Original Research Article

Comparative assessment of morning versus evening dose of levothyroxine in hypothyroid patients

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Abstract

Background: Hypothyroidism denotes the pathological condition of thyroid hormone deficiency. If untreated, it can lead to various adverse health effects. Treatment with thyroxine replacement can mitigate the impact of hypothyroidism.**Aims & Objectives:**To compare the efficacy of morning versus evening dose of levothyroxine and To compare the effect of morning versus evening dose of levothyroxine on lipid profile. **Materials and methods:** This observational study was conducted at Saraswati Medical College, Unnao on 76 subjects with hypothyrodism. **Result:**There was no statistically significant difference in the changes in serum TSH and T_4 level between patients taking evening dose of levothyroxine with those taking morning dose. Serum lipid profile over the 12 and 24 weeks period has not shown any statistically significant difference.**Conclusion:**Evening schedule of Levothyroxine dose is as efficacious as morning dose in terms of thyroid profile and lipid profile. Hence, change of scheduling can be effected if needed to achieve better complaince.

Keywords: Hypothyroidism,Thyroxine, Lipid profile, Metabolism

Introduction

Hypothyroidism denotes the pathological condition of thyroid hormone deficiency. If untreated, it can lead to various adverse health effects. As there is a large variation in clinical presentation and absence of symptom specificity, the definition of hypothyroidism is pre-dominantly biochemically determined. Overt or clinical primary hypothyroidism can be stated as thyroid-stimulating hormone above the referenced range and free thyroxine concentrations below the referenced range [1].

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Mild or subclinical hypo-thyroidism, which is quite common, is regarded as a sign of early thyroid failure, is defined by TSH concentrations above the referenced range and free thyroxine concentrations within the normal acceptable range.

Etiology

Hypothyroidism is classified as primary (because of thyroid hormone deficiency), secondary (due to TSH deficiency), tertiary (due to thyrotropin-releasing hormone deficiency), and peripheral (extra-thyroidal; panel). Central hypothyroidism (including both secondary and tertiary) and peripheral hypothyroidism are rare and account for less than 1-2% of cases [2].

Primary hypothyroidism

In iodine-sufficient areas based on geography, the commonest cause of hypothyroidism is chronic autoimmune thyroiditis (also known as Hashimoto's disease). High concentrations of anti-thyroid antibodies (predominantly thyroid peroxidase antibodies and anti-thyroglobulin antibodies) are present in most patients with autoimmune thyroiditis. Higher concentrations of

thyroid peroxidase antibodies are also detected in about 12% of the general population. In patients with subclinical hypothyroidism, thyroid peroxidase antibody measurements help to predict progression to overt diseas- The mechanisms underlying autoimmune thyroiditis are not known, but both genetic and environmental factors are involved. A higher genetic risk score—calculated using five genetic variants for thyroid peroxidase antibodies identified by genome-wide association studies—showed a graded association with higher TSH concentrations and clinical hypothyroidism [3].

Central hypothyroidism

Central hypothyroidism is quite rare It is associated with pituitary than hypothalamic disorders .It is defined by low or low-to-normal TSH concentrations and a disproportionately low concentration of free thyroxine. Sometimes, TSH concentration is mildly elevated, probably because of decreased bioactivity.Over half of central hypothyroidism cases are caused by pituitary adenomas.Other causes of central hypothyroidism include pituitary or hypothalamic dysfunction due to head trauma, pituitary apoplexy, Sheehan's syndrome, surgery, radiotherapy, genetic, and infiltrative disease. Several drugs are known to affect the hypothalamic–pituitary–thyroid axis (panel).

Peripheral hypothyroidism

Consumptive hypothyroidism is caused by aberrant expression of the deiodinase 3 enzyme (which inactivates thyroid hormone) in tumour tissues. It is of rare occurance but it can can induce severe hypothyroidism. Patients with very rare genetic disorders that can lead to a lower sensitivity to thyroid hormones usually have a normal TSH concentrations, but can also present with tissue-specific hypothyroidism.The treatment modality in both primary and secondary hypothyroidism is thyroxine (levothyroxine sodium). It is used as a replacement therapy due to its consistency and prolonged duration of action. On oral administration, thyroxine is absorbed in the stomach and small intestine and is not complete. About 80 – 82 % is absorbed, and it is increased when taken in before food. Interference with absorption has been seen with varios drugs like iron sulfate, calcium preparations, aluminum antacids, activated charcoal et al [4]. high fiber diet also shows reduced bioavailability of levothyroxine.Traditinally, the thyroxine is advised to be taken before food .Howevere,i it may be inconvenient to take the drug in the morning because of their schedule; For example, for Muslims in the month of Ramadan and intake of multiple other drugs in the morning due to comorbidity. They may request their practitioner to prescribe the drug at some other time of the day. The results of the study conducted by Visser *et al*. showed a significant improvement in the thyroid hormone profile of patients after shifting from morning to the evening dose [5].The study showed that changing the timing of thyroxine ingestion does not affect quality-of-life variables and plasma lipid levels provided it is taken on empty stomach.

Aims and objectives

- To compare the efficacy of morning versus evening dose of levothyroxine
- To compare the effect of morning versus evening dose of levothyroxine on lipid profile

Materials and methods

This observational study was be conducted at Saraswati Medical College, Unnao.

STUDY DESIGN: Observational, Interventional study

STUDY SITE: Department of General Medicine, Saraswati Medical College, Unnao.

SAMPLE SIZE:76

INCLUSION CRITERIA:

1. Patients aged 18 years or more
2. Patients with established hypothyrodism
3. Patients giving informed consent to participate in the study

EXCLUSION CRITERIA:

1. Patients aged less than 18 years
2. Patients with Thyroid cancers
3. Patients who underwent surgery for thyroid
4. Patients in ICU

STUDY PROCEDURE:A detailed history of the patient was taken and through clinical examination was done.Baseline visit was done at recruitment. Patients were asked to come for the second visit after 12 and 24 weeks .At baseline, blood samples were obtained for determination of plasma TSH, T_4, and lipid levels. The tests were repeated at subsequent visits .The recruited patients received levothyroxine sodium once daily. Patients in evening group were given levothyroxine minimum 2 h after dinner, and those in morning group were given the same in the morning minimum half an hour before breakfast. Initial dosage was calculated as 1.6 mcg/kg body weight, and the closest commercially available dosage was started. Provision of dose adjustment of levothyroxine was kept on 2 weekly basis based on serum TSH level. Blood was collected for analysis of serum TSH, serum T_4 and lipid profile. Blood sample was collected in the morning after 12 h of overnight fasting.

Observation and result

Table 1 : Demograhic characteristics

Demographics	Morning Group(n = 38)	Evening Group(n = 38)	P value
Mean age	44.3 ± 4.7	46.5 ±5.4	0.76
Male :Female	18:20	19:19	0.65
BMI (Kg/M^2)	26.3±2.4	27.2± 3.1	0.43

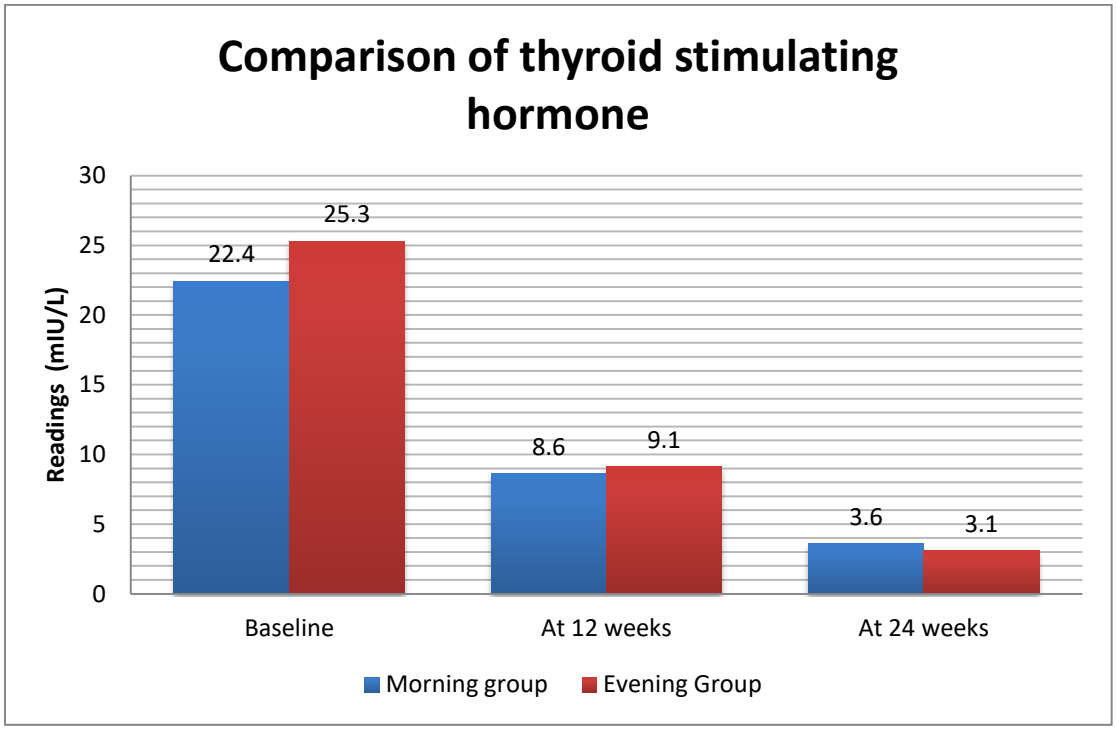

Fig 1:Comparison of thyroid stimulating hormone

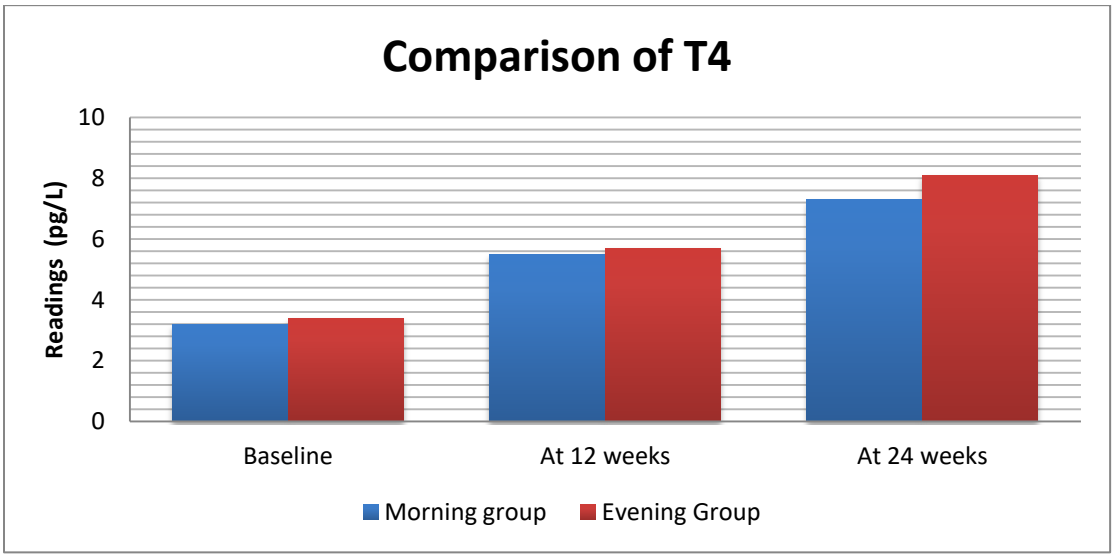

Fig 2:Comparison of T4

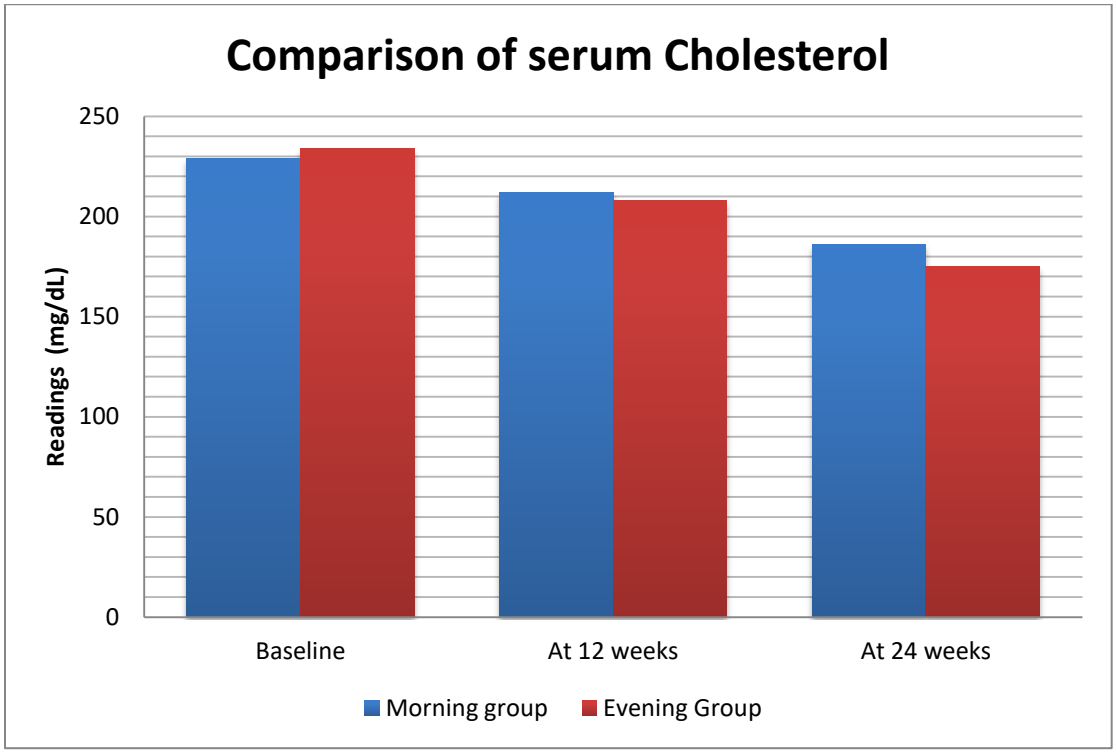

Fig 3:Comparison of serum cholesterol

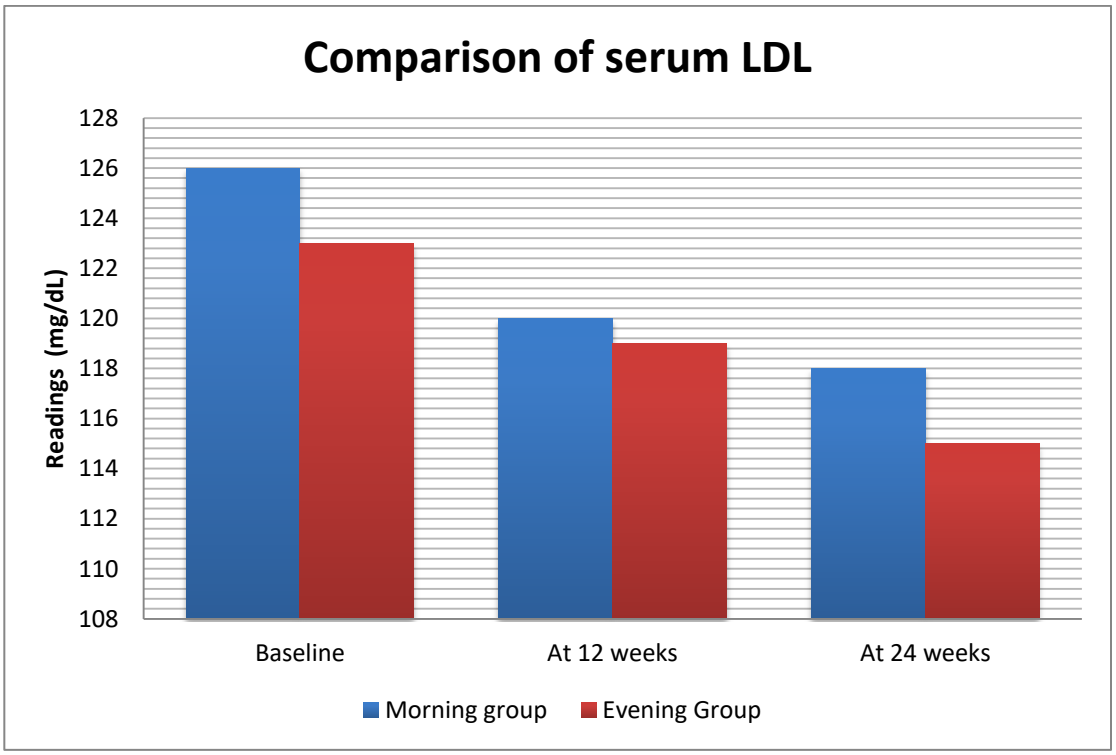

Fig 4:Comparison of serum LDL

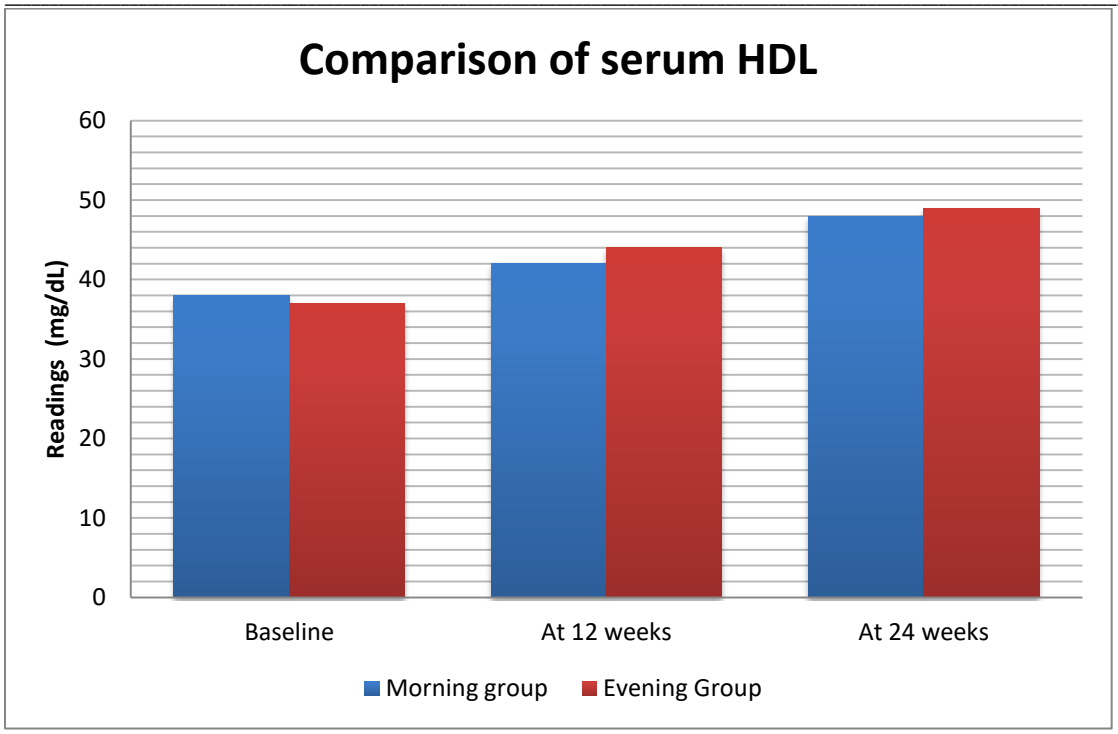

Fig 5:Comparison of serum LDL

Discussion

Present study noted that there was no statistically significant difference in the changes in serum TSH and T_4 level between patients taking evening dose of levothyroxine with those taking morning dose. Serum lipid profile over the 12 and 24 weeks period has not shown any statistically significant difference. Primary outcomes of this study are consistent with a similar study by Rajput et al [6].Analysis of present study suggest a possible option of changing the time of drug scheduling from the conventional morning dose to an evening dose. It will be beneficial to those who cannot remain compliant to every morning dose .The average dose of levothyroxine supplement needed to attain euthyroidism and the number of patients who achieved euthyroidism were minimally better in the evening group, although it was not statistically significant. Reason may be because of better absorption of drug in the evening schedule as to noninterference of food and relatively slowed gastric motility [7].Evening administration of levothyroxine may be advised for the drug to be taken at least 2 h after supper, so as to have hours of empty stomach. Consuming the levothyroxine in the morning, 30 minutes before breakfast might not result in significant bioavailability. In a study by Visser *et al*. ,they compared the outcome of morning with evening dose of administration of levothyroxine sodium. This study noted that levothyroxinescheduled at night significantly improved thyroid hormone levels, but plasma lipids showed no statistically significant change as compared to morning dose[5]. These observations prove the points of the present study that although night administration of levothyroxine is statistically may not be superior to morning schedule, it is also may not be inferior to morning dosing as far as total dose needed to achieve euthyroidism, number of patients achieving euthyroidism at 12 weeks and 24 weeks and lipid parameters. Major salient feature of the present study is that it involves optimum number of patients who are matched compared to all older studies.Majority of the subjects with levothyroxine as night dose in the present study find it more convenient and decided to continue with night schedule. Another significant issue was impact of levothyroxine on circadian rhythm and nocturnal TSH surge when given as night dose .The serum levels of TSH increase in the evening, reach a maximum near sleep-onset, and are followed by a progressive decrease during the night and low values during the day [8,9]. Visser *et al*. in their landmark study observed no change in the circadian rhythm of TSH when switching the time of levothyroxine ingestion to bedtime. There was no statistically significant change in T4, reverse 3,3',5'-triiodothyronine (rT3), albumin, and thyroxine binding globulin serum levels, or in the T3/rT3 ratio. Persani *et*

al. observed that bioactivity of Thyroid stimulating harmone has a circadian rythym with less bioactive and varied glycosylated TSH molecules secreted during night [10,11]. These notings bear important practical consequences inpresent study as the timed blood sampling for monitoring thyroid profiles can still be performed in the morning as per protocol even if the patient is scheduled levothyroxine as evening dose.Limitations of our study stand that exact interval between dinner and levothyroxine ingestion in the bedtime-dosing subjects was not documented. Meals are also standardised as fatty foods might interfere with absorption.

Conclusion

Present study concludes that evening schedule of Levothyroxine dose is as efficacious as morning dose in terms of thyroid profile and lipid profile. Hence, change of scheduling can be effected if needed to achieve better complaince.

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