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A study of glycated hemoglobin (HbA1C) in non diabetic hypothyroid population of Gujarat, India

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Abstract
Background: Glycated hemoglobin (HbA1c) can be altered in different conditions. We hypothesize that HbA1c levels may change due to altered thyroid status, possibly due to changes in red blood cell (RBC) turnover.
Objective: The Objective of the study is to measure glycated hemoglobin (HbA1C) in non diabetic hypothyroid population
Material and Methods: Study includes total 200 partcipants and they were divided in to case (n=100, Among them 50 hypothyroid and 50 euthyroid) [25 microcytic hypochromic anaemia, 25 normocytic normochromic anaemia and 50 non anemic patients] and age and sex matched healthy control (n=100) group**.**HbA1C level,plasma glucose level and anemia status of all participants were assessed. Anaemia status was determined by Hemoglobin, red cell indices and peripheral smear and Glycemic status was determined by fasting Plasma glucose and HbA1c.Obtained data was analyzed statistically and compared with each other to see the difference of significance by calculating p value.
Results: The Glycated hemoglobin (HbA1C) level in hypothyroid patients with microcytic hypochromic anaemia was 6.40 ± 0.57% and normocytic normochromic anaemia was 6.22 ± 0.41%. The HbA1C level levels in euthyroid patients with microcytic hypochromic anaemia was 6.42 ± 0.98% and normocytic normochromic anaemia was 6.0± 0.39 % While hypothyroid non anemic patients showed A1C levels of 5.9 ± 0.29% against 5.39 ± 0.68% of euthyroid non anemic controls.
Conclusion: Baseline HbA1c levels were found to be significantly higher in hypothyroid patients compared to control individuals despite similar glucose levels. HbA1c reduced significantly with treatment in hypothyroid patients without a significant change in glucose levels. Significant baseline or posttreatment change was not observed in hyperthyroid patients. Our study suggests that HbA1c data should be interpreted with caution in patients with hypothyroidism.

Keywords: HbA1C, Hypothyroidism, Diabetes, Anaemia

Introduction
HbA1C is widely used for the assessment of glycemic status of the diabetic patients and the American Diabetes Association (ADA) recommended its use for diagnosing diabetes [1]. Studies have shown variation in HbA1C levels in different conditions like Haemoglobinopathies, chronic kidney diseases, pregnancy even in the absence of diabetes mellitus [2]. Conditions that can affect erythrocyte turnover or survival may falsely elevate or lower the A1C levels [3]. Recent studies have shown its spurious elevation in hypothyroidism in the absence of diabetes.
Several factors influence HbA1c among them glucose is the most important one affecting HbA1c [4]. The type of assay used might also well influence the HbA1c value. Some haemoglobin traits, such as HbS, HbC, HbF and HbE, interfere with some HbA1c assay methods. Haemolytic anaemia, blood transfusion, major blood loss, malaria etc. are the some of the conditions where in HbA1c results many not be obtained accurately [5, 6]. Apart from the aforementioned conditions some other morbidities like renal failure, iron deficiency anaemia, uraemia etc. are also speculated to influence HbA1c levels. However, one cannot be conclusive as further research is going on.

Material and methods
This Retrospective study was conducted at Parul sevashram hospital, Parul institute of medical science and research, Vadodara, Gujarat from May 2017 to Nov 2018.
The data of the patients attending Parul sevashram hospital from May 2017 to Nov 2018 was collected.
We collected the data of 500 subjects aged 25 years and above who had HbA1C, peripheral smear, Haemoglobin, mean corpuscular Haemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular Haemoglobin concentration (MCHC), serum TSH and plasma glucose levels estimated.
A total of 200 were found to be non-diabetic who were diagnosed as having Hypothyroidism based on their TSH levels. It was made sure that the patients were non-diabetic (Fasting Plasma Glucose <100 mg/dl) and HbA1C estimation was carried out.
Of these 50 non anemic subjects and 150 anemic subjects were selected. Out of the anemic cases 25 subjects with hypochromic microcytic anaemia and 25 subjects with normocytic normochromic anaemia were selected and 100 were excluded based on exclusion criteria mentioned below.
Similarly 25 microcytic hypochromic anemic, 25 normocytic normochromic anemic and 50 non anemic euthyroid controls matched for sex and plasma glucose levels were included in our study.
Microcytic hypochromic anaemia was defined as microcytic hypochromic picture on peripheral smear, low Hb levels (<12g% in males, <11g% in female), predominantly microcytic indices (MCV<76 fL) and hypochromic indices

(MCH<27 pg/cell).
Normocytic normochromic anaemia was defined as low Hb levels, normocytic normochromic red cell indices and peripheral smear picture.

Exclusion criteria
Patients having any hemolytic diseases, Haemoglobinopathies, kidney disorder, Pregnant patients or any major systemic disorder were excluded from our study.
Estimation of Glycated hemoglobin Hba1c was done on Alere Affinion AS100 based on affinity chromatography along with Quality control material.
Measurement of thyroid hormone TSH and ferritin was done on Beckman coulter Access 2 based on chemiluminance.
Haemoglobin and red cell indices were estimated using 5 part Bene sphera automated cell counter
Plasma glucose estimation was done by glucose oxidase peroxidase method using transasia ERBA EM 200.
Data was analysed by using online student t-test calculator. P-valueless than 0.01 was consider as a significant.

Results
Study includes total 200 participants and they were divided in to case (n=100) group [25 microcytic hypochromic anaemia, 25 normocytic normochromic anaemia and 50 non anemic patients] and age and sex matched healthy control (n=100) group
Subject characteristic are as shown in [Table -1].
Females showed more predisposition towards being hypothyroid and anemic than males.

Table 1: showing various hematology and biochemical parameter of case group (n=100) and subgroups

Type	Microcytic hypochromic(n=25)	Normocytic normochromic(n=25)	Non anemic(n=50)
Hemoglobin(gm/dl)	9.36 ± 1.1	10.8±0.50	13.2±1.10
Ferittin(ng/ml)	10.32±5.1	156.3±35.12	220.0±19.2
TSH (μIU/ml)	15.3±5.0	18.0±6.0	20.5±8.1
Plasma Glucose(mg/dl)	94±5.1	88±6.5	86±7.1
MCV(fl)	50.56±12	80.5±8.9	86.9±5.1
MCH(pg/cell)	16.2±5.7	26.9±6.1	30.5±2.4
Female:male ratio	20:5	18:7	35:15

Table 2: Distribution of HbA1C (%) in hypothyroid and euthyroid case group

Group	Hypothyroid [HbA1C (%)]			Euthyroid [HbA1C (%)]		
	Total (50)	Male (35)	Female (25)	Total(50)	Male(25)	Female(25)
Microcytic Hypochromic	6.40±0.57	6.50±0.33	6.70±0.81	6.42±0.98	6.46±0.77	6.39±1.2
Normocytic Normochromic	6.22±0.41	5.77±0.31	6.67±0.51	6.0±0.39	6.12±0.23	5.9±0.56
Non anemic	5.9±0.29	5.72±0.20	5.61±0.25	5.45±0.55	5.39±0.68	5.51±0.43

Table 3: Comaparision of HbA1C (%) in hypothyroid anemic VS Non anemic

Group	Comparision	Subject(N)	Result [HbA1C (%)]	P-value
Microcytic Hypochromic VS Non anemic	Microcytic Hypochromic	25	6.40	<0.01
	Non anemic	50	5.90	
Normocytic Hypochromic VS Non anemic	Normocytic Hypochromic	25	6.20	<0.01
	Non anemic	50	5.90	

Table 4: Comaparision of HbA1C (%) in Euthyroid anemic VS Non anemic

Group	Comparision	Subject(N)	Result [HbA1C (%)]	P-value
Microcytic Hypochromic VS Non anemic	Microcytic Hypochromic	25	6.42	<0.01
	Non anemic	50	5.45	
Normocytic Hypochromic VS Non anemic	Normocytic Hypochromic	25	6.0	<0.01
	Non anemic	50	5.45	

HbA1C levels in different types of anaemia are as shown in [Table/Fig-2]. According to the table HbA1C levels in normocytic normochromic anaemia were lower (6.22 ± 0.41) as compared to the microcytic hypochromic anaemia (6.40 ± 0.57) and differences between their respective control groups were statistically significant.
Difference in level of HbA1c between anemic and non anemic group of both hypothyroid and euthyroid patients was calculated by using P-value. There was significant difference was found between anemic and non anemic group of both hypothyroid and euthyroid patients.

Discussion
In Indian population hypothyroidism and diabetes are the most common endocrine disorders. 10-15% of prevelance is seen with thyroid disease and diabetes [7, 8]. Patients showed elevated HbA1C not only in the presence of diabetes but also in non-diabetic subjects in hypothyroid individuals. Hence the role of HbA1C as a marker of diabetes was questioned in such conditions. Studies were done to evaluate the cause of these elevated HbA1C, Kim *et al*. [9] found in their study that they were attributed to anaemia associated with it. A number of studies have shown association with iron deficiency anaemia and elevated HbA1C levels.
Chronic kidney diseases and pregnancy are conditions where iron deficiency anaemia play a pivotal role in elevating HbA1C levels [10, 11]. Normocytic normochromic anaemia is seen in hypothyroidism which may be early iron deficiency anaemia due to nutritional deficiency.
Hypothyroidism and anaemia is more in females and these

are more vulnerable to have elevated HbA1C even in the absence of diabetes mellitus. We had more females than males in our study.

Kim *et al*. [9] found elevated A1C in overt hypothyroid patients and by giving thyroxine therapy it was lowered. Since we could not obtain the post therapy data of the patients, our study could not explain the effect of thyroid hormone therapy on HbA1C levels.

Kim *et al.* found improvement in red cell indices after thyroid hormone therapy and Hardikar *et al*. [12] found in their study that blood indices were lower in prediabetic and diabetic group classified on the basis of HbA1C levels when compared to normoglycemic group. Previous studies have found association between red cell survival and elevated A1c levels. Hence, red cell survival time gives a better explanation than red cell mor phology for HbA1c levels. We did not measure the erythrocyte lifespan, which was one of the limitations of our study.

Our results showed elevation of HbA1C in microcytic hypochromic and normocytic normochromic anaemia patients. Elevation was more in microcytic hypochromic anaemia. Etiology of microcytic anaemia may be iron deficiency, early stages of anaemia due to endocrine diseases, thalassemia and anaemia of chronic diseases [13].

There was no significant correlation found between plasma glucose levels and TSH. Patients suffering from diabetes showed association in previous studies. Our study subjects were non-diabetic, hence presence of diabetes could be a criteria for plasma glucose levels to be associated with TSH.

All the cases are non-diabetic and most of the factors which can interfere with glycation of Haemoglobin like chronic kidney diseases, Haemoglobinopathies, pregnancy and Haemolytic anaemia were excluded, which strengthen our study.

Conclusion

Baseline HbA1c levels were found to be significantly higher in hypothyroid patients compared to control individuals despite similar glucose levels. HbA1c reduced significantly with treatment in hypothyroid patients without a significant change in glucose levels. Significant baseline or posttreatment change was not observed in hyperthyroid patients. Our study suggests that HbA1c data should be interpreted with caution in patients with hypothyroidism.

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