Introduction

Hyperprolactinemia is an endocrine disorder involving hypothalamic–pituitary axis. Prolactin (PRL) secretion is stimulated by dopamine antagonism and thyroid-releasing hormone. Hyperprolactinemia has been reported in subclinical hypothyroidism (SCH) but results are markedly variable and studies on SCH are very few. The objective of this study was to find out prevalence of hyperprolactinemia in newly diagnosed subclinical hypothyroid patients. Materials and Methods: In this cross-sectional study, serum PRL levels of 150 newly diagnosed subclinical hypothyroid patients were determined using electrochemiluminescence method. Results: Raised PRL levels were found in 18 (%) patients with SCH. There was positive correlation between serum thyroid-stimulating hormone and PRL levels. Prevalence of infertility was significantly higher with presence of hyperprolactinemia than normoprolactinemia in subclinical hypothyroid patients. Conclusion: Routine prolactin estimation and subsequent treatment is required in patients with subclinical hypothyroidism.
Sirohi and Singh: Hyperprolactinemia in subclinical hypothyroidism

Aims and objectives

1. To estimate and correlate serum PRL levels in subjects with SCH
2. To determine the prevalence of hyperprolactinemia in SCH.

Materials and Methods

The present cross-sectional study was conducted at Sri Balaji Action Medical Institute, Paschim Vihar, New Delhi, from 1st January 2017 to 31st December. All the patients from the outpatient department of medicine and gynecology were enrolled, and the number required for the study to be statistically significant was 150, using Daniel sample size formula (1999); prevalence of hyperprolactinemia in SCH is reported to be 0%–40% in the literature.

Inclusion criteria

1. Subjects between 18 and 45 years of age
2. Subjects with TSH levels between 5 and 10 mIU/L with normal free T3 and free T4 levels.

Exclusion criteria

Pregnant and breastfeeding females; patients using antidepressants and drugs, OCP pills, antilipidemic drugs, and thyroid medications; patients after thyroid surgery, irradiation, and suprasellar surgery; patients who are known case of diabetes mellitus, congestive heart failure, chronic renal failure, post myocardial infarction, prolactinoma, acromegaly, and thyroid disorder.

Thyroid functions and serum PRL levels were evaluated by electrochemiluminescence assay. The reference range of free tri-iodothyronine (free T3), free tetra-iodothyronine (free T4), TSH, and serum PRL in our laboratory is 0.9–1.7 ng/dl, 2.0–4.4 ng/dL, 0.27–4.2 uIU/mL, and 1.9–25 ng/mL, respectively. IBM SPSS version 17.0 software was used for statistical analysis. Ethical clearance was obtained by the institutional ethics committee and a written informed consent was obtained from the patient.

Results and Discussion

The clinical profile of the patients is summarized in Table 1.

The mean age of the patients was 31.82 ± 6.18 years, 90% being females and 10% being male. Of 150 patients with SCH, 27 (18%) had hyperprolactinemia. About 0%–40% are reported in the literature. On comparison, patients with SCH showed prevalence of hyperprolactinemia to be 19%. About 18.5% females and 13.3% males had hyperprolactinemia. Similar results were obtained in a study by Bahar et al. (2011).

The majority of patients in our study group were asymptomatic, which was expected as patients with SCH lack frank symptoms of hypothyroidism. Ovulatory dysfunction or corpus luteum dysfunction occurs in hypothyroidism as thyroid hormones affect granulosa cells, corpus luteum, and oocytes directly and also hypothyroidism causes decreased binding activity of sex-hormone-binding globulin, increased PRL levels, and delayed lutinizing hormone response to gonadotropin-releasing hormone. Overall, the most common complaints in the study group were menstrual abnormalities, followed by infertility (16.7%). Hair loss was found in 12.7%, and same was the frequency of bowel disturbance (constipation).

A similar association was observed by Binita Goswami in her study between hyperprolactinemia and menstrual disturbances in the background of subclinical hypothyroid, thereby explaining the causative role of hyperprolactinemia in infertility. A similar report of increase in the serum PRL levels in infertile women when compared with those in the fertile by Turankar et al. corroborates the aforesaid association. In our study, positive correlation was found between low TSH and elevated serum PRL (r = 0.219, P = 0.007). A similar finding was observed in the study by Hekimsoy et al. On comparison, patients with...
TSH in higher range (7.5–10 mIU/L) had significantly higher prevalence of hyperprolactinemia (33%) than in patients with TSH (5–7.4 mIU/L) who had prevalence of 13.7%, which is explained as higher TRH levels in patients with more severe hypothyroidism (higher TSH levels) leads to a greater TRH mediated PRL release from lactotrophs. Shenenerberger and Klachko reported that production of PRL is stimulated by thyrotropin-releasing hormone, epidermal growth factor, dopamine receptor antagonists, and vasoactive intestinal peptide wherein they concluded that primary hypothyroidism with high levels of thyrotropin-releasing hormone can lead to hyperprolactinemia.

The clinical profile of the patients is summarized in Table 1. On comparison of clinical symptoms in subjects with SCH in two groups with TSH (5.1–7.49) and TSH (7.5–10.0), we found that fatigue and hair loss were significantly more in patients with TSH in higher range (7.5–10 mIU/L). Carlé A et al. (2014) similarly reported fatigue and hair loss in 81% and 4.15% of hypothyroid patients, respectively. Hypothyroidism and hyperprolactinemia have effective roles in stimulating androgenic alopecia, Therefore, coexistence of these two disorders can cause intensive alopecia. Sharma LK et al. (2016) in their study reported that hyperprolactinemia and SCH coexist commonly and a TSH level higher than 8 mIU/L has a very high specificity of approximately 90% in detecting hyperprolactinemia, a landmark observation. They were of the opinion that further studies like this study were required to exude confidence in the statistically significant association of hyperprolactinemia and SCH.

### Conclusion

Routine PRL evaluation is required in patients with SCH, especially in those with TSH 7.5 mIU/L, and elevated PRL levels may be one of the indications for treatment of asymptomatic SCH. Being a cross-sectional study, the impact of levothyroxine supplementation on PRL levels in SCH could not be evaluated. More studies are required to validate the routine treatment of SCH in patients with hyperprolactinemia without elevated levels of anti-TPO antibodies, a parameter the authors were unable to exclude.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.

### References

1. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinical thyroid disease: Scientific review and guidelines for diagnosis and management. JAMA 2004;291:228-38.
2. Raber W, Gessl A, Nowotny P, Vierhapper H. Hyperprolactinaemia in hypothyroidism: Clinical significance and impact of TSH normalization. Clin Endocrinol (Oxf) 2003;58:185-91.
3. Serri O, Chik CI, Ur E, Ezzat S. Diagnosis and management of hyperprolactinemia. CMAJ 2003;169:575-81.
4. Katznelson L, Riskind PN, Saxe VC, Klubanski A. Prolactin pulsatile characteristics in postmenopausal women. J Clin Endocrinol Metab 1998;83:761-4.
5. Jacobs LS, Snyder PJ, Utiger RD, Daughaday WH. Prolactin response to thyrotropin releasing hormone in normal subjects. J Clin Endocrinol Metab 1973;36:1069-73.
6. Asa SL, Ezzat S. The pathogenesis of pituitary tumours. Nat Rev Cancer 2002;2:836-49.
7. Foord SM, Peters JR, Dieguez C, Jasani B, Hall R, Scanlon MF, et al. Hypothyroid pituitary cells in culture: An analysis of thyrotropin and prolactin responses to dopamine (DA) and DA receptor binding. Endocrinology 1984;115:407-15.
8. Davis JR, Lynam TC, Franklyn JA, Docherty K, Sheppard MC. Tri-iodothyronine and phenythoin reduce prolactin messenger RNA levels in cultured rat pituitary cells. J Endocrinol 1986;109:407-15.
9. Davis JR, Lynam TC, Franklyn JA, Docherty K, Sheppard MC. Tri-iodothyronine and phenythoin reduce prolactin messenger RNA levels in cultured rat pituitary cells. J Endocrinol 1986;109:359-64.
10. Biller BM, Baum HB, Rosenthal DI, Saxe VC, Charpie PM, Klibanski A, et al. Progressive trabecular osteopenia in women with hyperprolactinemic amenorrhea. J Clin Endocrinol Metab 1992;75:692-7.
Faccioli G, et al. Bone marker and bone density responses to dopamine agonist therapy in hyperprolactinemic males. J Clin Endocrinol Metab 1998;83:807-13.

11. Douglas S. Ross subclinical hypothyroidism. In: Braverman LE, Utiger RD, editors. Werner and Ingbar’s the Thyroid: A Fundamental and Clinical Text. 8th ed. Philadelphia: Lippincott Williams and Wilkins; 2000. p. 1001-6.

12. Ayala AR, Danese MD, Ladenson PW. When to treat mild hypothyroidism. Endocrinol Metab Clin N Am 2000;29:399-415.

13. Tunbridge WM, Evered DC, Hall R, Appleton D, Breslin M, Clark F, et al. The spectrum of thyroid disease in a community: The Whickham survey. Clin Endocrinol (Oxf) 1977;7:481-93.

14. Sawin CT, Castelli WP, Hershman JM, McNamara P, Bacharach P. The aging thyroid. Thyroid deficiency in the Framingham study. Arch Intern Med 1985;145:1386-8.

15. Geul KW, van Sluisveld IL, Grobbee DE, Docter R, de Bruyn AM, Hooykaas H, et al. The importance of thyroid microsomal antibodies in the development of elevated serum TSH in middle-aged women: Associations with serum lipids. Clin Endocrinol (Oxf) 1993;39:275-80.

16. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in community: A 20 year follow-up of the Wickham survey. Clin Endocrinol 1993;43:55-68.

17. Cooper DS. Subclinical hypothyroidism. JAMA 1987;258:246-7.

18. Evers MC. The infertile couple. Am Fam Physician 1996;54:1001-10.

19. Fritz MA, Speroff L. Clinical Gynaecologic Endocrinology and Infertility. Philadelphia: Wolters Kluver; 2010. p. 12.

20. Ionescu O, Vulpoi C, Cristea C. Hyperprolactinemia and pregnancy. Rev Med Chir Soc Med Nat Iasi 2002;106:60-4.

21. Meier C, Christ-Crain M, Guglielmetti M, Huber P, Staub JJ, Müller B, et al. Prolactin dysregulation in women with subclinical hypothyroidism: Effect of levothyroxine replacement therapy. Thyroid 2003;13:979-85.

22. Bahar A, Akha O, Kashi Z, Vesgari Z. Hyperprolactinemia in association with subclinical hypothyroidism. Caspian J Intern Med 2011;2:229-33.

23. Ross DS. Serum thyroid-stimulating hormone measurement for assessment of thyroid function and disease. Endocrinol Metab Clin North Am 2001;30:245-64, vii.

24. Bals-Pratsch M, De Geyter C, Müller T, Frielings U, Lerchl A, Pirke KM, et al. Episodic variations of prolactin, thyroid-stimulating hormone, luteinizing hormone, melanotin and cortisol in infertile women with subclinical hypothyroidism. Hum Reprod 1997;12:896-904.

25. Col NF, Surks MI, Daniels GH. Subclinical thyroid disease: Clinical applications. JAMA 2004;291:239-43.

26. Binita G, Suprava P, Mainak C, Koner BC, Alpana S. Correlation of prolactin and thyroid hormone concentration with menstrual patterns in infertile women. J Reprod Infertil 2009;10:207-12.

27. Turankar S, Sonone K, Turankar A. Hyperprolactinemia and its comparison with hypothyroidism in primary infertile women. J Clin Diagn Res 2013;7:794-6.

28. Hekimsoy Z, Kafesciller S, Guclu F, Ozmen B. The prevalence of hyperprolactinaemia in overt and subclinical hypothyroidism. Endocr J 2007;14:307.

29. Goel P, Kahkasha NS, Gupta BK, Goel K. Evaluation of serum prolactin level in patients of subclinical and overt hypothyroidism. J Clin Diagn Res 2015;9:BC15-7.

30. Shenenberger D, Klachko DM. Drug and diseases, endocrinology. Hyperprolactinemia 2018;03:121784.

31. Carlé A, Pedersen IB, Knudsen N, Perrild H, Ovesen L, Laurberg P, et al. Hypothyroid symptoms and the likelihood of overt thyroid failure: A population-based case-control study. Eur J Endocrinol 2014;171:593-602.

32. Sharma LK, Sharma N, Gadpayle AK, Dutta D. Prevalence and predictors of hyperprolactinemia in subclinical hypothyroidism. Eur J Intern Med 2016;35:106-10.