Adequacy of Thyroid Hormone Replacement in a Tertiary Care Hospital in Nepal-An Observational Study

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Abstract

Background: The therapeutic goal in hypothyroidism is to achieve patients’ well-being and restore serum thyrotropin (TSH) to levels within the reference range. However, inadequate or over replacement is common in patients receiving levothyroxine. The Objective is to assess the treatment outcome of hypothyroid patients visiting outpatient clinic of medicine department of Kathmandu University Hospital, Dhulikhel, Nepal. Method: This is a cross sectional study on diagnosed Primary Hypothyroid patients who were taking levothyroxine replacement for at least six months. Patients were defined as euthyroid if their TSH was in the normal range (0.3-3.6 mmol/L) according to the hospital laboratory. Similarly patients were defined as over treated if TSH is <0.3 mmol/L and undertreated if TSH is >3.6 mmol/L. Results: A total number of 126 patients were enrolled for this study where mean age of participants was 40.88 ± 11.47 years and only 15 (11.1%) were male. Mean duration of hypothyroidism was 3.45 ± 2.57 years and mean Levothyroxine dose was 58.93 ± 26.89 mcg. In this study, nearly 70% of participants have normal TSH level. Similarly, 21% of participants have higher level of TSH and 9% have low TSH level. Multivariate logistic regression analysis did not show any significant correlation between treatment outcome and various variables. Conclusion: Treatment of hypothyroidism with levothyroxine being most effective, easily available, simple regimen and not costly, still one third of patients are not meeting the treatment outcome. However, being the pioneer study from Nepal, this study suggests improved treatment outcomes compared to similar studies from other countries.

Keywords: Primary Hypothyroidism, Treatment Outcome, Levothyroxine

Introduction

Diseases of the thyroid gland are amongst the most abundant endocrine disorder in the world second only to diabetes mellitus.¹ The spectrum of thyroid disorders includes hypothyroidism, subclinical hypothyroidism, hyperthyroidism and subclinical hyperthyroidism. The worldwide prevalence of spontaneous overt hypothyroidism is between 1% and 2% and ten times more common in women than in men.² The prevalence of overt hypothyroidism has been reported between 3.5% and 4.2% in various studies across India.³,⁴ Several studies in different parts of Nepal showed wide variation in prevalence of the thyroid dysfunctions.⁵,⁶,⁷

Thyroid hormone replacement with synthetic levothyroxine is the treatment of choice for hypothyroidism, commonest thyroid disorder.¹,⁷ The therapeutic goal in hypothyroidism is to achieve
patients’ well-being and restore serum thyrotropin (TSH) to levels within the reference range.\(^8\)

However, inadequate or over replacement is common in patients receiving levothyroxine.\(^9,10\) Abnormal thyroid function tests were also detected in a third of patients who self-reported thyroid disease or use of thyroid medications in the National Health and Nutritional Examinations Survey (NHANES III).\(^11\) Likewise, a study in older levothyroxine users showed that only 43% were biochemically euthyroid.\(^12\) Unfortunately, to the best of our knowledge, we do not have outcome study on diagnosed hypothyroid patients from Nepal. Thus, this study aim to assess the treatment outcome of hypothyroid patients visiting outpatient clinic of medicine department of Kathmandu University Hospital, Dhulikhel, Nepal.

**Methods**

This is a cross sectional study on diagnosed Primary Hypothyroid patients attending the Medicine OPD of Dhulikhel Hospital, Kathmandu University Hospital from November 2017 to April 2018. People aged 18 years or above and who are taking Levothyroxine for at least 6 months were included in this study. Once patients visit the outpatient clinic of medicine, their socio-demographic data including duration of hypothyroidism, recent TSH level, medicine they are taking, current dose and lab investigations are documented in one demography form after written consent. Patients were defined as euthyroid if their TSH was in the normal range (0.3-3.6 mmol/L) according to the hospital laboratory. Similarly patients were defined as over treated if TSH is <0.3 mmol/L and undertreated if TSH is >3.6 mmol/L. Adherence to Thyroxine therapy was assessed by asking the patients the number of doses missed in the last 1 month and was categorized as non-adherent if misses >15% of doses in last month.\(^13\) Data was analyzed using SPSS version 21.0 for windows. Descriptive statistics, such as frequency, percentage, mean and standard deviation was used to summarize patients’ baseline characteristics. Multivariable logistic regression model was fitted to determine independent predictors of treatment outcome when the p-value ≤ 0.1 on bivariate analysis. Statistical significance was considered at p-value < 0.05. This study was approved by KUSMS-IRC.

**Results**

A total number of 126 patients were enrolled for this study whose characteristics variables are shown on Table 1. The mean age of participants was 40.88 ± 11.47 years, where only 15 (11.1%) were male. Majority of them (62%) have education level below SLC. Mean duration of hypothyroidism was 3.45 ± 2.57 years and mean Levothyroxine dose was 58.93 ± 26.89 mcg. All of the participants were neither smoker nor alcoholic. Likewise, none of the participants were non adherent in this study.

Forty percentage of participants were on Levothyroxine 50 mcg. Likewise, 23% of participants were on Levothyroxine 25 and 50 mcg each as shown on (figure 1).

In this study, nearly 70% of participants have normal TSH level. Similarly, 21% of participants have higher level of TSH and 9% have low TSH level as shown in (figure 2). Multivariate logistic regression analysis did not show any significant co relation between treatment outcome and age, gender, education level, disease duration, other comorbid conditions.
Adequacy of thyroid hormone replacement in a tertiary care

Table 1: Characteristics of participants

| Variables                          | Mean ± SD / Number (%) |
|------------------------------------|------------------------|
| Age (years)                        | 40.88 ± 11.47          |
| Gender                             |                        |
| Male                               | 15 (11.1%)             |
| Female                             | 111 (88.1%)            |
| Education                          |                        |
| Below SLC                          | 78 (61.9%)             |
| Intermediate                       | 21 (16.66%)            |
| Bachelor & above                   | 27 (21.44%)            |
| Duration of Hypothyroidism (years) | 3.45 ± 2.57            |
| TSH level (current)                | 3.36 ± 2.84            |
| Free T4 level (mmol/L)             | 1.05 ± 0.24            |
| Daily Levothyroxine Dose (Mcg)     | 58.93 ± 26.89          |
| Weight (Kg)                        | 63.83 ± 15.07          |
| Blood Pressure                     |                        |
| SBP (mmHg)                         | 81.61 ± 15.78          |
| DBP (mmHg)                         | 81.61 ± 15.78          |
| Total Cholesterol (mmol/L)         | 171.83 ± 68.89         |
| HDL (mmol/L)                       | 43.01 ± 19.37          |
| LDL (mmol/L)                       | 98.66 ± 42.54          |
| TG (mmol/L)                        | 145 ± 72.07            |
| Diabetes Mellitus                  | 9 (7.12%)              |
| Hypertension                       | 9 (7.12%)              |
| Dyslipidemia                       | 9 (7.12%)              |

Figure 1: Proportion of patients taking daily Levothyroxine dose

Figure 2: Number of patients based on TSH level

Discussion

In this study, almost 70% of participants have achieved euthyroid status, similar to the National Health and Nutritional Examinations Survey14 and a general population study15 published on 2011. Several other studies have shown that less than half of hypothyroid patients achieved euthyroid status despite of regular dose titration and follow up13,16,17. The proportion of undertreated hypothyroid patients was 21% in our study15, which was 17% and much higher to other studies up to 45%13,16,17. Nearly 20% of participants had over replacement in one study15, in contrast which was only 9% in this study, similar to the other studies13,17. Whatever the percentage, there is similar trend on treatment outcome between various studies that overtreatment being the least prevalent.

Both under and over replacement with levothyroxine could lead to potential unwanted consequences. Hypothyroidism is associated with harmful effects on body weight18, lipid profile19, blood pressure20, and increased risk of sleep apnea21.

The mean daily dose of levothyroxine in this study was 0.92 mcg/Kg. This dose is much lower to the daily recommended dose of 1.6 mcg/Kg by various western guidelines such as the American Thyroid Association and American Association of Clinical Endocrinologists guidelines22. There is one Asian
Adequacy of thyroid hormone replacement in a tertiary care study from Singapore stating mean daily dose of levothyroxine was 1.1 mcg/kg\(^\text{17}\). In addition, this study also found that participants who were over replaced had a higher daily levothyroxine dose of 1.4 mcg/kg. Similarly this daily levothyroxine dose was 1.23 mcg/kg in an Indian study\(^\text{13}\).

Similar daily dose of levothyroxine in the euthyroid and under replaced group was seen in our study, similar to the study from Singapore, which suggests that the under replacement may be due to factors other than dosages, such as medication adherence and decreased bioavailability. However no participants reported non adherent in this study; in contrast it was 10% in an Indian study\(^\text{13}\) and 51.5% in another study\(^\text{17}\).

### Strength and limitations
To the best of our knowledge, this is the first study from Nepal on treatment outcome of primary hypothyroid patients. It highlighted the actual scenario of treatment outcome of primary hypothyroidism especially the magnitude of levothyroxine under and over replacement among this population. This study can be regarded as a pilot study especially on advocating the daily replacement dose of levothyroxine among Nepalese population.

Nevertheless, it has limitations. This is a cross sectional study and only provides a snapshot of the state of the management of condition, so it can not reflect the dynamic nature of the clinical practices amongst the physicians to achieve euthyroidism. Likewise, small sample size and only enrolling patients from a tertiary hospital may not be the representative data of Nepal.

### Conclusion
Treatment of hypothyroidism with levothyroxine being most effective, easily available, simple regimen and not costly, still one third of patients are not meeting the treatment outcome. However, being the pioneer study from Nepal, this study suggests improved treatment outcomes compared to similar studies from the other part of the world.

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### Conflicts of interest
The author declares there is no conflict of interest.

### Declarations

#### List of abbreviations

- TSH: Thyroid Stimulating Hormone
- NHANES: National Health and Nutritional Examinations Survey
- OPD: Outpatient Department
- SPSS: Statistical Package for The Social Sciences
- KUSMS IRC: Kathmandu University School of Medical Sciences Institutional Review Comittee
- SD: Standard Deviation
- SLC: School Leaving Certificate
- LDL: Low Density Lipoprotein
- HDL: High Density Lipoprotein
- TG: Triglyceride
- SBP: Systolic Blood Pressure
- DBP: Diastolic Blood Pressure

### Ethics approval
The study was conducted after the ethical approval from the Institutional Review Committee, Kathmandu University School of Medical Sciences. Participants were explained about the research detail, its significance, the benefit and harm in Nepali language before obtaining the consent, their queries were answered. A statement indicating that the participants have understood all the information in the consent form and are willing to participate voluntarily was obtained. Participants were able to withdraw from the study at any time without giving any reason during the study period. The confidentiality of participants was assured and code number was used in each interview schedule and name of the participants was not mentioned anywhere.
Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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Authors’ contributions
HKS: conceptualized, collected data, analyzed and wrote the manuscript. RT: collected data, AS: collected data. MU: collected data and analyzed, BS: analyzed data. All authors read and approved the final manuscript.

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