J Med Biochem 2010; 29 (4) DOI: 10.2478/v10011-010-0037-4

UDK 577.1 : 61 **ISSN 1452-8258**

J Med Biochem 29: 231–236, 2010

Review article
Pregledni članak

DIAGNOSIS OF THYROID DISEASE: PRINCIPLES AND PROBLEMS

DIJAGNOSTIKA TIROIDNE BOLESTI: PRINCIPI I PROBLEMI

Miloš Žarković

School of Medicine, University of Belgrade, Belgrade, Serbia
Clinic of Endocrinology, Clinical Center of Serbia, Belgrade, Serbia

Summary: Conceptually, thyroid disorders can be classified into four groups, namely: 1. disorders of thyroid morphology, 2. disorders of thyroid function, 3. presence of thyroid autoimmunity, and 4. diagnosis and follow-up of thyroid carcinoma. Of course, these groups are non-exclusive, and often there is overlap between the groups. Ultrasound exam is a standard for the diagnosis of the disorders of thyroid morphology. To diagnose disorders of thyroid function TSH and thyroid hormones should be measured. Presence of thyroid autoimmunity is confirmed by measuring antibodies against thyroid-specific antigens. Thyroid peroxidase (TPO), thyroglobulin (Tg) and TSH receptors antibodies are used in the diagnosis, follow-up and prognosis of autoimmune thyroid disorders. The measurement of serum thyroglobulin has no role in the diagnosis of thyroid cancer, but it is used in the follow-up of patients treated for differentiated thyroid carcinoma of the follicular epithelium. Medullary thyroid cancer (MTC) produces calcitonin and carcinoembryonic antigen (CEA), but calcitonin is specific for MTC. In subjects with MTC, genetic testing should be done, and in positive cases family screening is necessary.

Keywords: autoantibodies, calcitonin, thyroglobulin, thyroid diseases, thyroid function tests, thyroid hormones

Kratak sadržaj: Konceptualno, poremećaji štitaste žlezde se mogu svrstati u četiri grupe: 1. poremećaji morfologije štitaste žlezde, 2. poremećaji tiroidne funkcije, 3. prisustvo tiroidne autoimunosti i 4. dijagnoza i praćenje karcinoma štitaste žlezde. Naravno, ove grupe se često preklapaju. Za dijagnostiku poremećaja morfologije štitaste žlezde najbitniji je ultrazvučni pregled. Za dijagnozu poremećaja tiroidne funkcije neophodno je određivanje TSH i tiroidnih hormona. Prisustvo tiroidne autoimunosti potvrđuje se merenjem antitela na tiroidno specifične antigene. Za dijagnozu, praćenje i prognozu autoimunih bolesti štitaste žlezde koriste se antitela na tiroidnu peroksidazu (TPO), tireoglobulin (TG) i antitela na TSH receptore. Određivanje tireoglobulina u serumu nema značaj u dijagnostici karcinoma štitne žlezde, ali se koristi u praćenju bolesnika lečenih od diferentovanog karcinoma tiroide. Medularni tiroidni karcinom (MTK) sekretuje kalcitonin i karcinoembrioni antigen (CEA), ali je kalcitonin specifičan za MTK. Kod obolelih od MTK neophodno je genetsko testiranje a u pozitivnim slučajevima potrebno je i gensko testiranje srodnika.

Ključne reči: autoantitela, kalcitonin, tireoglobulin, tiroidna bolest, testovi tiroidne funkcije, hormoni štitaste žlezde

Introduction

Conceptually, thyroid disorders can be classified into four groups. These groups are: 1. Disorders of the thyroid morphology, 2. Disorders of the thyroid function, 3. Presence of thyroid autoimmunity and 4. Diagnosis and follow-up of thyroid carcinoma. Of course, these groups are non-exclusive, and often there is overlap between the groups.

Address for correspondence:

Miloš Žarković
Clinic of Endocrinology
Dr Subotića 13, 11000 Belgrade
PAK 112113, Serbia
Fax: +381-11-3639-776
e-mail: mzarkov@eunet.rs

Disorders of thyroid morphology

Among the most common disorders in the human pathology are disorders of the thyroid morphology. The thyroid could be enlarged, presenting as goiter, or nodules could be present. A thyroid nodule is any focal lesion different from the normal gland, and can be a cyst, carcinoma, lobule of normal tissue or adenoma (1). Using palpation as the sole diagnostic method, the established thyroid nodule prevalence is 3% in the whole population, 6.4% in

females and 1.5% in males (2, 3). However, using the ultrasound thyroid nodules can be detected in about 60% of the population, what correlates well with the autopsy data of 50% prevalence (4, 5). About 5% of all thyroid nodules, regardless of the size, are malignant (6). Ultrasound can also be used in the diagnosis of different types of thyroiditis (7). Therefore, ultrasound exam is a standard for the diagnosis of disorders of the thyroid morphology. Thyroid scintigraphy is less used today, but it gives a functional morphology of the thyroid.

Disorders of thyroid function

Although disorders of the thyroid morphology are among the most common conditions in the human pathology, disorders of the thyroid function are among the most frequent reasons for the endocrine testing. Thyroid function is evaluated by measuring TSH and thyroid hormones.

Disorders of the thyroid function can be caused by diseases of the thyroid gland (primary thyroid disease) or diseases of the pituitary or hypothalamus (secondary thyroid disease). In addition, there are disorders caused by the TSH receptor mutations or by the resistance to thyroid hormone. Differential diagnosis of primary and secondary thyroid dysfunction depends on measuring both TSH and thyroid hormones, so they should both be measured at least once in every patient.

When a thyroid function disorder is caused by a primary thyroid disease, the TSH is a cornerstone of diagnosis. In the same patients, TSH is the single most important analyte in the assessment of the treatment effect. There are multiple reasons for this. First, TSH is a major regulator of the morphologic and functional states of the thyroid. Secondly, TSH is a measure of thyroid hormone influence on the brain and pituitary. Thirdly, there is a log linear relationship between thyroxine and TSH, meaning that small changes in thyroxine will cause large changes in TSH (8). Recent data suggest that the relationship between TSH and thyroxine might be even more complex (9). However, it takes 6–12 weeks for pituitary TSH secretion to re-equilibrate to the new thyroid hormone status, when the thyroid status is changed (10). Therefore, TSH is good for long-term monitoring, especially of hypothyroid patients, as it does not depend on the relation of TSH sampling and time of thyroxine treatment. However, during periods of unstable thyroid status, such as occurs in the early phase of treating hyper- or hypothyroidism or changing the thyroxine dose, the TSH concentration can be diagnostically misleading (10). TSH isoforms with different biologic activity can also be a diagnostic problem (11). In addition, interference from heterophilic antibodies can produce unexpected results (12). Nevertheless, recent research showed that majority of TSH assays have excellent quality of performance (13).

Some drugs cause TSH suppression. Most often used are glucocorticoids, dopamine agonists and somatostatin analogs. Metformin has also been reported to cause TSH suppression (14).

During the last few years, establishing the upper limit of the TSH reference range has been the subject of numerous discussions and considerable research (15–17). The key question is whether the upper limit should be reduced from about 4 mIU/L to 3 or 2.5 mIU/L, and if there is a need for race, age and gender specific reference ranges (17–19). These discussions are caused by the specific distribution of TSH values. In a reference population (one considered to be without thyroid disease), the TSH distribution is rightskewed. However, the reason for the right skew of the TSH distribution is a matter of controversy. Some authors suggest that occult thyroid dysfunction is the cause of increased TSH values, while others suppose that a mixture of several normal distributions, due to sex, age, genetics, causes the right-skewed distribution (16, 20). Therefore, interpretation of the TSH reference range will depend on the conceptual framework explaining reasons for the TSH distribution. Another confounding factor is the method used to measure TSH. The use of older analytical methods to measure TSH resulted in a lower upper limit of the TSH reference range as compared to contemporary ones (21, 22).

Another problem, related to the upper reference range of TSH, is a question of mild (subclinical) hypothyroidism. Subclinical (mild) hypothyroidism is defined as an increased serum TSH in the presence of a normal serum FT4 concentration. Please note that increased and normal refer to values above or within the population-based reference ranges of these hormones (23). Clinical symptoms are usually very vague or even absent, and are often not specific to hypothyroidism. However, we still do not have adequate studies to assess the benefit of treatment of these patients. Most experts are inclined to treat patients with subclinical hypothyroidism. However, all agree that fertile women with subclinical hypothyroidism must be treated, even before conception, and that they should be treated and carefully monitored throughout pregnancy (24).

For a long time total thyroid hormone measurements (TT4 and TT3) have been the cornerstone of thyroid dysfunction diagnosis. It should be noted that biological markers of tissue hypothyroidism (ankle reflex time, clinical severity score, total cholesterol and creatinine kinase) do not correlate with TSH, but have very good correlation with the free T4 (FT4) and free T3 (FT3) concentration (25). Interestingly, psychological well-being, measured using General Health Questionnaire-12 and Thyroid Symptom Questionnaire correlated well with the TSH and FT4 concentration, but not with the FT3 concentration (26).

Thyroxine in the circulation is approximately 99.97% bound to the plasma proteins (TBG 60–75%, TTR/TBPA 15–30%, albumin about 10%). In the circulation, 99.7% of triiodothyronine is protein-bound, primarily to TBG (12, 14). During the previous fifty years, different technologies were used to measure total thyroxine (TT4) in the circulation. However, despite changes in the methodology it has remained a remarkably robust determination, with minimal changes in reference values (11). Total hormone measurement should be proportional to that of free hormone in patients with similar binding protein concentrations. Unfortunately, many conditions in clinical practice are associated with binding protein changes. Additionally, some patients have abnormal thyroid hormone binding proteins such as thyroid alterations, so that total hormone measurement becomes unreliable. Therefore, free hormone measurements are more commonly used. Regrettably, separating the free hormone from the protein-bound is technically very demanding (equilibrium dialysis and ultrafiltration), and available only in reference laboratories (27, 28). In routine clinical practice FT4 and FT3 are not directly measured, but estimated using different methods. It should be noted that all current FT4 and FT3 estimate tests are to some extent binding-protein dependent. In fact, a recent study has shown that FT4 immunoassays correlate better with total than free T4 concentrations, although this conclusion has been disputed (29–32). Due to these considerations, there is a renewed interest in using TT4 measurements instead of FT4 estimates in pregnancy. Reference range is adjusted by a factor of 1.5 to compensate for the pregnancy induced TBG elevation (33–35).

Presence of thyroid autoimmunity

Tests for antibodies against thyroid-specific antigens, thyroid peroxidase (TPO), thyroglobulin (Tg) and TSH receptors are used in the diagnosis, follow-up and prognosis of autoimmune thyroid disorders.

TPO Ab is considered a marker of Hashimoto thyroiditis. Presence of TPOAb significantly increases the risk of developing hypothyroidism (Odds ratio of 6.1), while an isolated increase in TgAb does not confirm the risk of hypothyroidism (odds ratio of 0.6). If both TPOAb and TgAb are present, the risk of developing hypothyroidism is very high (Odds ratio of 34.7) (36). Whickham survey also showed the importance of TPOAb as a risk factor for the development of hypothyroidism. Interestingly, there was a sexual dimorphism, with males having higher risk compared to females. Odds ratio of developing hypothyroidism when TPOAb were present in females with normal TSH was eight. If both TPOAb and TSH were increased the odds ratio was 38 in females and 178 in males (37). TPOAb prevalence is about 10% in males older than 20 years. In adult females, TPOAb prevalence rises with age. The lowest prevalence is found in the age group from 20 to 29 years (12.6%) and the highest in persons over 80 (31.4%) (36).

However, serial measurements of the TPOAb concentration are not recommended. This is because the treatment addresses thyroid dysfunction and not the thyroid autoimmunity. On the other hand, it is important to determine TPOAb as a risk factor for developing thyroid dysfunction in patients receiving Amiodarone, Interferon-alpha, Interleukin-2 or Lithium therapies (11).

During pregnancy, the presence of TPOAb has been linked to reproductive complications such as miscarriage, infertility, IVF failure, fetal death, pre-eclampsia, pre-term delivery and post-partum thyroiditis and depression. However, it seems that the main cause of these complications is a mild hypothyroidism, and that thyroxine supplementation prevents complications (38). Recently, it was found that both subclinical hypothyroidism and the autoimmune thyroid disorder are independently associated with very early pregnancy loss (39). Therefore, determination of TPOAb should be considered in pregnant females, or in females planning pregnancy. However, there is still no formal recommendation with regard to this.

TgAb measurement is primarily used as an adjunctive test to the serum Tg measurement when monitoring patients with differentiated thyroid cancers (DTC). Current guidelines recommend that TgAb should be measured by a sensitive immunoassay method, prior to serum Tg determination (10, 40). Measurement of TgAb in patients with autoimmune thyroid disease is less useful (36).

The major antigen of Graves' disease is the TSH receptor. In Graves' disease TSH receptor antibodies (TRAb) bind to the TSH receptor, induce thyroid growth and cause an increased rate of thyroid hormone production and secretion. These antibodies are referred to as thyroid-stimulating antibodies. However, a receptor antibody can act as a TSH antagonist (thyroid-inhibiting or blocking antibodies). TRAbs are not detectable in the normal population by the use of currently available methods (41). To define whether the TRABs are stimulating or inhibitory, bioassay must be used. However, in clinical settings receptor-based assays are used. Receptor-based assays cannot differentiate between stimulating and inhibiting TRAbs, so the measured antibodies are sometimes referred to as thyroid-binding inhibitory immunoglobulins (TBII). Serial measurements of the TRAb concentration are useful, as it correlates with prognosis in Graves' disease. A TRAb concentration less than 1.5 IU/L after 12 months of treatment implies good prognosis, while a TRAb concentration over 5.1 IU/L after 12 months or 2.8 IU/L after 24 months of treatment indicates a severe course of disease (42).

Diagnosis and follow-up of thyroid carcinoma

The diagnosis of differentiated thyroid carcinoma of the follicular epithelium is based on the clinical exam, ultrasound and fine needle aspiration biopsy (FNAB) (43, 44). The measurement of serum thyroglobulin has no role in the diagnosis of thyroid cancer (40, 43, 45, 46). In subjects with the thyroid gland, thyroglobulin concentration correlates with the size, and not with the nature of thyroid pathology (47). Thyroglobulin concentration is also dependent on iodine intake (48). In patients treated for differentiated thyroid carcinoma by total thyroidectomy and ablative dose of radioactive iodine, thyroglobulin is a marker of tumor presence. Measuring thyroglobulin preoperatively has been suggested, as it provides information regarding the tumor's intrinsic ability to secrete Tg. This obviously influences the utility of using serial serum Tg measurements to serve as a tumor marker to detect cancer recurrence postoperatively (11). Blood for the thyroglobulin determination should be sampled either before or more than two weeks after FNAB (10). During the follow-up thyroglobulin should be determined after TSH stimulation using recombinant TSH or thyroxine withdrawal (43). The measurement of thyroid-specific mRNA in the blood may provide better markers in the future.

Medullary thyroid cancer (MTC) presents as part of an inherited disorder in about 20–25% of cases and in others as a sporadic tumor. MTC produces calcitonin and carcinoembryonic antigen (CEA), but calcitonin is specific for MTC. Tumor dedifferentiation is associated with a fall of CT and increasing CEA, and this is a bad sign (49). Diagnosis is based on the calcitonin measurement, and calcitonin measurement is recommended in all subjects with thyroid nodules (43). In subjects with MTC genetic testing should be done, and in positive cases family screening is necessary (50).

For the diagnosis of a thyroid disorder and the patient follow-up, it is essential to correlate the clinical findings, visualization data and laboratory results. Therefore, close collaboration between different medical profiles is necessary for the proper care of thyroid patients.

Conflict of interest statement

The author stated that there are no conflicts of interest regarding the publication of this article.

References

1. De Groot LJ, Pacini F. Thyroid Nodules. Available at: http://www.thyroidmanager.org/Chapter18/18-nodulesframe.htm. Accessed 28.06.2010.
2. Tunbridge WM, Evered DC, Hall R, et al. The spectrum of thyroid disease in a community: the Whickham survey. Clin Endocrinol (Oxf). 1977; 7 (6): 481–93.
3. Vander JB, Gaston EA, Dawber TR. The significance of nontoxic thyroid nodules. Final report of a 15-year study of the incidence of thyroid malignancy. Ann Intern Med 1968; 69 (3): 537–40.
4. Mortensen JD, Woolner LB, Bennett WA. Gross and microscopic findings in clinically normal thyroid glands. J Clin Endocrinol Metab 1955; 15 (10): 1270–80.
5. Tan GH, Gharib H. Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. Ann Intern Med 1997; 126 (3): 226–31.
6. Gharib H, Papini E. Thyroid Nodules: Clinical Importance, Assessment, and Treatment. Endocrinol Metab Clin N Am 2007; 36 (3): 707–35.
7. Blum M. Ultrasonography of the Thyroid. Available at: http://www.thyroidmanager.org/Chapter6c/chapter6c_frame.htm. Accessed 28.06.2010.
8. Larsen PR, Davies TF, Schlumberger MJ, Hay ID. Thyroid physiology and diagnostic evaluation of patients with thyroid disorders. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR, eds. Williams Textbook of Endocrinology. 11 ed. Philadelphia: Saunders Elsevier; 2008; 299–331.
9. Hoermann R, Eckl W, Hoermann C, Larisch R. Complex relationship between free thyroxine and TSH in the regulation of thyroid function. Eur J Endocrinol 2010; 162 (6): 1123–9.
10. Baloch Z, Carayon P, Conte-Devolx B, et al. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid 2003; 13 (1): 3–126.
11. Spencer CA. Thyroid function tests: Assay of Thyroid Hormones and Related Substances. Available at: http://www.thyroidmanager.org/Chapter6a/6a-frame.htm. Accessed 08.06.2010.
12. Ross HA, Menheere PP, Thomas CM, Mudde AH, Kouwenberg M, Wolffenbuttel BH. Interference from heterophilic antibodies in seven current TSH assays. Ann Clin Biochem 2008; 45 (Pt 6): 616.
13. Thienpont LM, Van Uytfanghe K, Beastall G, et al. Report of the IFCC Working Group for Standardization of Thyroid Function Tests; part 1: thyroid-stimulating hormone. Clin Chem 2010; 56 (6): 902–11.
14. Haugen BR. Drugs that suppress TSH or cause central hypothyroidism. Best Pract Res Clin Endocrinol Metab 2009; 23 (6): 793–800.
15. Surks MI, Goswami G, Daniels GH. The thyrotropin reference range should remain unchanged. J Clin Endocrinol Metab 2005; 90 (9): 5489–96.

16. Spencer CA, Hollowell JG, Kazarosyan M, Braverman LE. National Health and Nutrition Examination Survey III thyroid-stimulating hormone (TSH)-thyroperoxidase antibody relationships demonstrate that TSH upper reference limits may be skewed by occult thyroid dysfunction. J Clin Endocrinol Metab 2007; 92 (11): 4236–40.

17. Wartofsky L, Dickey RA. The evidence for a narrower thyrotropin reference range is compelling. J Clin Endocrinol Metab 2005; 90 (9): 5483–8.

18. Baskin HJ, Cobin RH, Duick DS, et al. American Association of Clinical Endocrinologists medical guidelines for clinical practice for the evaluation and treatment of hyperthyroidism and hypothyroidism. Endocr Pract 2002; 8 (6): 457–69.

19. Boucai L, Surks MI. Reference limits of serum TSH and free T4 are significantly influenced by race and age in an urban outpatient medical practice. Clin Endocrinol (Oxf) 2009; 70 (5): 788–93.

20. Surks MI, Boucai L. Age- and Race-Based Serum Thyrotropin Reference Limits. J Clin Endocrinol Metab 2010; 95: 496–502.

21. Kratzsch J, Fiedler GM, Leichtle A, et al. New reference intervals for thyrotropin and thyroid hormones based on National Academy of Clinical Biochemistry criteria and regular ultrasonography of the thyroid. Clin Chem 2005; 51 (8): 1480–6.

22. Hamilton TE, Davis S, Onstad L, Kopecky KJ. Thyrotropin levels in a population with no clinical, autoantibody, or ultrasonographic evidence of thyroid disease: implications for the diagnosis of subclinical hypothyroidism. J Clin Endocrinol Metab 2008; 93 (4): 1224–30.

23. Wiersinga WM. Adult Hypothyroidism. Available at: http://www.thyroidmanager.org/Chapter9/9-frame.htm. Accessed 19.06.2010.

24. Feldt-Rasmussen U. Is the treatment of subclinical hypothyroidism beneficial? Nat Clin Pract Endocrinol Metab 2009; 5 (2): 86–7.

25. Meier C, Trittibach P, Guglielmetti M, Staub JJ, Muller B. Serum thyroid stimulating hormone in assessment of severity of tissue hypothyroidism in patients with overt primary thyroid failure: cross sectional survey. BMJ 2003; 326 (7384): 311–12.

26. Saravanan P, Visser TJ, Dayan CM. Psychological well-being correlates with free thyroxine but not free 3,5,3'-triiodothyronine levels in patients on thyroid hormone replacement. J Clin Endocrinol Metab 2006; 91 (9): 3389–93.

27. Holm SS, Hansen SH, Faber J, Staun-Olsen P. Reference methods for the measurement of free thyroid hormones in blood: evaluation of potential reference methods for free thyroxine. Clin Biochem 2004; 37 (2): 85–93.

28. Stockigt JR. Free thyroid hormone measurement. A critical appraisal. Endocrinol Metab Clin North Am 2001; 30 (2): 265–89.

29. Fritz KS, Wilcox RB, Nelson JC. A direct free thyroxine (T4) immunoassay with the characteristics of a total T4 immunoassay. Clin Chem 2007; 53 (5): 911–15.

30. Midgley JE, Christofides ND. Point: legitimate and illegitimate tests of free-analyte assay function. Clin Chem 2009; 55 (3): 439–41.

31. Nelson JC, Wilcox RB, Pandian MR. Dependence of free thyroxine estimates obtained with equilibrium tracer dialysis on the concentration of thyroxine-binding globulin. Clin Chem 1992; 38 (7): 1294–300.

32. Wilcox RB, Nelson JC. Counterpoint: legitimate and illegitimate tests of free-analyte assay function: we need to identify the factors that influence free-analyte assay results. Clin Chem 2009; 55 (3): 442–4.

33. Lee RH, Spencer CA, Mestman JH, et al. Free T4 immunoassays are flawed during pregnancy. Am J Obstet Gynecol 2009; 200 (3): 260 e1–6.

34. Tolino A, De Conciliis B, Montemagno U. Thyroid hormones in the human pregnancy. Acta Obstet Gynecol Scand 1985; 64 (7): 557–9.

35. Whitworth AS, Midgley JE, Wilkins TA. A comparison of free T4 and the ratio of total T4 to T4-binding globulin in serum through pregnancy. Clin Endocrinol (Oxf) 1982; 17 (3): 307–13.

36. Hollowell JG, Staehling NW, Flanders WD, et al. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002; 87 (2): 489–99.

37. Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf) 1995; 43 (1): 55–68.

38. Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in euthyroid pregnant women with autoimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab 2006; 91 (7): 2587–91.

39. De Vivo A, Mancuso A, Giacobbe A, et al. Thyroid function in women found to have early pregnancy loss. Thyroid 2010; 20 (6): 633–7.

40. Biochemistry AfC, Association BT, Foundation BT. UK Guidelines for the Use of Thyroid Function Tests. Available at: http://www.british-thyroid-association.org/info-for-patients/Docs/TFT_guideline_final_version_July_2006.pdf. Accessed 29.06.2010.

41. Davies TF, Larsen PR. Thyrotoxicosis. In: Kronenberg HM, Melmed S, Polonsky KS, Larsen PR, eds. Williams textbook of endocrinology. Philadelphia: Saunders Elsevier; 2008; 333–76.

42. Eckstein AK, Plicht M, Lax H, et al. Thyrotropin receptor autoantibodies are independent risk factors for Graves' ophthalmopathy and help to predict severity and outcome of the disease. J Clin Endocrinol Metab 2006; 91 (9): 3464–70.

43. Pacini F, Schlumberger M, Dralle H, Elisei R, Smit JW, Wiersinga W. European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium. Eur J Endocrinol 2006; 154 (6): 787–803.

44. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines

for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2009; 19 (11): 1167–214.

45. Savin S, Cvejić D, Mijatović Lj, Živančević-Simonović S. Measuring thyroglobulin concentrations in patients with differentiated thyroid carcinoma. Journal of Medical Biochemistry 2010; 29: 245–53.
46. Perros P. Guidelines for the management of thyroid cancer. Book Guidelines for the management of thyroid cancer. 2 ed. City: Royal College of Physicians of London; 2007.
47. Guarino E, Tarantini B, Pilli T, et al. Presurgical serum thyroglobulin has no prognostic value in papillary thyroid cancer. Thyroid 2005; 15 (9): 1041–5.
48. Vejbjerg P, Knudsen N, Perrild H, et al. Thyroglobulin as a marker of iodine nutrition status in the general population. Eur J Endocrinol 2009; 161 (3): 475–81.
49. Trbojević B, Nedeljković-Beleslin B. Importance of hormones and proteins determination in the material obtained by fine-needle aspiration. Journal of Medical Biochemistry 2010; 29: 237–44.
50. Kloos RT, Eng C, Evans DB, et al. Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid 2009; 19 (6): 565–612.

Received: July 4, 2010

Accepted: July 15, 2010