Journal of Clinical and Translational Endocrinology: Case Reports 10 (2018) 21–24

Contents lists available at ScienceDirect

Journal of Clinical and Translational Endocrinology: Case Reports

journal homepage: www.elsevier.com/locate/jctecasereports.com

Support for the upregulation of serum thyrotropin by estrogens coming from the increased requirement of levothyroxine in one gynecomastic patient with excess of thyroxine-binding globulin secondary to exposure to exogenous estrogens

Salvatore Benvenga[a,b,c], Giovanni Capodicasa[a,*], Sarah Perelli[a], Roberto Vita[a]

[a] Endocrinology Section, Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy
[b] Master Program on Childhood, Adolescent and Women's Endocrine Health, University of Messina, Messina, Italy
[c] Interdepartmental Program of Molecular & Clinical Endocrinology, and Women's Endocrine Health, University Hospital, Policlinico G. Martino, Messina, Italy

ARTICLE INFO

Keywords:
Thyroxine-binding globulin
Estrogens
Thyrotropin
Levothyroxine therapy
Refractory hypothyroidism

ABSTRACT

Thyroxine-binding globulin (TBG) is the liver-synthesized and estrogen-upregulated major plasma carrier of thyroid hormones with an affinity binding greater for T4 than T3. It is known that pregnancy, a physiologic state of estrogen-driven elevation of serum TBG, raises the requirement of L-T4 dose in hypothyroid women, especially those with no residual thyroid function. Similar increased requirement was reported for postmenopausal women during estrogen therapy. One known cause of relative hyperestrogenemia, gynecomastia and acquired TBG excess is liver disease, but very rarely chronic liver disease is mentioned as a cause of increased L-T4 requirement. One hypothyroid man with cirrhosis-associated gynecomastia and increased serum levels of both estradiol and TBG was reported recently. His requirement of L-T4 was no longer increased after liver transplantation. We now report the case of a man with primary hypothyroidism under stable replacement therapy with L-T4 until exposure to an exogenous cause of hyperestrogenemia caused increased L-T4 requirement associated to TBG excess. In addition to increased TBG, the high levels of estrogens had caused the appearance of gynecomastia. We fully corrected primary hypothyroidism upon eliminating his exposure to the source of estrogens. Hyperestrogenism can be a cause of increased L-T4 requirement through the rise of circulating levels of TBG also in man with no residual thyroid function.

1. Introduction

Primary hypothyroidism is a common endocrine disorder with an approximate prevalence and incidence of 5% and 250/100,000 per year in adults [1,2]. Hypothyroidism is managed by general practitioners and specialists [3]. Therapy is based on daily administration of oral levothyroxine (L-T4) [3], with monitoring relying on periodic assays of serum thyrotropin (TSH) [3]. The target serum TSH for adults is recommended to be ≤ 4.12 mU/L [3].

Around 20% of primary hypothyroid patients have undertreated (or refractory) thyroid failure, namely TSH above target levels despite adequate doses of L-T4 [4]. Refractory hypothyroidism requires a thorough diagnostic work-up [4]. However, because of the common practice of trying to bring down serum TSH levels by increasing the daily dose of L-T4, some patients do not come to observation and, hence, they are not investigated. This practice may or may not be effective.

An increased requirement of L-T4 may derive from gastro-intestinal disorders, co-ingestion of medicines/supplements that impair the intestinal absorption of L-T4 or that increase its catabolism, or from increased urinary loss of thyroid hormone [4,5]. Typical examples are celiac disease, simultaneous therapy with calcium salts or carbamazepin, pregnancy and nephrotic syndrome [4,5]. Whatever the cause, the increased requirement of L-T4 concerns most frequently patients with no residual thyroid function, because no endogenous output of thyroid hormone can compensate the impaired intestinal absorption or the increased catabolism/loss of the exogenous hormone.

Here we report one man with no residual thyroid function, in whom the increased requirement of L-T4 was associated with increased serum levels of thyroxine-binding globulin (TBG), which is the liver-

* Corresponding author. Department of Clinical and Experimental Medicine, University of Messina, Padiglione H, 4 piano, A.O.U. Policlinico G. Martino, 98125 Messina, Italy.
E-mail address: capodicasagio@gmail.com (G. Capodicasa).

https://doi.org/10.1016/j.jecr.2018.10.001
Received 16 July 2018; Accepted 2 October 2018

Table 1
Exemplary summary of evidence for the upregulation of serum TSH and TBG by estrogens, and for increased thyroid hormone binding by increased levels of thyroid hormone plasma carriers, with subsequent increased requirement of levothyroxine therapy during hyperestrogenic states.[a]

Author (ref.)	Comment
Hall R, Scanlon MF [7]	Especially in the **pre-menstrual phase of the cycle**, women show a **greater TSH** response to TSH-releasing hormone (TRH) **compared to men**. The **TSH** response to TRH is enhanced by **estrogens**, both in women under **oral contraceptives** and in men being treated with **estrogens**.
Kratzsch J et al. [8]	Median serum **TSH** in 108 females under **oral contraceptives** was 1.56 mU/L, but it was 1.29 mU/L (−17.3%) in 66 females not using oral contraceptives.
Panesar et al. [9] Bocos-Terraz et al. [10] Glinoer et al. [11]	Serum **TSH increases** progressively **during gestation**. For instance, median (5th-95th percentiles) in the first, second and third trimester reported by Panesar et al. (9) are 0.8 (0.03–2.30), 1.10 (0.03–3.10) and 1.30 (0.13–3.50). The corresponding levels reported by Bocos-Terraz et al. (10) are 0.92 (0.03–2.65), 1.12 (0.12–2.64) and 1.29 (0.23–2.56). Glinoer et al. (11) reported **TSH** levels of 0.75 ± 1.0, 1.05 ± 1.0, 1.29 ± 1.0 mU/L (mean ± SD), **parallelling increases** in **TBG levels** (21.2 ± 7.4, 28.5 ± 9.8 and 31.5 ± 7.4 mg/L).
Kutluturk F et al. [12] Sriphrapradang C et al. [13] Kim M et al. [14]	**Higher** serum levels of **TSH** in **females compared to males**. For instance, in a well-characterized, disease-free population, Kim et al. (14) found that median (2.5th-95th percentile) serum **TSH** levels of **females** aged 20–39 years were 2.49 (0.75–7.90), **greater than** 2.23 (0.70–6.50) of age-matched **males.**
Benvenga S et al. [15]	Two regularly menstruating women with Hashimoto's thyroiditis were treated with approximately 1.5 μg/kg body weight/day L-T4. Under this replacement therapy, they had **TSH levels consistently > 3 mU/L (and sometimes above target levels) during mid-cycle coinciding with high levels of E2**, but **consistently lower serum levels during the follicular and luteal phases of menstrual cycle, coinciding with much lower E2 levels**. In one patient, prior to L-T4 therapy, **TSH was 19.7 mU/L (mid-cycle),** but it was **13.2 mU/L** upon repeating the assay 19 days later (**early follicular phase**).
Benvenga S et al. [16]	A 10-year-old boy with congenital adrenal hyperplasia and associated hyperplastic testicular adrenal rests **had high serum concentrations of E2** (> 440 pmol/L), basal and TRH-stimulated **TSH** (12–16 mU/L, peak of 34 mU/L) and PRL. **Serum E2 correlated** directly with PRL (r = 0.98) and **TSH** (r = 0.85). Upon dexamethasone therapy, **E2** (< 40 pmol/L), **TSH** (1.8 mU/L) and PRL returned progressively normal
Alexander EK et al. [17]	The **increased requirement for T4 (or exogenous LT4)** occurs as early as 4–6 weeks of **pregnancy**. Such requirements gradually increase through 16–20 weeks of pregnancy, and thereafter plateau until time of delivery. There is a **parallelism between this increased requirement** and the **increase of serum TBG during gestation**. Serum **TBG** increases a few weeks after conception and reaches a plateau during midgestation.
Arafah BM [18]	Study on 25 postmenopausal women with hypothyroidism treated with L-T4 (for replacement purposes in 18/25) who received conjugated estrogens in a daily oral dose of 0.625 mg for 48 weeks. Serum **TBG and TSH increased during estrogen therapy**. Particularly, **TSH increased** from 0.9 ± 1.1 to 3.2 ± 3.1 mU/L, and the **peak time of TSH and TBG coincided** (12th week). **Serum TSH increased to more than 7 mU/L in approximately 40% of the L-T4 replaced women, and their dose of L-T4 was therefore increased**.
Burr M et al. [19]	Inherited TBG abnormalities have X-linked transmission. In 14 males with **hereditary excess of TBG** and 44 heterozygotic females, there were three instances of **hypothyroidism**.
Heufelder AE et al. [20]	In a series of 29 consecutive patients with **familial dysalbuminemic hyperthyroxinemia (FDH)**, 2 patients (7%) had hypothyroidism (postablative hypothyroidism), and **in both patients hypothyroidism was undertreated**. Seven of the 29 patients (24%) had either diffuse or nodular goiter not due to Hashimoto's thyroiditis. Unfortunately, serum TSH levels (reference values 0.4–7.0 mU/L) were given for the whole cohort (in which there were the 2 hypothyroid patients and the single hyperthyroid patient). Nevertheless, mean serum TSH levels were 5.2 ± 8.3 mU/L, that may suggest lower availability of thyroid hormones for tissues (including the thyrotrops) and somewhat higher 24-h daily secretion of TSH, with subsequent induction of diffuse or nodular goiter.
Pohlenz J et al. [21]	**Familial dysalbuminemic hyperthyroxinemia (FDH)** was detected in a 5-month-old boy with **congenital hypothyroidism** who had a blood TSH level of 479 mU/L but normal serum T4 and higher than normal T3 levels. **Thyroid hormone substitution** began at 5 weeks of age when T4 and T3 concentrations were below normal. Until the age of 5 months, **treatment with L-T4 was suboptimal on the basis of high serum TSH levels despite above-normal T4 levels**.
Benvenga S et al. [22]	**Thyroid hormone antibodies (THAb) directed against T3 and T4** of both the IgM and IgG class were detected in two twins. At age 10 months, **a rise in TSH occurred** in both infants and measurement of THAb at the same time revealed the **appearance of IgM-T4 and IgG-T4** and an increase in IgG-T3 levels in twin 1 (permanent congenital **hypothyroidism**), and with a **slight increase of IgM-T4 and IgG-T4 levels** and appearance of IgM-T3 in twin 2 (**transient congenital hypothyroidism**). **Daily dose of L-T4 had to be progressively increased** in twin 1. In twin 2, L-T4 was started and then withdrawn. It was restarted on month 10 and then **progressively increased**, though not as much as in twin 1.
Trimarchi F et al. [23]	A case of **primary hypothyroidism** was reported in a 68-yr-old patient with Waldenström's disease. His thyroid failure was accompanied by an **abnormal, greatly elevated binding of thyroid hormones in the gamma-globulin fraction**. The **thyroid gland was normal at autopsy**. The binding of the thyroid hormones by **circulating IgM and IgG**, which reduced T4 and T3 availability for their metabolic action at the tissue level, could have contributed to the clinical picture.
Moreira RM et al. [24,25]	The **thyrotrops have estrogen receptors**, though not as abundant as other anterior pituitary cell types. Isolated hemipituitaries from **ovariectomized (OVX) rats have decreased basal TSH release and tend to have reduced TRH-stimulated TSH release** compared to control female rats. In OVX rats, **increasing serum estrogen levels** within the physiological range **increase both basal and TRH-stimulated TSH release** as well as PRL release. (24). **Neuromedin B (NB)**, a bombesin-like peptide, **inhibits TSH release**. TSH release from isolated hemipituitaries of OVX rats is significantly reduced in the presence of low dose of NB. However, pituitary glands from **hyperestrogenized rats** (OVX + estradiol benzoate) **require a higher dose of NB to inhibit TSH release** (24).
Liu SR et al. [26]	The spontaneous and TRH-induced release of TSH *in vitro* from rat anterior pituitary cells, and pituitary TSH content are increased by T3 compared to vehichle. **Estradiol benzoate (EB) inhibits the effect of T3 on TSH release** *in vitro*. Application of T3 *in vitro* prevented the release of TSH in response to TRH. **EB dose-dependently relieved the inhibitory effect of T3 on TRH-induced TSH release** *in vitro*. **TRH release** from mediobasal hypothalamus was **increased by EB** and inhibited by T3 or progesterone. **EB prevented the inhibitory effect of T3 on TRH release**.
Kimura N et al. [27]	Treatment of GH3 cells with **E2 increased TRH receptor** mRNA activity. **E2 up-regulates the TRH receptors of the pituitary cells** at the mRNA level by increasing both the transcription rate and stability.
Schomburg L [28]	TRH is inactivated by the **TRH-degrading ectoenzyme**, a TRH-specific metallopeptidase. **Compared with male rats**, only about one-third of the enzymatic activities and the messenger RNA levels were detected in the anterior pituitary of **female rats**. *In vivo* and with GH3 cells *in vitro*, **E2 effectively counteracted the increase in enzymatic activity induced by T3**, whereas neither testosterone nor progesterone showed any significant effects.

[a] Literature from references 7–23 concerns humans, while literature from references 24–28 is experimental and concerns animals.

synthesized and estrogen-upregulated major plasma transporter of thyroid hormones. Serum TBG levels were elevated, similar to those observed in pregnant women, an increase that was driven by exposure to exogenous estrogens. This patient complements another gynecomastic patient we have reported recently [6], in whom the cause for hyperestrogenism was endogenous (liver cirrhosis). That patient also had no residual thyroid function.

2. Case report

A 35-yr old man was referred to us because of bilateral gynecomastia that started to appear about 6 months earlier. History and physical examinations were irrelevant except for changes in dietary habits and total thyroidectomy for multinodular goiter, so that he was on replacement doses of L-T4 (100 μg/d). The dietary changes consisted in increased consumption of veal meat from a local farm, which later on was found to illicitly use dietary estrogens in animal feeds.

Four months and just a few days before our observation, serum TSH was 4.4 and 5.7 mU/L, T4 11.2 and 12.5 μg/dl, T3 142 and 153 ng/dl, respectively (corresponding reference ranges: 0.30–5.5 mU/L, 5.4–11.0 μg/dl and 80–170 ng/dl). These data contrasted with serum levels measured before the appearance of gynecomastia (TSH = 1.2–2.8 mU/L, T4 = 8.7–9.5 μg/dl, T3 = 92–108 ng/dl). At observation, serum free thyroxine (FT4) and free triiodothyronine (FT3) were normal (15.7 pg/ml [n.v. 9–19] and 3.2 pg/ml [n.v. 2.0–4.2]). The discrepancy between total thyroid hormones (increased) and free thyroid hormones (normal), led us to suspect elevated circulating TBG. Indeed, serum TBG was high (45 μg/ml; reference range 12–30 [men], 15–36 [nonpregnant women]). Upon stopping the consumption of veal meat, gynecomastia progressively disappeared, and biochemical indices progressively normalized. Approximately one year after observation, serum TSH, T4, and TBG progressively fell while maintaining the regimen of 100 μg/d L-T4 (TSH = from 3.8 to 2.7 mU/L, from T4 = 12.0 to 10.2 μg/dl, and TBG = from 41 to 27 μg/ml).

3. Discussion

Summarized in Table 1 is evidence for the upregulation of both serum TSH and TBG by estrogens, and for enhanced thyroid hormone binding by elevated levels of thyroid hormone plasma carriers, with subsequent requirement for increased daily of L-T4 during hyperestrogenic states [7–28]. Serum TSH is also upregulated by the cold environment and, therefore, cold months but not in all individuals. For instance, in the Northern hemisphere, persons aged > 80 years have a TSH reference interval of 0.55–5.12 mU/L (males) or 0.52–5.20 mU/L (females) in September, but 0.61–6.20 mU/L (males) or 0.58–6.28 mU/L (females) in January. However, in the 21–40 years age band (which applies to our patient), there are no seasonal fluctuations in TSH, as the reference interval varies from 0.56 to 4.23 in August to 0.57–4.47 mU/L in February (males) or 0.53–4.31 in August to 0.54–4.55 mU/L in February (females) [29].

Approximately 50% of hypothyroid premenopausal women or postmenopausal women being treated with exogenous L-T4 need to increase dosing during pregnancy or simultaneous therapy with oral conjugated estrogens [17,18,30]. In postmenopausal women with L-T4 treated hypothyroidism who received conjugated estrogens, serum TSH increased to more than 7 mU/L in 7/18 (39%), so that their dose of L-T4 had to be increased [18]. Androgen therapy in L-T4 treated hypothyroid women with breast cancer decreases both TBG and requirement of L-T4 dose [31].

The incremental increase of L-T4 dosing depends, in part, on the etiology of the hypothyroidism. There is a greater likelihood that dose increase will be required in hypothyroid pregnant women without functional thyroid tissue (e.g., due to radioablation, surgery) in comparison with patients with non-atrophic Hashimoto's thyroiditis [17,32]. The increased requirements for T4 (or exogenous L-T4) occurs as early as 4–6 weeks of pregnancy [17]. Such requirement gradually increases through 16–20 weeks of gestation, and thereafter plateaus until time of delivery. There is a parallelism between this increased requirement and the increase of serum TBG during gestation. Serum TBG increases a few weeks after conception and reaches a plateau during midgestation [33]. At plateau, circulating TBG has increased by two-to threefold, and such increase is due to the estrogen-induced stimulation of both TBG liver-synthesis and TBG sialylation [34,35]. Estrogen up-regulation and androgen down-regulation of TBG [36] has been observed also in men, whereas progestins exert no regulation [37]. Concerning liver disease, increased serum levels of TBG are considered to be secondary to both leakage from damaged hepatocytes and synthesis from regenerating hepatocytes [38–43].

4. Conclusion

In summary, taking into account the other male patient described recently [6], we have provided evidence for increased serum TSH (and associated increased requirement of L-T4 dosing) in two gynecomastic male hypothyroid patients under L-T4 replacement therapy with no residual thyroid function (because of either total thyroidectomy or atrophic Hashimoto's thyroiditis), and with acquired elevation of serum TBG (due to exogenous or endogenous exposure to estrogens). However, based on literature [6,24–28], a contribution to the increased serum TSH may come from a direct, TBG-unrelated effect of the estrogens on the hypothalamus-pituitary-thyroid axis. Because either autoimmune or post-thyroidectomy hypothyroidism is relatively common, and so is chronic liver disease, their coexistence may not be rare. In patients with such coexistence, surveillance for possible undertreated hypothyroidism is suggested.

Ethics statement

The patient gave written informed consent for the publication of this case report.

Author contributions

All the authors contributed equally to recruited patients and wrote the present work.

Conflict of interest

The authors declare they have no conflicts of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] Garmendia Madiaraga A, Santos Palacios S, Guillén-Grima F, Galofré JC. The incidence and prevalence of thyroid dysfunction in Europe: a meta-analysis. J Clin Endocrinol Metab 2014;99:923–31.
[2] Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, 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;87:489–99.
[3] Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, et al. Clinical practice guidelines for hypothyroidism for hypothyroidism in adults: cosponsored by the American association of clinical endocrinologists and the American thyroid association. Thyroid 2012;22:1200–35.
[4] Benvenga S. When thyroid hormone replacement is ineffective? Curr Opin Endocrinol Diabetes Obes 2013;20:467–77.
[5] Colucci P, Seng Yue C, Ducharme M, Benvenga S. A Review of the pharmacokinetics of levothyroxine for the treatment of hypothyroidism. Eur Endocrinol 2013;9:40–7.
[6] Benvenga S, Capodicasa G, Perelli S, Ferrari SM, Fallahi P, Antonelli A. A Increased requirement of replacement doses of levothyroxine caused by liver cirrhosis. Front Endocrinol (Lausanne) 2018https://doi.org/10.3389/fendo.2018.00150.

[7] Hall R, Scanlon MF. Thyrotropin-releasing hormone in clinical practice. J Clin Pathol Suppl (Assoc Clin Pathol) 1976;7:55–7.
[8] Kratzsch J, Fiedler GM, Leichtle A, Brügel M, Buchbinder S, Otto L, 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;51:1480–6.
[9] Panesar LS, Li CY, Rogers MS. Reference intervals for thyroid hormones in pregnant Chinese women. Ann Clin Biochem 2001;38:329–32.
[10] Bocos-Terraz JP, Izquierdo-Alvarez S, Bancalero-Flores JL, Alvarez-Lahuerta R, Aznar-Sauca A, Real-López E, et al. Thyroid hormones according to gestational age in pregnant Spanish women. BMC Res Notes 2009;2:237.
[11] Glinoer D, de Nayer P, Bourdoux P, Lemone M, Robyn C, Van Steirteghem A, et al. Regulation of maternal thyroid during pregnancy. J Clin Endocrinol Metab 1990;71:276–87.
[12] Kutluturk F, Yildirim B, Ozturk B, Ozyurt H, Bekar U, Sahin S, et al. The reference intervals of thyroid stimulating hormone in healthy individuals with normal levels of serum free thyroxine and without sonographic pathologies. Endocr Res 2014;39:56–60.
[13] Sriphrapradang C, Pavarangkoon S, Jongjaroenprasert W, Chailurkit LO, Ongphiphadhanakul B, Aekplakorn W. Reference ranges of serum TSH, FT4 and thyroid autoantibodies in the Thai population: the national health examination survey. Clin Endocrinol (Oxf) 2014;80:751–6.
[14] Kim M, Kim TY, Kim SH, Lee Y, Park SY, Kim HD, et al. Reference interval for thyrotropin in a ultrasonography screened Korean population. Korean J Intern Med 2015;30:335–44.
[15] Benvenga S, Di Bari F, Granese R, Antonelli A. Serum thyrotropin and phase of the menstrual cycle. Front Endocrinol (Lausanne) 2017;8:250.
[16] Benvenga S, Smedile G, Lo Giudice F, Alesci S, Amato A, Trimarchi F. Euthyroid hyperthyrotropinemia secondary to hyperestrogenemia in a male with congenital adrenal hyperplasia. Horm Metab Res 2000;32:321–35.
[17] Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. N Engl J Med 2004;351:241–9.
[18] Arafah BM. Increased need for thyroxine in women with hypothyroidism during estrogen therapy. N Engl J Med 2001;344:1743–9.
[19] Burr WA, Ramsden DB, Hoffenberg R. Hereditary abnormalities of thyroxine-binding globulin concentration. A study of 19 kindreds with inherited increase or decrease of thyroxine-binding globulin. Q J Med 1980;49:295–313.
[20] Heufelder AE, Klee GG, Wynne AG, Gharib H. Familial dysalbuminemic hyperthyroxinemia: cumulative experience in 29 consecutive patients. Endocr Pract 1995;1:4–8.
[21] Pohlenz J, Sadow PM, Koffler T, Schönberger W, Weiss RE, Refetoff S. Congenital hypothyroidism in a child with unsuspected familial dysalbuminemic hyperthyroxinemia caused by a mutation (R218H) in the human albumin gene. J Pediatr 2001;139:887–91.
[22] Benvenga S, Ordookhani A, Pearce EN, Tonacchera M, Azizi F, Braverman LE. Detection of circulating autoantibodies against thyroid hormones in an infant with permanent congenital hypothyroidism and her twin with transient congenital hypothyroidism: possible contribution of thyroid hormone autoantibodies to neonatal and infant hypothyroidism. J Pediatr Endocrinol Metab 2008;21:1011–20.
[23] Trimarchi F, Benvenga S, Fenzi G, Mariotti S, Consolo F. Immunoglobulin binding of thyroid hormones in a case of Waldenstrom's macroglobulinemia. J Clin Endocrinol Metab 1982;54:1045–50.
[24] Moreira RM, Lisboa PC, Curty FH, Pazos-Moura CC. Dose-dependent effects of 17-beta-estradiol on pituitary thyrotropin content and secretion in vitro. Braz J Med Biol Res 1997;30:1129–34.
[25] Moreira RM, Curty FH, Lisboa PC, Amaral D, Ortiga-Carvalho TM, Pazos-Moura CC. Estrogen modulates neuromedin B effects on thyrotropin and prolactin release in vitro. Life Sci 2003;72:917–23.
[26] Liu SR, Tsai SC, Lu CC, Lee KY, Liu TC, Pu HF, et al. Interaction between triiodothyronine and ovarian steroid hormones on the regulation of the release of thyrotropin and thyrotropin-releasing hormone in vitro. Chin J Physiol 1997;40:221–6.
[27] Kimura N, Arai K, Sahara Y, Suzuki H, Kimura N. Estradiol transcriptionally and posttranscriptionally up-regulates thyrotropin-releasing hormone receptor messenger ribonucleic acid in rat pituitary cells. Endocrinology 1994;134:432–40.
[28] Schomburg L, Bauer K. Regulation of the adenohypophyseal thyrotropin-releasing hormone-degrading ectoenzyme by estradiol. Endocrinology 1997;138:3587–93.
[29] Ehrenkranz J, Bach PR, Snow GL, Schneider A, Lee JL, Ilstrup S, et al. Circadian and circannual rhythms in thyroid hormones: determining the TSH and free T4 reference intervals based upon time of day, age, and sex. Thyroid 2015;25:954–61.
[30] Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, et al. American Thyroid Association Taskforce on thyroid disease during pregnancy and postpartum. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid 2011;21:1081–125.
[31] Arafah BM. Decreased levothyroxine requirement in women with hypothyroidism during androgen therapy for breast cancer. Ann Intern Med 1994;121:247–51.
[32] Loh JA, Wartofsky L, Jonklaas J, Burman KD. The magnitude of increased levothyroxine requirements in hypothyroid pregnant women depends upon the etiology of the hypothyroidism. Thyroid 2009;19:269–75.
[33] Skjoldebrand L, Brundin J, Carlstrom A, Pettersson T. Thyroid associated components in serum during normal pregnancy. Acta Endocrinol 1982;100:504–11.
[34] Glinoer D, Gershengorn MC, Dubois A, Robbins J. Stimulation of thyroxine-binding globulin synthesis by isolated rhesus monkey hepatocytes after in vivo beta-estradiol administration. Endocrinology 1977;100:807–13.
[35] Ain KB, Mori Y, Refetoff S. Reduced clearance rate of thyroxinebinding globulin (TBG) with increased sialylation: a mechanism for estrogen-induced elevation of serum TBG concentration. J Clin Endocrinol Metab 1987;65:686–96.
[36] Bisschop PH, Toorians AW, Endert E, Wiersinga WM, Gooren LJ, Fliers E. The effects of sex-steroid administration on the pituitary-thyroid axis in transsexuals. Eur J Endocrinol 2006;155:11–6.
[37] Chen JJ, Ladenson PW. Progesterone has no effect on serum thyroxine-binding globulin concentration in men. J Clin Endocrinol Metab 1985;61:983–5.
[38] Schussler GC, Schaffner F, Korn F. Increased serum thyroid hormone binding and decreased free hormone in chronic active liver disease. N Engl J Med 1978;299:510–5.
[39] Shigemasa C, Tanaka T, Mitani Y, Ueta Y, Taniguchi S, Urabe K, et al. Are increases in thyroxin-binding globulin in patients with acute hepatitis ascribable to synthesis by regenerating hepatocytes? Clin Chem 1988;34:776–80.
[40] Huang MJ, Liaw YF. Thyroxine-binding globulin in patients with chronic hepatitis B virus infection: different implications in hepatitis and hepatocellular carcinoma. Am J Gastroenterol 1990;85:281–4.
[41] Danilovic DL, Mendes-Correa MC, Chammas MC, Zambrini H, Barros RK, Marui S. Thyroid disturbance related to chronic hepatitis C infection: role of CXCL10. Endocr J 2013;60:583–90.
[42] Shimada T, Higashi K, Umeda T, Sato T. Thyroid functions in patients with various chronic liver diseases. Endocrinol Jpn 1988;35:357–69.
[43] Nagasue N, Ohmori H, Hashimoto N, Tachibana M, Kubota H, Uchida M, et al. Thyroxine-binding globulin and thyroid hormones after resection of hepatocellular carcinoma. Am J Gastroenterol 1997;92:1187–9.