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Effects of Thyroxine Replacement on Glycosylated Haemoglobin Levels in Non-Diabetic Patients with Overt Hypothyroidism

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I. Introduction

The American Diabetes Association (ADA) endorsed using HbA1C for diagnosing diabetes and pre-diabetes. HbA1C is commonly used for assessing glycemic control.Normal HbA1c values are 4% to 5.7%.Pre-diabetes 5.7%–6.5%; diabetes mellitus > 6.5%.(1) It depends on both the RBC turnover from the bone marrow and the average levels of glycemia during the previous two to three months. In circumstances of altered erythrocyte turnover, the level of glycemia may not be accurately reflected by HbA1c.A falsely increased HbA1c is linked to diseases that have a limited RBC turnover (hypo proliferative anaemias).One of the causes of hypo proliferative anaemia, hypothyroidism, may induce a misleading rise of HbA1c, leading to a false diagnosis of pre-diabetes or diabetes.(2,3)

The main sign of hypothyroidism is decreased thyroid hormone production. Dilutional hyponatremia, anaemia, and hyperlipidaemia are common co-occurring conditions. In hypothyroidism, anaemia can be macrocytic, microcytic hypochromic, or normochromic. Normochromic normocytic anaemia is the most common form to occur in hypothyroidism. The cause of anaemia in hypothyroidism can be traced to either a nutritional iron deficit or the endocrine illness itself, where the diminished thyroid hormone levels suppress the bone marrow often leading to decreased erythrocyte production which may impact the life span of erythrocytes. The false rise of HbA1C values may be partially caused by altered erythrocyte life span.(4,5)

II. Aims And Objectives

- Identifying the impact of hypothyroidism on HbA1c levels in non-diabetic individuals.
- To check whether HbA1c decreases after treatment in hypothyroid patients.
- To evaluate the reliability of utilising HbA1c to identify diabetes in individuals with hypothyroidism.

III. Materials And Methods

This is a prospective study conducted in Department of General Medicine in tertiary care centre in Nellimarla during the study period of 1year i.e., from July 2021 to June 2022. 100 adult patients with overt hypothyroidism whoattended the OPD or admitted and who gave consent were included in the study. Patients with Diabetes mellitus (FBS ≥ 126 mg/dl, PPBS ≥ 200 mg/dl), impaired glucose tolerance (2h post 75g OGTT is between 140- 199 mg/dl), Hb< 10 g/dl, known hemoglobinopathies, Renal or Liver disorders, recent blood transfusions (<3 months) andpregnant women were excluded.

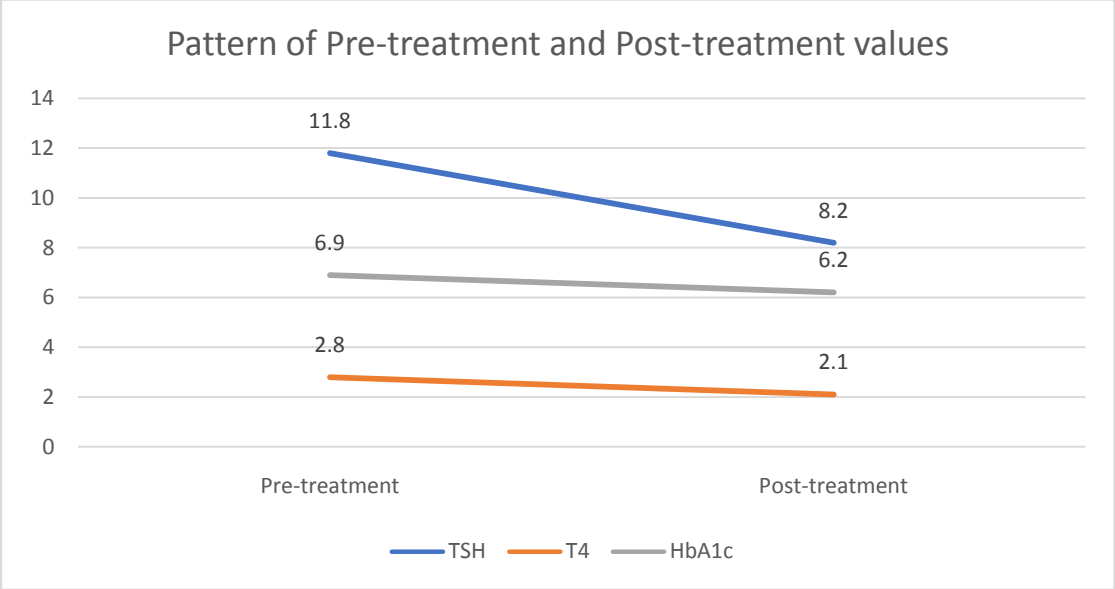
Subsequently, for three months, the patients started taking thyroxin supplements. According to TSH estimates, the medicine dose was gradually increased on a regular basis (every 4-6 weeks) until the patients were declared euthyroid, that is, had TSH between 0.5 and 5 IU/ml. The patient was permitted to continue receiving the same dose of thyroxin after being returned to euthyroid health for three months.

Both before and three months after being returned to a euthyroid condition, patients underwent testing for haemoglobin, HbA1c, reticulocyte count, andTSH/T4 in addition to a standard oral glucose tolerance test and results tabulated. Independent of changes in glucose indicators, the change in HbA1c was the primary outcome measured.

IV. Results

A total of 100 patients were included in the study. The mean age of the population was 39.5 ±3.4 years. Most patients belonged to the age group 31-40. 18% were males and 82% were females. The mean baseline TSH values were 11.8 IU/L. The mean baseline T4 values were 2.8 ng/dL. The mean pre-treatment HbA1c was 6.9. After 3 months of treatment, the mean TSH values were 8.2 IU/L, the mean T4 values were 2.1 ng/dL, and the mean HbA1c value was 6.2. The difference in pre-treatment and post-treatment values of TSH, T4 and HbA1c was statistically significant with *p*-value <0.05.

Variable	Mean Pre-treatment Values	Mean Post-treatment values
TSH (IU/L)	11.8	8.2
T4 (ng/dL)	2.8	2.1
HbA1c	6.9	6.2



V. Discussion

Even though the American Diabetes Association recommends HbA1c for diabetes mellitus diagnosis, HbA1c can misrepresent glycemia in certain settings. By changing the average lifespan of RBCs, RBC turnover disorders can affect HbA1c independently of diabetic state.Thus, conditions like iron insufficiency, vitamin B12 deficiency, or renal failure that have lower RBC turnover and mostof the older RBCs in circulation may have a falsely increased HbA1c.(2)Of the latter group, hypothyroidism is a prevalent endocrine disorder. Subclinical hypothyroidism dominates. Subclinical hypothyroidism affects 8-10%, 15% of women and 3% of males.Indeed, research conducted in our nation reveals that 3.9% to 10.95% of the general population exhibit overt hypothyroidism. Compared to the Western population, where the prevalence of overt hypothyroidism is only 0.3-0.4% of the adult population, these prevalence rates are substantially greater.(6,7) India therefore appears to have a significantly higher prevalence of hypothyroidism. Therefore, any effects of hypothyroidism on HbA1c are likely to be more of a problem in India than in Western nations. Thyroid hormones control metabolism and blood glucose. Hypothyroidism causes delayed digestion, gastric emptying, and insulin sensitivity. Diabetics have 10-15% thyroid disease.(8,9)

Our study included 100 overt hypothyroidism patients. Patients with FBS or PPBS in the diabetic range (i.e., FBS ≥ 126 mg/dl, PPBS ≥ 200 mg/dl) and impaired glucose tolerance (2h post 75g OGTT is between 140-199 mg/dl)were excluded from the study because they would need anti-diabetic medication or therapeutic lifestyle changes in addition to thyroxin treatment, which would introduce a confounding factor of diabetes treatment's effect on HbA1c. Only patients with normal glucose values or IFG/IGT were included.Due to the RBCs in circulation having a lifespan of about 120 days, a three-month follow-up was chosen.(2)

We recorded a female predominance in our study as with the previous studies. (2,3)The mean age of our study population was 39.5 ±3.4 years, which correlated well with the studies in literature. The mean baseline TSH and T4 values were 11.8 IU/L and 2.8 ng/dL respectively. The mean levels post treatment with thyroxine of TSH and T4 8.2 IU/L and 2.1 ng/dL respectively. The results were significantly significant. The mean pre-treatment HbA1c was 6.9 and post treatment was 6.2. The average HbA1c at baseline was already in the

prediabetes range, despite the average FBS and PPBS being normal. Therefore, if HbA1c alone is employed as the diagnostic test for hypothyroidism, there is a very significant false positive rate for the diagnosis of dysglycaemia.Kim et. al. also demonstrated this erroneous rise of HbA1c who demonstrated that despite the lower level of plasma fasting glucose in the hypothyroid people, the HbA1c in 45 hypothyroid patients was greater than that in control subjects (5.54 ± 0.43% vs. 5.34 ± 0.31% in hypothyroid patients and controls, respectively; $p < 0.001$).(3)Similar results were seen noted by Anantarapu et. al., (2) who found that almost 42% of overt hypothyroid patients had a false diagnosis of dysglycaemia.

Even while the FBS and the PPBS remained unchanged, the initially increased mean HbA1c was shown to decrease to a normal value after the hypothyroidism was corrected and maintained in the euthyroid state for up to 3 months. Kim et. al. reported results that was similar. thirty hypothyroid patients who had resumed using thyroxine. In their study, HbA1c decreased from 5.57± 0.26% at baseline to 5.37 ± 0.32% one month after starting thyroxin replacement, which correlated with our results. (3)

Similar findings were seen in Anantarapu et. al.'s study which showed a fall in the mean HbA1c levels from5.8 ± 0.7%pre-treatment to 5.6 ± 0.5% post treatment with thyroxine ($p = 0.009$). (2)This study also demonstrated that HbA1c did not correlate with reticulocyte % or haemoglobin.Reasons may include these. First, while the trial was powered to identify changes in HbA1c across pre- and post-treatment time periods, it may not be powered to assess causal relationships with reticulocyte percentage changes. Second, reticulocytes only represent the "youngest" RBCs in circulation. This work would have benefitted from a method to analyse the average age of RBCs in circulation at two different times, but none exists.

VI. Conclusion

To conclude, patients with hypothyroidism have HbA1c readings that are erroneously elevated and out of proportion to their level of glycemia. However, following treatment for hypothyroidism, it is decreased without affecting plasma glucose. Therefore, if HbA1c alone is utilised for diagnosis in patients with overt hypothyroidism, an erroneous diagnosis of dysglycemia may be made. Therefore, to identify prediabetes or type 2 diabetes in hypothyroid patients, only fasting plasma glucose or the oral glucose tolerance test (OGTT) should be used. Normalization of TSH levels results in a decrease in postprandial glucose levels, CRP, HbA1c, and lipids. This shows that L-thyroxine therapy has a considerable impact on glycemic management in people with subclinical hypothyroidism.

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