 changes occurred among the 3 groups evaluated. However, when considering the FT_3/FT_4 ratio, a marker of 5' deiodination activity, a significant decrease of this parameter was evident in old subjects, and particularly, in centenarian women. The decline of 5' deiodinase activity may be age-dependent or linked to nonthyroidal illness, to a reduced stimulatory effect of TSH, or to both.[20,33-36] Also, the age-related increase of cytokines may have a pathogenetic role,[37] because an inhibitory modulation of tumor necrosis factor (TNF)-α, interleukin (IL)-1 and IL-6 has been described on the 5'-deiodinase activity.[38,39]

The clear increase of serum rT_3 in old subjects, and especially in centenarians, by comparison to young controls, confirms the hypothesis of a reduced 5'-deiodination activity, but raises the question if malnutrition or undernutrition are involved in the increase of rT_3 levels. In fact, caloric restriction reduces T_3 levels in experimental animals[40,41] and, furthermore, also in humans malnutrition may give rise to the well-known "low T_3 syndrome".[10]

Our centenarians were thinner than old subjects, but had clinical and biochemical markers of the nutritional status within the normal range. In elderly subjects, the MAC is a good index of somatic protein, while albumin, total protein, total cholesterol, and total lymphocyte count are strongly related to the increased risk of morbidity and mortality and are widely considered as nutritional markers.[42] Despite the normalcy of these parameters, the FT_3 levels were significantly linked to BMI, hemoglobin, total protein, albumin, transferring, and total lymphocyte count, suggesting that even subtle changes of the nutritional pattern may affect thyroid function.[43] However, the increase of rT_3 levels was significantly related to fat distribution, BCM, and BMR, but not to the biochemical markers of malnutrition.

Thus, an age-related decline of the 5'-deiodinase activity, independent of nonthyroidal illness and nutritional status, may be suggested.

In conclusion, the thyroid function seems to be preserved during physiologic aging for both quantitative and qualitative aspects. Only in centenarians, significant changes in rT_3 levels became apparent. A trend towards an age-related increase in anti-TG and anti-TPO autoantibodies was not evident in our study, suggesting the importance of the immune system in determining life span.

Finally, longitudinal studies will clarify if a low caloric intake and the maintenance of a juvenile body composition might effectively affect survival throughout changes of thyroid function.

REFERENCES

1. Müller MJ: Thyroid and ageing. Eur J Endocrinol 130:242-243, 1994

2. Robuschi G, Safran M, Braverman LE, et al: Hypothyroidism in the elderly. Endocr Rev 8:142-153, 1987

3. Morley JE: The aging endocrine system. Evaluation and treatment of age-related disorders. Postgrad Med 73:107-120, 1983

4. Berghout A, Wiersinga WM, Smits N-J, et al: Determination of thyroid volume as measured by ultrasonography in healthy adults in a non-iodine deficient area. Clin Endocrinol (Oxf) 26:273-280, 1987

5. Felicetta JV: Thyroid changes with aging: Significance and management. Geriatrics 42:86-92, 1987

6. Hintze G, Windeler J, Baumert J, et al: Thyroid volume and goitre

prevalence in the elderly as determined by ultrasound and their relationships to laboratory indices. Acta Endocrinologica (Copenh) 124: 12-18, 1991

7. Kunikate JM, Pekary AE, Hershman JM: Aging and the hypothalamic-pituitary-thyroid axis, in Morley JE, Korenman SG (eds): Endocrinology and Metabolism in the Elderly. Boston, MA, Blackwell, 1992, pp 92-110

8. Gregerman RI, Gaffney GW, Shock NW: Thyroxine turnover in euthyroid man with special reference to changes with age. J Endocrinol Invest 41:2065-2074, 1962

9. Nishikawa M, Inada M, Naito K, et al: Age related changes of serum 3,3'-diiodothyronine, 3'-5'-diiodothyronine and 3-5-diiodothyronine concentrations in man. J Clin Endocrinol Metab 52:517-552, 1981

10. Danforth E, Burger AG: The impact of nutrition on thyroid hormone physiology and action. Annu Rev Nutr 9:201-227, 1989

11. Tomer Y, Shonfeld Y: Ageing and autoantibodies. Autoimmunity 1:141-149, 1988

12. Mariotti S, Sansoni P, Barbesino G, et al: Thyroid and other organ-specific autoantibodies in healthy centenarians. Lancet 339: 1506-1508, 1992

13. Potacka-Plazak K, Pituch-Noworolska A, Kocemba J: Prevalence of autoantibodies in the very elderly: Association with symptoms of ischemic heart disease. Aging Clin Exp Res 7:218-220, 1995

14. Mariotti S, Barbesino G, Chiovato L, et al: Circulating thyroid autoantibodies in a sample of Italian octo-nonagenarians: Relationship to age, sex, disability, and lipid profile. Aging Clin Exp Res 11:362-366, 1999

15. Kushner RF: Bioelectrical impedance analysis: A review of principles and applications. J Am Coll Nutr11:199-209, 1992

16. Snyder PJ, Utiger RD: Response to thyrotropin releasing hormone (TRH) in normal man. J Clin Endocrinol Metab 34:380-385, 1972

17. Felicetta JV: The thyroid and aging, in Sowers JR, Felicetta JV (eds): The Endocrinology of Aging. New York, NY, Raven, 1988, pp 15-39

18. Erfurth EM, Norden NE, Hedner P, et al: Normal reference interval for thyrotropin response to thyroliberin: Dependence on age, sex, free thyronine index and basal concentration of thyrotropin. Clin Chem 30:196-199, 1984

19. Harman SM, Wehmann RE, Blackman MR: Pituitary-thyroid hormone economy in healthy aging men: Basal indices of thyroid function and thyrotropin responses to constant infusions of thyrotropin releasing hormone. J Clin Endocrinol Metab 58:320-326, 1984

20. Herrmann J, Rusche HJ, Kroll HJ, et al: Free triiodothyronine (T3) and thyroxine (T4) serum levels in old age. Horm Metab Res6: 239-240, 1974

21. Ohara H, Kobayashi M, Shiraishi M, et al: Thyroid function of the aged as viewed from the pituitary-thyroid system. Endocrinology 21:377-386, 1974

22. Chakraborti S, Chakraborti T, Mandal M, et al: Hypothalamic-pituitary-thyroid axis status of humans during development of ageing process. Clin Chim Acta 288:137-145, 1999

23. Jakicic JM, Donelly JE, Jaward AF, et al: Association between blood, lipid and different measures of body fat distribution: Effect of BMI and age. Int J Obes 17:131-137, 1993

24. Turcato E, Bosello O, Francesco VD, et al: Waist circumference and abdominal sagittal diameters as surrogates of body fat distribution in the elderly: Their relation with cardiovascular risk factors. Int J Obes Relat Metab Disord 24:1005-1010, 2000

25. Paolisso G, Gambarella A, Balbi V, et al: Body composition, body fat distribution, and resting metabolic rate in healthy centenarians. Am J Clin Nutr 62:746-750, 1995

26. Meyer B, Gionet M, Abeau C, et al: Iodine intake probably affects the incidence of hypothyroidism and Hashimoto's thyroiditis in elderly women. J Nucl Med 27:909A, 1986 (abstr)

27. Bagchi N, Brown TB, Parish RF: Thyroid dysfunction in adults over age 55 years. A study in an urban US community. Arch Intern Med 150:785-778, 1990

28. Mokshagundam S, Barzel US: Thyroid disease in the elderly. J Am Geriatr Soc 41:1361-1368, 1993

29. Szabolcs I, Wolfdieter B, Horster FA: Thyroid autoantibodies in hospitalized chronic geriatric patients: Prevalence, effects of age, nonthyroidal clinical state, and thyroid function. J Am Geriatr Soc 43:670-673, 1995

30. Mariotti S, Barbesino G, Caturegli P, et al: Complex alteration of thyroid function in healthy centenarians. J Clin Endocrinol Metab 77:1130-1134, 1993

31. Ligthart GJ, Corberand JX, Geertzen HC, et al: Necessity of the assessment of health status in human immunogerontological studies: Evaluation of the SENIUER Protocol. Mech Ageing Dev 55:89-105, 1990

32. Mariotti S, Franceschi C, Cossarizza A, et al: The aging thyroid. Endocr Rev 16:686-715, 1995

33. Bermudez F, Surks MI, Oppeheimer JH: High incidence of decreased serum triiodothyronine concentration in patients with nonthyroidal disease. J Clin Endocrinol Metab 41:27-39, 1975

34. Olsen T, Laurberg P, Weeke J: Low serum triiodothyronine and high serum reverse triiodothyronine in old age: An effect of disease not age. J Clin Endocrinol Metab 47:1111-1116, 1978

35. Kabadi UM: Thyroid disorders and the elderly. Compr Ther 15:53-65, 1989

36. Greenspan SL, Sparrow D, Rowe JW: Dopaminergic regulation of gonadotropin and thyrotropin hormone secretion is altered with age. Horm Res 36:41-46,1991

37. Fagiolo U, Cossarizza A, Santacaterina S, et al: Increased cytokine production by peripheral blood mononuclear cells from healthy elderly people. Ann N Y Acad Sci 663:490-493, 1992

38. Pekary AE, Berg L, Santini F, et al: Cytokines modulate type I iodothyronine deiodinase mRNA levels and enzyme activity in FRTL-5 rat thyroid cells. Mol Cell Endocrinol 101:R31-R35, 1994

39. Tang KT, Braverman LE, De Vito WJ: Tumor necrosis factor-α and interferon-γ modulate gene expression of type I 5'-deiodinase, thyroid peroxidase and thyroglobulin in FRTL-5 rat thyroid cells. Endocrinology 136:881-888, 1995

40. Herlihy JT, Stacy C, Bertrand HA: Long-term food restriction depresses serum thyroid hormone concentrations in the rat. Mech Ageing Dev 53:9-16, 1990

41. Stokkan KA, Reiter RJ, Vaughan MK, et al: Endocrine and metabolic effects of life-long food restriction in rats. Acta Endocrinol (Copenh) 125:93-100, 1991

42. Sullivan DH, Walls RC: Impact of nutritional status on morbidity in a population of geriatric rehabilitation patients. J Am Geriatr Soc 42:471-477, 1994

43. Goichot B, Schlienger JL, Grunenberger F, et al: Thyroid hormone status and nutrient intake in the free-living elderly. Interest of reverse triiodothyronine assessment. Eur J Endocrinol 130:244-252,1994