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Diagnosis of diabetes mellitus on the basis of HbA1c: Is this true in hypothyroidism also?

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ABSTRACT

Background: Hypothyroidism may leads to hypoproliferative anemia. It is possible that this reduced erythropoiesis might result to false elevation of HbA1c in some cases and further leading to an erroneous diagnosis of pre diabetes or diabetes. **Aims and Objectives:** This study was designed to assess changes in HbA1c after initiation of thyroxine replacement in patients with subclinical and overt hypothyroidism. **Settings and Design:** This prospective study was conducted at Department of General Medicine of a tertiary care centre over one year. **Materials and Methods:** One-hundred subjects were recruited for the study. Fasting blood glucose, serum creatinine, hemoglobin, HbA1c, reticulocyte count, serum free T4 and TSH estimation done in all subjects. Hypothyroid patients were started on thyroxine. After three months of documentation of euthyroidism, same investigations were repeated.**Statistical Analysis Used:** Statistical software, SPSS version 17.0 was used for analysis. **Results:** After correction of hypothyroidism, TSH decreased from 92.3(±30.9) to 3.4±2.9 μIU/L in overt hypothyroidism and from 12.2(±4.5) to 4.4±2.9 μIU/ml in subclinical hypothyroidism respectively. There was a statistically significant fall in the HbA1c (SD) from 5.9% (0.8) to 5.6% (0.6) and 6.0% (0.3) to 5.7% (0.3) following the correction of hypothyroidism in overt hypothyroidism and subclinical hypothyroidism respectively. However, there were no statistically significant changes in the fasting as well as postprandial blood glucose. **Conclusions:** Our study demonstrated that HbA1c values are falsely increased in patients with hypothyroidism. This falsely raised HbA1c became normal after thyroxine supplement.

Key words: Hypothyroidism, Anemia, Glycosylated haemoglobin, Euthyroidism, Reticulocyte count

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INTRODUCTION

Glycosylated hemoglobin (HbA1C) is commonly used for diagnosing diabetes mellitus as well as assessment of glycemic status of the diabetic patients. A value ≥ 6.5% is considered diagnostic of diabetes mellitus while value ≥ 5.7% but < 6.5% was considered to represent pre-diabetes.[1,2] Conditions that are associated with decreased red blood cells (RBC) production, with a predominance of older RBCs in circulation are associated with a falsely elevated HbA1c. Hypothyroidism may lead to either microcytic hypochromic anemia, normocytic normochromic or macrocytic anemia.[3,4] The etiology of anemia in hypothyroidism can be related to the nutritional iron deficiency or to the endocrine disorder itself where the lowered thyroid hormone levels often results in decreased erythrocyte production which may affect the life span of erythrocytes. It is possible that this reduced erythropoiesis might results in false elevation of HbA1c in some cases and further leading to an erroneous diagnosis of pre diabetes or diabetes.[5] Hence this study was designed to evaluate the changes in HbA1c after initiation of thyroxine replacement in patients with subclinical and overt hypothyroidism.

MATERIALS AND METHODS

Study design

This is a prospective study.

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Study setup
This study is conducted at Department of General Medicine of a tertiary care centre.

Study duration
The duration of study was one year; November-2014 to October-2015.

Sampling
Purposive sampling technique is used for selection of desired samples according to inclusion criterion.

Sample size
One thousand patients of general medicine department of a tertiary care centre were evaluated for possible inclusion in study. Out of these 100 subjects were recruited for the study after fulfilling inclusion criteria.

Inclusion criteria
All adults with symptoms of hypothyroidism with thyroid stimulating hormone (TSH) > 5.5 μIU/mL were included in this study.

Exclusion criteria
Patients with history of diabetes mellitus, chronic kidney disease, hemolytic anemia, bone marrow suppression or blood transfusion in last 3 months were excluded from the study.

METHODS

Demographic characters like age, sex, height, weight of all subjects were noted. Fasting blood glucose (FBG), serum creatinine, hemoglobin (Hb), HbA1c, reticulocyte count, serum free T4 and TSH estimation was done in all participants. Patients were classified into three groups based on HbA1c as per ADA guidelines. Patients were labelled as euglycemia (HbA1c < 5.7%), prediabetes (HbA1c 5.7-6.5) and diabetes mellitus (HbA1c ≥ 6.5%). Blood sample for blood glucose was collected again 2 hours after breakfast. Patients with fasting blood glucose (FBG) ≥ 110 but < 126 mg/dl were labelled as having impaired fasting glucose (IFG), while those with 2 hrs postmeal blood glucose (PBG) ≥ 140 mg/dl but < 200 mg/dl were labelled having impaired glucose tolerance (IGT). Prediabetics had either IFG or IGT or both. Patients with FPG ≥ 126 mg/dl or PBG ≥ 200 mg/dl were excluded from the study.

The diagnosis of hypothyroidism was based on clinical grounds, biochemically on suppressed levels of free Thyroxine T4 (58-161 nmol/L) and increased TSH (> 5.5 μIU/L) using immune assay.

Patients were started on thyroxine supplements in the dose of 25-50 mcg. The dose of the drug increased every 6 weeks step wise, based on TSH estimations till the patients were rendered euthyroid (TSH 0.3-5.5 μIU/ml). After three months of documentation of euthyroidism, all investigations as done before were repeated.

Ethical consideration
Prior to conduct of the present study, the protocol of the study was submitted to ethical and scientific committee of hospital. After getting due approval from these two committees, the present study was initiated. Also prior to conduct of study related procedure/investigation, a voluntary written informed consent was taken from the patient/legally acceptable representative.

Statistical technique
The demographic data of 100 subjects was analysed by statistical software, SPSS version 17.0. Continuous variables were compared with same parameters measured 3 months after the restoration of euthyroidism using two tailed paired t test with a p value of < 0.05 being considered as significant.

Financial input and funding
The patient underwent procedures as per protocol laid down by our institution for management of such patients. Hence there was no financial burden on patient or institution. This project was not funded by any of pharmaceutical/diagnostic industry.

RESULTS

A total of 100 subjects with symptoms of hypothyroidism with TSH > 5.5 μIU/mL were recruited for the study over a period of one year. Baseline patient characteristics are given below in Table 1.

Mean age (SD) of overt hypothyroid and subclinical hypothyroidism subjects was 40.2 (9.8) and 46.6 (10.8) years respectively. Female preponderance was seen in both groups. Baseline BMI was 28.5 and 25.7 in overt hypothyroidism and subclinical hypothyroidism subjects respectively. After treatment with thyroxine, BMI decreased in both groups. Serum creatinine was normal in all subjects and it remained same after treatment also. Free T4 was low in overt hypothyroidism and it increased significantly after treatment while in subclinical hypothyroidism, free T4 was within normal limits before and after treatment. After correction of hypothyroidism, TSH decreased from 92.3(±30.9) to 3.4±2.9 μIU/L and 12.2(±4.5) to 4.4±2.9 μIU/ml in overt hypothyroidism and subclinical hypothyroidism respectively. Hemoglobin and reticulocyte count was normal before and after treatment in both groups.

Table 1: Baseline characteristics of recruited subjects

Parameters	Overt hypothyroidism			Subclinical hypothyroidism		
	Pre-therapy	Post-therapy	p value	Pre-therapy	Post-therapy	p value
Age (years)	40.2±9.8		-	46.6±10.8		-
Sex (F:M Ratio)	27:3		-	60:10		-
BMI (kg/m^2)	28.5±3.2	27.2±2.2	NS	25.7±1.8	24.4±1.1	NS
Serum creatinine (mg/dl)	0.78±0.2	0.77±0.18	NS	0.79±0.19	0.80±0.20	NS
Free T4 (nmol/L)	38±12.8	90.2±20.1	p<0.005	78.1±16.4	100±11.4	p<0.005
TSH (μIU/L)	92.3±30.9	3.4±2.9	p<0.005	12.2±4.5	4.4±2.9	p<0.005
Hb (gm/dl)	12.1±1.2	12.2±1.1	NS	11.9±2.6	11.8±2.9	NS
Reticulocyte count (%)	1.4±0.1	1.3±0.2	NS	1.2±0.2	1.1±0.4	NS
FBG (mg/dl)	85.4±12.4	86.3±11.3	NS	88.2±10.7	90.1±9.9	NS
PBG (mg/dl)	121±14.5	120±11.9	NS	122.7±12.8	121.7±9.9	NS
HbA1c (%)	5.9±0.8	5.6±0.6	p=0.04	6.0±0.3	5.7±0.3	p=0.04

NS: Nonsignificant (p>0.05)

There was a statistically significant fall in the HbA1c (SD) from 5.9% (0.8) to 5.6% (0.6) and 6.0% (0.3) to 5.7% (0.3) following the correction of hypothyroidism in overt hypothyroidism and subclinical hypothyroidism respectively. However, there were no statistically significant changes in the fasting and the 2 hr post postprandial blood glucose.

DISCUSSION

HbA1c has been recommended for the diagnosis of diabetes mellitus by American Diabetes Association.[6] However, HbA1c use remained controversial in certain conditions, where RBC turnover is low. In these conditions HbA1c does not accurately reflect sugar levels. Thus disorders with decreased RBC lifespan and dominance of older RBCs in circulation, like iron deficiency anemia,[7,8] megaloblastic anemia,[7] or chronic renal failure,[9] can have a falsely elevated HbA1c.

We enrolled newly diagnosed patients with overt and subclinical hypothyroidism. Those patients with FBG or PBG in the diabetic range (i.e FPG ≥ 126 mg/dl and PBG ≥ 200 mg/dl) were excluded from the study as they would require oral hypoglycemic drugs immediately. These oral hypoglycemic drugs will also lower HbA1c and thus we will unable to see effect of thyroxine on HbA1c. Only patients with normal glucose values were thus included. Despite the mean FPG and PBG being normal, the mean HbA1c at baseline was already in the prediabetes range. Therefore in hypothyroidism there is a very high false positive rate for the diagnosis of diabetes mellitus, if HbA1c alone is used as the diagnostic test. This false elevation of HbA1c was also demonstrated by Kim et al.,[10] who showed that HbA1c in 45 hypothyroid patients was higher than that in control subjects (5.54 ± 0.43% vs. 5.34 ± 0.31% in hypothyroid patients and controls respectively; $p < 0.001$), despite the lower level of plasma fasting glucose in the hypothyroid individuals.

Another study by Christy et al selected 30 hypothyroid, non diabetic patients with normocytic normochromic anemia and compared these patients with 30 euthyroid non diabetic patients also with normocytic normochromic anemia. HbA1c in the hypothyroid patients was 6.32 ± 0.75% vs. 5.87 ± 0.46% in the euthyroid group, the difference being statistically significant.[11] The correlation which was seen in this study was also shown by another study which significantly correlated TSH and HbA1c ($r = 0.46$, $p < 0.05$).[12]

Anantarapu et al.[13] showed the comparison between the HbA1c, FBG and PBG at baseline and at 3 months after the correction of hypothyroidism. While there was a fall in the HbA1c from 5.8 ± 0.7% to 5.6 ± 0.5% ($p = 0.009$) following the treatment of hypothyroidism, there were no corresponding changes in the FBG and PBG.

After achieving euthyroidism for at least 3 months, HbA1c decreased to a normal value, despite there being no change in the FBG and the PBG. Similar findings were also reported by Kim et al.[10] in their 30 hypothyroid patients who were reported to have normal HbA1c after thyroxin replacement.

Though there was a mean fall in BMI of approximately 1.3 kg/m^2 from baseline following the treatment of hypothyroidism, the blood glucose values remained unchanged. Decrease in the HbA1c cannot be attributed to the fall in the BMI. Because only mechanism by which BMI can affect HbA1c is through the level of sugar, which has remained unaffected between baseline and post therapy in our study.

CONCLUSION

Our study demonstrated that HbA1c values are falsely increased in patients with hypothyroidism. This falsely raised HbA1c became normal after thyroxine supplement.

Therefore in hypothyroid patients, diagnosis of diabetes mellitus should be done after fulfilling fasting sugar, postprandial sugar and oral glucose tolerance test criteria.

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Authors Contribution:
AS and PK - Concept and design of the study, definition of intellectual content, literature search, clinical studies, experimental studies, data acquisition and analysis, manuscript preparation and final approval.

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