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ORIGINAL RESERCH

Evaluation of variation in glycosylated hemoglobin (HbA1c) levels by thyroxine replacement therapy in non-diabetic patients with overt hypothyroidism

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Abstract

Background: HbA1c is used for screening as well as for diagnosing Diabetes Mellitus (1)

- HbA1c - 4% – 5.7% - normal
- 5.7%- 6.5% - pre-diabetes
- 6.5%- diabetes mellitus.

It depends on ambient levels of glycemia over the preceeding 2-3 months but also on the RBC turnover from the bone marrow. HbA1c may not accurately reflect thelevel of glycemia in conditions of altered erythrocyte turnover. In which Conditions where RBCs turnover (hypo-proliferative anemias) is low, HbA1c level is falsely elevated.
Hypothyroidism being one of the causes of hypoproliferative anemia may lead to false elevation of HbA1c resulting in erroneous diagnosis of pre diabetes or diabetes (9).
Aim: To determine the effects of hypothyroidism on HbA1c levels in individuals without diabetes and to observe whether HbA1c falls in hypothyroid patients following treatment and o assess the validity of using HbA1c for diagnosing diabetes in hypothyroid patients.
Methods: This cross sectional observational study was conducted on 200 patients who were admitted and attending OPD in department of Medicine and ENT in tertiary care hospital, central india.
Results: Result from the our study is , HbA1c are falsely elevated out of proportion to the level of glycemia in patients with hypothyroidism which leads to false diagnosis of dysglycemia and it is lowered without any change in blood sugar levels after thyroine replacement and achievement of a euthyroidal state.
Keywords: HbA1c- glycosylated hemoglobin, GLUT 2- glucose transporter type 2, rT3- reverse T3, Overt Hypothyroidism, TSH, TRH, TFT.

Introduction

Hypothyroidism and diabetes mellitus are the two most common endocrine disorders encountered in clinical practice. Diabetes and hypothyroidism mutually influence each other and associations between both conditions have long been reported. Thyroid hormones

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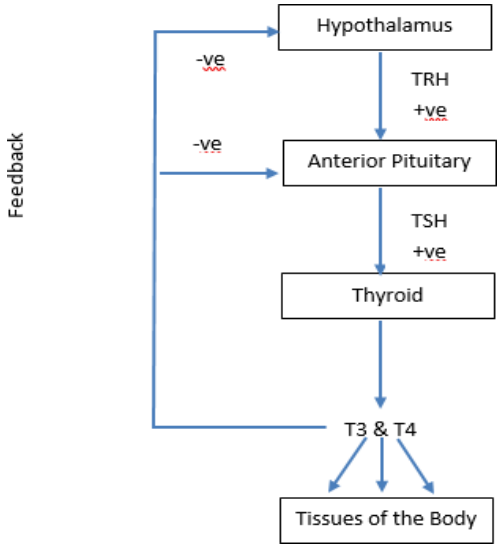
contribute to the regulation of carbohydrate metabolism and pancreatic function, and diabetes affects thyroid function tests to variable extents. In hypothyroidism glucose metabolism is affected via several mechanisms. Are duced rate of liver glucone ogenesis is observed in hypothyroidism a disresponsible for lower insulin requirement in hypothyroid diabetic patients. Recurrent hypoglycemic episodes are the presenting signs for the development of hypothyroidism in patients with type 1 diabetes. On the other hand, both clinical and subclinical hypothyroidisms have been recognized as insulin resistant states (7). Reduced glucose absorption from gastrointestinal tract accompanied by prolonged peripheral glucose accumulation; gluconeogenesis, decreased glycogenolysis and reduced disposal of glucose are hallmark sof hypothyroidism (4). In overtorsub clinical hypothyroidism, insulin resistance leads to glucose-stimulated insulin secretion. In subclinical hypothyroidism, diminished rate of insulin stimulated glucose transport rate caused by perturbed expression of glucose transporter type 2gene (GLUT 2) translocation may lead to insulin resistance. Moreover, due to reduced renal clearance of insulinin hypothyroid conditions, physiological requirements of insulin were diminished. Anorectic conditions in hypothyroidism may also contribute to reduced insulin in this state. An enhanced dose of insulin is required to ameliorate hypothyroidism, but the therapy warrants caution for adrenal or pituitary failure. Unmanaged diabetes, both type 1 and type 2, may induce a“low T3 state” characterized by low serum total and free T3 levels, increase inreverseT3 (rT3) but near normal serumT4 and TSH concentrations.

Hypothalamo pituitary axis

The hypothalamus produces Thyrotrophin Releasing Hormone **(TRH).** TRH stimulates thryotroph cells in the anterior pituitary to produce Thyroid Stimulating Hormone (TSH).

TSH is released in low amplitude pulses, following a circadian rhythm (In this case, there are higher levels at night and lower levels in the morning). TSH binds to receptors on follicular cells of the thyroid gland, stimulating the production of thyroid hormones: Tri-iodothyronine **(T3)** and Tetra-iodothyronine **(T4),** also known as Thyroxine. Control of this system is by a negative feedback mechanism: high levels of T3 and T4 inhibit TRH and TSH production by the hypothalamus and anterior pituitarygl and, respectively (5).



Reference values of thyroid function test

TSH	0.5 -4.7mU/L
T3	0.92-2.78nmol/L
FT3	0.22-6.78 pmol/L

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T4	58-140 nmol/L
FT4	10.3-35pmol/L

Causes of hypothyroidism (2)

Primary hypothyroidism	Iodine deficiency, auto immune thyroid it is, granulomato us thyroiditis, sub acute lymphocytic thyroiditis, postpartum thyroiditis, previous thyroidectomy, radio iodine treatment, previous radio therapyto the neck. Medication: lithium, amiodarone, interferonalpha, tyrosinekinaseinhibitors
Central hypothyroidism	Lesionsn of pituitaryeg pituitaryadenoma, craniopharyngioma, meningioma, glioma, metastasis, empty sella, surgery or radiation to the pituitary, drugs, injury, pituitary apoplexy, Sheehan syndrome, subarachnoidhemorrhage, autoimmune diseases (lymphocytic hypophysitis, polyglandular disorders), infiltrative diseases and infections like tuberculosis, mycoses, syphilis
Congenital hypothyroidism	Thyroid dysgenesis (75%), thyroid dyshormonogenesis (20%), maternal antibody orgeneticmutations Transiently: due to maternal liodine deficiency or excess, anti-TSH receptor antibodies, neonatal illness Central: pituitary dysfunction (idiopathic, septo-optic dysplasia, deficiency of PIT1, isolated TSH deficiency)

Central hypothyroidism

In this the TSH level is normal or low and free T_4 levels are low, this is suggestive of central hypothyroidism. There can also be other features of hypopituitarism.

Primary over thypothyroidism

TSH levels are high and T_4 and T_3 levels are low. Over thypothyroidism is diagnosed in those with a TSH of greater than10mIU/L.

Subclinical hypothyroidism

Subclinical hypothyroidism is characterized by an elevated serum TSH level, but with anormal serum free T4. The presentation of subclinical hypothyroidism is variable and classic signs and symptoms of hypothyroidism may not be observed (3).

Of people with subclinical hypothyroidism, a proportion will develop over thypothyroidism each year. Patient who have subclinical hypothyroidism are treated if thepatient is pregnant or TSH above 10 or if the patient has any underlying heart disease or positive TPO antibodies.

Diabetic practice guidelines for thyroid screening in patients with diabetes

- American Thyroid Association guidelines for detection of thyroid dysfunction–Patients with diabetes may require more frequent testing Recommends TSH 35 yrs, and every 5 yrs thereafter in all adults (6).
- American Association of Clinical Endocrinologists recommends TSH at diagnosis and at regular intervals, especially if goitre or other autoimmune disease is suspected.
- British Thyroid Association and Association of Clinical Biochemistry Guidelines, 2006 recommends TFT at baseline but routine annual TFT is not recommended. TSH and antibodies are recommended in diabetic patients in pregnancy and postpartum (8).

Material and methods

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This was a cross sectional observational study conducted in department of Internal medicine and ENT, in tertiary care center , central India. A total 200 patients diagnosed to Hypothyroidism in OPD and treated with thyroxine replacement. It was a Prospective study for duration of 6 Months. The study was conducted on non diabetic overt hypothyroid patients meeting the following criteria

Inclusion criteria

All patients with overt Hypothyroidism.

Exclusion criteria

- Diabetes mellitus (FBS>=126mg/dl, PPBS:>=200mg/dl)
- Impaired glucose tolerance (2hpost75gOGTTisbetween140-199mg/dl).
- Hb<10g/dl
- Known hemoglobin opathies
- Renal or Liver diseases.
- Recent blood transfusions (<3months)
- Pregnant patients

History from the patient was collected. Patients were followed up for a period of 6 months to check for FBS, PPBS and HbA1c levels before and after thyroxine replacement.

Laboratory investigations includes Complete blood count, Reticulocyte count, Fasting blood glucose, Post prandial blood glucose, HbA1c,TSH/T4, Liver and renal function tests

Observation and results

Table 1: Sample sized is tribution in the study group

Age	No. of cases	Percentage %
< 25	10	5%
26 – 35	30	15%
36 – 45	86	43%
> 45	74	37%
Total	200	100%

Table 2: Sex Distribution Among Participants

Sex	No. of cases
MALE	30
FEMALE	170
Total	200

Table 3: Baseline TSH Values of The Study Population

TSH	No. of cases
10 -20	132
21 -30	44
31 -40	14
>40	10
Total	200

Table 4: Baseline Total T4 In The Study Population

T4	No. of cases
≤1	60
1.1-2.0	98
2-4.5	42

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Total	200

Table 5: Pre-Treatment HbA1C

HbA1c	No. of cases
<5 .7	66
5 .7-6.5	120
>6.5	14
Total	200

From this chart we can infer that the baseline HbA1c was significantly high around 67% in hypothyroid patients inspite of having normal blood sugar levels. 14 out of 200 patients even had HbA1c in the diabetic range.

After 6 months of follow up these patients were again investigated for thyroid hormone profile (TSH) and HbA1c.

Table 6: Post-treatment TSH values among study population

TSH	No. of cases
≤3	56
3-4	70
4-5	74
Total	200

From this chart we can see that the TSH has significant declinedin our study population after thyroxine replacement.

Table 7: TSH values before and after thyroxine replacement

TSH	PRE	POST
Mean	20.00	3.66
S.D	9.16	0.81
P'	<0.001	Sig

The mean TSH before and after thyroxine treatment has significantly declined andit is statistically significant with a standarad deviation of 0.81 after treatment. Pvalue<0.001

Table 8: T4 levels before and after thyroxine replacement

T4	PRE	POST
Mean	1.55	7.85
S.D	0.81	1.94
P'	<0.001	Sig

From this table we see that the T4 levels have significantly increased post treatment with a standard deviation of 1.94. p value <0.001 which is statiscally significant.

Table 9: HBA1C Post Thyroxin Replacement

HbA1c	No. of cases
<5.7	200
≤5.7-6.5	0
>6.5	0
Total	200

This table shows that all the patients in the study population had a normal HbA1c level after thyroxine replacement and achievement of a euthyroid state.

Table 10: HbA1c levels before and after thyroxine replacement

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HbA1c	PRE	POST
Mean	5.83	5.25
S.D	0.35	0.21
P'	<0.001	Sig

The mean HbA1c significantly decreased post thyroxine replacement and achievement of euthyroid alstate. P value is <0.001which is statistically significant.

Discussion

In our study majority of the patients belong to age group 36-45 (43%). Females were more in number (85%).The baseline TSH values on an average was between (10-20) in 66% of the study population. T4 levels were between 1.1-2.0 in 49% of patients. In these patients the post treatment FBS and PPBS were with normal limits. The HbA1c estimation was done and was found to be increased. The average HbA1c was around5.83%.

This lead to false diagnosis of dysglycemia in 67% of patients. False diagnosis of impaired glucose tolerance 60% and diabetes was 7%. This false elevation ofHbA1c was also demonstrated by Kim and cols who showed that HbA1c in 45 hypothyroid patients was higher than in control group A study by Anantarapu et al. (3) also demonstrated false elevation of HbA1c values in patients with hypothyroidism which was lowered by thyroid hormone replacement without any change in fasting or OGTT values (1).

After thyroxine replacement and achievement of euthyroidal state, followup was done for 3 months post achieving euthyroidal state on account of approximately 120 days of life span of RBC. The T4 and T4 on the average was found to be TSH-3.66 and T4- 7.85 within normal range, although there was no difference in fasting and post prandial blood sugars the mean HbA1c decreased to 5.25% These findings were similar to a study done by Kwon H S et al published in diabetes care journal in 2010 which show ednochanges in FBS and PPBS following correction of hypothyroidism.

Treatment of hypothyroidism

Thyroid hormone can be started at anticipated full replacement doses in individual's that are young and otherwise healthy. In elderly patients and those with known ischemic heart disease, treatment should begin with one fourth to one half the expected dosages, and the dosage should be adjusted in small increments after no less than 4-6 weeks. For mostcases of mild to moderate hypothyroidism, a starting levothyroxine dosage of 50-75µg/day will suffice (10).

Clinical benefits begin in 3-5 days and level off after 4-6 weeks. Achieving a TSH level within the reference range may take several months because of delayed readaptation of the hypothalamic-pituitary axis. In patients receiving treatment with LT4, dosing changes should be made every 6-8 weeks until the patient's TSH is intargetrange. In patients with central (i.e., pituitary or hypothalamic) hypothyroidism, T4 levels rather than TSH levels are used to guide treatment.

The updated guidelines on hypothyroidism issued by the American Thyroid Association in 2014 maintain the recommendation of levothyroxine as the preparation of choice for hypothyroidism, with the following considerations:

- If levothyroxine dose requirements are much higher than expected, consider evaluating for gastro intestinal disorders such as Helicobacterpylori–related gastritis, atrophic gastritis,or celiac disease; if such disorders are detected and effectively treated, re-evaluation of thyroidfunction and levothyroxine dosage is recommended.
- Initiation or discontinuation of estrogen and androgens should be followed by reassessment of serum TSH at steady state, since such medications may alter levothyroxine requirement.

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- When deciding on a starting dose of levothyroxine, the patient's weight, lean body mass, pregnancy status, etiology of hypothyroidism, degree of TSH elevation, age, and general clinical context, including the presence of cardiac disease, should be considered. The serum TSH goal appropriate for the clinical situation should also be considered.
- Thyroid hormone therapy should be initiated as an initial full replacement or as partial replacement with gradual increments in the dose titrated upward using serum TSH as the goal.
- Dose adjustments should be made upon significant changes in body weight, with aging, and with pregnancy; TSH assessment should be performed 4-6 weeks after any dosage change.

Conclusion

Its concluded from the above study that HbA1c are false lyelevated out of proportion to the level of glycemia in patients with hypothyroidism which leads to false diagnosis of dysglycemia and it is lowered without any change in blood sugar levels after thyroine replacement and achievement of a euthyroidal state.

Therefore in hypothyroid patients diagnosis of pre diabetes or diabetes should only be based on fasting blood glucose and post prandial blood glucose.

So we conclude that HbA1c is not a valid test for diagnosis of pre diabetes or diabetes in the presence of hypothyroidism.

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