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STUDY OF EFFECTS OF THYROID DYSFUNCTION ON GLYCATED HAEMOGLOBIN IN NON-DIABETIC SUBJECTS

Endocrinology

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ABSTRACT

Introduction: Glycated hemoglobin (HbA1c) has been considered as an important marker of long term glycemic control. A value between 5.7% and 6.5% represents prediabetes while a value 6.5% is considered as diabetes mellitus. Conditions which are associated with a low RBC turnover, with a predominance of older cells in circulation are associated with a falsely elevated HbA1c in which hypothyroidism is an important and common etiological factor. We designed this study to determine the effects of thyroid dysfunction on HbA1C level in non diabetic subjects.

Material and method: HbA1c level and reticulocyte count were measured in 100 non diabetic subjects those were newly diagnosed hypothyroidism and hyperthyroidism (Group I) and who were already diagnosed hypo and hyperthyroidism in euthyroid state after treatment (Group II). We compared HbA1C and RC between group I and group II.

Results: HbA1C level significantly high in newly diagnosed hypothyroidism in comparison to treated hypothyroid patients (5.95±0.57 vs 5.34 ± 0.45, P value =0.0001) and among hyperthyroid patients HbA1C level (5.34±0.36 vs 5.2 ± 0.39 , P value= 0.2176) which was not significant (>0.05). A positive Correlation between the levels of TSH and HbA1C in hypothyroid patient by Pearson's correlation coefficient.

Reticulocyte count also significantly low in newly diagnosed hypothyroidism patients(1.14 ±0.43 vs 1.54 ± 0.38 P value=0.0012).Correlation between the levels of Reticulocyte count and HbA1C in Group I by Pearson's correlation coefficient is negative {r = -0.3585, p < 0.0001 (S)} which means there is a tendency for high HbA1C scores to go with low RC scores.

Conclusion: HbA1C levels was significantly higher among hypothyroidism patients which was in pre-diabetic range despite normal blood sugar levels. Significant difference not observed in hyperthyroid patient.

KEYWORDS

HbA1C (Glycosylated hemoglobin), TSH(Thyroid stimulating hormone), RC(Reticulocyte count).

INTRODUCTION:

The American Diabetes Association has suggested the use of glycated hemoglobin (HbA1c) as a screening as well as diagnostic tool for prediabetes and diabetes. A value between 5.7% and 6.5% represents pre diabetes while a value ≥6.5% is considered as diabetes mellitus[1,2]. The glycated hemoglobin represents the fraction of haemoglobin that undergoes nonenzymatic glycation over the circulatory life span of the erythrocyte (usually 120 days)[3,4]. It is not only depends on the ambient level of glycemia but also on the average period of exposure of the circulatory red blood cell (RBC)[5]. There are many well established factors which also affect the HbA1c level independent to blood glucose level include hypoplastic anaemia ie. Iron deficiency anaemia[6,7], Vitamin B12 deficincy and Renal failure[8] .Among the hypoplastic anaemia hypothyroidism[9,10] is an important and common etiological factor , which may be associated with false elevation of HbA1c.

Indeed studies in our country show that overt hypothyroidism is found in 3.9% to 10.95% of the general population[11,12]. India seems to be having a much higher burden of hypothyroidism. Thus any impact of hypothyroidism on HbA1c is likely to be a bigger issue in India than in the Western countries[13]. Present study was planned to assess correlation between thyroid dysfunction and glycosylated haemoglobin level in non-diabetic patients.

AIMS AND OBJECTIVES:

The objective of our study was to determine the the effects of thyroid dysfunction on HbA1c level in non diabetic subjects with overt hypothyroidism and hyperthyroidism.

MATERIAL AND METHODS:

This cross sectional study was conducted in Department of medicine at J.L.N. Medical college, Ajmer from June 2017 to May 2018. After taking informed consent we enrolled 100 number of patients from both genders between 18 and 60 years of age group visiting to medicine OPD and admitted in different wards. Those who were newly diagnosed hypothyroidism(n=25) and hyperthyroidism(n=25) include in Group I and who were already diagnosed hypothyroidism(n=25) and hyperthyroidism(n=25) taking treatment in euthyroid state include in Group II.

Selected patients investigated for routine investigation like fasting and postprandial (after 2 hrs) blood sugar, haemoglobin, S.creatinine, Blood urea and lipid profile. We also measured T3,T4,TSH by Chemiluminescence immuno assay(CLIA) method, HbA1c by latex agglutination inhibition assay with HbA1C R1-Antibody and HbA1C R2-Agglutinator reagent. Reticulocyte count by staining of peripheral blood smear with a supravital stain (new methylene blue) and expressed as a percentage of total red blood cells. HbA1c was compared in both groups respectively.

The baseline variables were compared using student t-test (unpaired). Rates and proportions among categorical variable were calculated using Chi-square test. Pearson's correlation coefficient was conducted to assess associations between variables HbA1c, TSH and reticulocyte count. P value <0.05 was considered statistically significant.

Exclusion Criteria:

1. Patients with diabetes (defined as fasting plasma glucose ≥126mg/dl or 2h post prandial plasma glucose ≥200mg/dl.
2. Patients with anemia(hemoglobin < 10g/dl) and hemoglobinopathies, hemolytic anaemia, bone marrow disorder like aplastic anaemia, myelodysplastic syndrome or recent (<3 months) blood transfusion were excluded.
3. Chronic kidney disease, chronic liver disease, other chronic illness and pregnancy.
4. Patient on drugs like aspirin, Dapsone or Vitamin C (>500mg/day) and erythropoietin

OBSERVATION:

Among studied groups baseline parameters in Group I and Group II are given below in table 1.

Table – 1: Baseline Parameters in Group I and Group II

Parameters	Group I (n=50)		Group II (n=50)	
	Hypothyroidism	Hyperthyroidism	Hypothyroidism	Hyperthyroidism
	(n=25)	(n=25)	(n=25)	(n=25)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Age	38.16 ± 12.18	40.48 ± 9.44	43.44 ± 9.45	43.36 ± 7.4

BMI	24.78 ± 2.78	21.27 ± 2.45	25.26± 2.47	23.70 ± 2.25
Hb	12.10 ± 1.71	11.82 ± 1.15	12.36 ± 1.36	12.58 ± 1.67
Blood Urea	24.24 ± 4.01	28.96 ± 5.9	26.4 ± 4.94	30.2 ± 5.06
S.Creatinine	0.85 ± 0.16	0.86 ± 0.19	0.86 ± 0.15	0.88 ± 0.14
Total Chol.	175.32 ± 14.41	164.52 ± 24.61	141.5 ± 26.49	156.7 ± 26.45
TG	138.04 ± 7.87	127.16 ± 19.30	118 ± 24.1	120 ± 23.2
LDL	119.44 ± 20.82	121.44 ± 19.83	120 ± 22.9	130 ± 16.4
B.Sugar(F)	83.48 ± 7.28	83.32 ± 6.78	85.32 ± 8.17	82.8 ± 7.71
B.Sugar(PP)	116.5 ± 6.09	114.72 ± 6.07	114.88 ± 6.08	114.88 ± 5.79

In our study most of the cases were in age group between 30-50 years with female predominance (76% in hypothyroid cases and 72% in hyperthyroid cases).

There was no statistically significant difference between the Group-I and Group II for age , sex, fasting blood sugar, post prandial blood sugar, hemoglobin, serum urea , serum creatinine and lipid profile. So we can say that the levels of HbA1C and reticulocyte count were not affected by age , sex, blood sugar levels, hemoglobin, renal function and lipid profile.

Table:2

	HbA1C	P value	RC	P value
Hypothyroidism (Group I)	5.95±0.57	**P = 0.0001 (S)**	1.14 ±0.43	**P= 0.0012 (S)**
Hypothyroidism (Group II)	5.34 ± 0.45		1.54 ± 0.38	
Hyperthyroidism (Group I)	5.34±0.36	**P = 0.2176 (NS)**	1.72 ± 0.40	**P = 0.0401 (S)**
Hyperthyroidism (Group II)	5.2 ± 0.39		1.48 ± 0.41	

The mean HbA1C among patients with hypothyroidism in Group I was 5.95±0.57 and in Group II was 5.34 ± 0.45.After applying student t-test(unpaired) p value comes 0.0001 which is statistically significant(<0.05) . Among hyperthyroid patients mean HbA1c in Group I was 5.34±0.36 and in Group II was 5.2 ± 0.39 having p value 0.2176 which was not significant (>0.05).

A positive association was observed between HbA1C and Hypothyroidism patients (Group I and Group II) by chi-square test (x2=11.5385,p value-.000682) and this association was statistically significant (<0.05). A weak association was observed between HbA1C and Hyperthyroidism patients (Group I and Group II) and this Association was not statistically significant (>0.05) (x2=1.495, p value-0.22144).

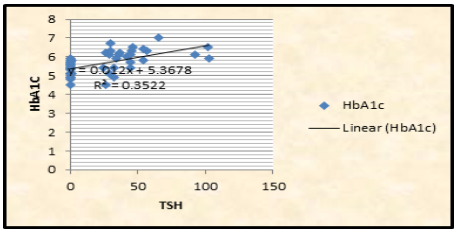

Figure:1 A positive Correlation found between the levels of TSH and HbA1C in Group I by Pearson's correlation coefficient which means there is a tendency for high TSH scores go with high HbA1C scores (and vice versa).

The mean RC among patients with hypothyroidism in Group I was 1.14 ±0.43 and in Group II was 1.54 ± 0.38.After applying student unpaired t-test p value comes 0.0012 which was statistically significant (<0.05) and among hyperthyroid patients in Group I was 1.72 ± 0.40 and in Group II was 1.48 ± 0.41 and having p value =0.0401 which was statistically significant(<0.05).

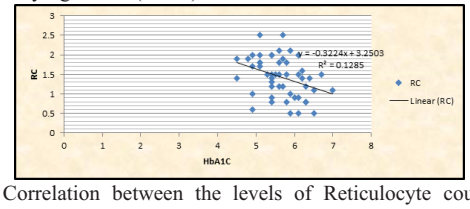

Fig.2 Correlation between the levels of Reticulocyte count and HbA1C in Group I by Pearson's correlation coefficient is negative {r = -0.3585, p < 0.0001 (S)} which means there is a tendency for high HbA1C scores to go with low RC scores (and vice versa).

DISCUSSION:

HbA1C is a well established diagnostic marker of diabetes mellitus. However, there has been concern about the use of HbA1C in certain conditions where it does not accurately reflect the level of glycemia. Conditions which have reduced turnover of RBCs shows falsely elevated HbA1C levels. These conditions include iron deficiency anaemia,vitamin B12 deficiency, renal failure, hemoglobinopathies and pregnancy[6,7].

Among the hypoplastic erythropoiesis, an important and common etiological factor is hypothyroidism[9,10] which is associated with reduced erythropoiesis may result in a false elevation of HbA1c.

The mean serumTSH level significantly heigher in Group I newly diagnosed hypothyroidism compared with GroupII hypothyroidism in euthyroid state on treatment (p <0.0001).

In our study the mean HbA1C among patients with hypothyroidism in Group I was 5.95±0.57 and in Group II was 5.34 ± 0.45 with p value =0.0001 which is statistically significant (<0.05). In this study we also found that there was statistically significant correlation by Pearson's correlation coefficient between the levels of serum TSH and HbA1c in Group I subjects. This effect was possibly due to low RBC turnover in hypothyroid patients.

Kim MK et al(2010)[14] in their study found that HbA1c in 45 hypothyroid patients was higher than in control subject (5.54 ± 0.43% *vs*. 5.34 ± 0.31%). Difference was statistically significant with p value < 0.001, despite the normal level of plasma fasting glucose in the hypothyroid individuals. They also found that level of HbA1C was fall to normal value after thyroxine replacement despite no change in fasting and postprandial blood glucose.

Anantarapu S et al(2015)[15] study found similar result that false elevation of HbA1c values in patients with hypothyroidism which was lowered by thyroxine replacement without any change in fasting or OGTT values. HbA1c fall from 5.8 ± 0.7% to 5.6 ± 0.5% (p = 0.009) at 3 months following the correction of hypothyroidism.

A study by Bhattacharjee R et al(2016)[16] studied in 47 hypothyroid and 46 controls and found level of HbA1c value higher in hypothyroid group (5.6 ± 0.07 vs. 5.2 ± 0.04 in controls); which was statistically significant higher with p value < 0.001 .

In our study mean HbA1c among newly hyperthyroid patients in Group I was 5.34±0.36 and in Group II was 5.2 ± 0.39 with p value=0.2176 which was not statistically significant (>0.05)**.** Similar result was observed by Bhattacharjee R et al[83] who observed that mean HbA1C among hyperthyroid patients was 5.3 ±0.5 vs 5.2 ± 0.04 in controls which was not statistically significant.(p=0.174).

A weak association was observed between HbA1C and Hyperthyroidism patients (Group I and Group II) and this association was not statistically significant with [x2=1.495, p value-0.22144(>0.05)].

This could possibly be due to promotion of glycation by malondialdehyde which is produced by lipid peroxidation induced by excessive thyroid hormones[17]. This phenomenon might have counterbalanced an increased RBC turnover seen in hyperthyroid patients. Thus mean HbA1c value did not change significantly after treatment of hyperthyroidism.

HbA1c and Reticulocyte count

In hypothyroid patients the mean reticulocyte count in Group I was

1.14 ±0.43 and in Group II was 1.54 ± 0.38 which was statistically significant with p value=0.0012 and among hyperthyroid patients in Group I was 1.72 ± 0.40 and in Group II was 1.48 ± 0.41 (p=0.0401) which was statistically significant(<0.05). This suggests hypothyroidism is a state of hypoproliferation which is associated with reduced RBC turnover and low reticulocyte count.

In our Group I and Group II hyperthyroidism patients there is significant difference between reticulocyte count which shows mean reticulocyte count decrease in Group II hyperthyroidism patient receiving treatment which favours Bhattacharjee R et al(2016)[16] study. They found that among hypothyroid patients the reticulocyte count was lower compared to control and increased significantly following treatment in hypothyroid patients (0.9 ± 0.575 vs. 1.9 ± 0.77; $P <$ 0.001), however, decreased significantly after treatment in hyperthyroid group, (1.485 ± 0.56 vs. 1.035 ± 0.39; $P < 0.001$).

Kim MK et al(2010)[14] also found similar result that there was increase in reticulocyte count in hypothyroid patients after treatment with l-thyroxine (p<0.001).

There is a negative correlation between the levels of Reticulocyte count and HbA1C in Group I by Pearson's correlation coefficient [r = -0.3585, p < 0.0001 (S)] , which means there is a tendency for high HbA1C scores to go with low RC scores (and vice versa).

CONCLUSION:

We found that HbA1C levels was significantly higher among hypothyroidism patients which was in pre-diabetic range despite normal blood sugar levels. The reason for this might be due to effect of thyroid hormones on erythropoiesis. Hypothyroidism is a state of decreased RBC turnover leading to falsely elevated HbA1C levels. Hence in our study we concluded that in hypothyroidism patient falsely elevated HbA1c should be keep in mind while interpretating HbA1c level.

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