To See Correlation of Elevated HBA1C in Hypothyroid Individuals with Anaemia: If Any.

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ABSTRACT

Introduction: Glycosylated Hemoglobin A1c (HbA1c) is formed by the glycation of the valine of the β-chain of hemoglobin and used commonly as a screening test for diabetes in clinical practice. (1) ADA endorsed an HbA1c ≥ 6.5% as diagnostic for diabetes. Hence current research aimed to study whether elevated Hba_{1C} in Hypothyroidism has any correlation with anaemia.

Material and methods: 140 non diabetic hypothyroid patients were selected and their Hba_{1C} was done (40 microcytic hypochromic anaemia, 40 normocytic normochromic, 60 non anaemia) and 140 age, sex, fasting glucose level and anaemia status matched controls were selected. Diabetes was excluded by doing fasting and post prandial blood sugar levels. We excluded pregnant patients, patients having haemolytic anaemia, other haemoglobinopathies, anaemia due to other chronic illnesses, renal disease that shorten erythrocyte survival may proportionately decrease Hba_{1C} levels and are also associated with iron deficiency.

Results: In hypothyroid individuals Hba_{1C} with microcytic hypochromic anaemia and normocytic normochromic anaemia was 6.94 ± 0.28% and 6.29 ± 0.62 while in euthyroid anaemic matched control it was 6.02± 0.26 and 5.24 ± 0.24%. Hypothyroid non anaemic patients showed HbA1c level of 5.28± 0.24% and that of euthyroid it was 5.34±0.48% and patient of Hba_{1C} > 6.5 in hypothyroid patients had significant odds ratio. Diabetes was excluded by doing fasting and post prandial blood sugar levels.

Conclusion: Non diabetic hypothyroid patients may show elevated Hba_{1C} of pre diabetic range with anaemia. So in such patients we should take care before making diagnosis of diabetes.

Keywords: Hypothyroidism, Hba_{1C}, Diabetes.

INTRODUCTION

Glycosylated Hemoglobin A1c (HbA1c) is formed by the glycation of the valine of the β-chain of hemoglobin and used commonly as a screening test for diabetes in clinical practice.[1] ADA endorsed an HbA1c ≥ 6.5% as diagnostic for diabetes.[1]

Many studies have reported that depletion of iron stores may alter the glycation rate of hemoglobin and elevate Hba_{1C} concentrations, independent of glucose level.[2] Iron deficiency is the most common nutritional deficiency,[3] Very few studies had been done to see the correlation of HbA1c with iron deficiency anemia. Menstruation and pregnancy is an important cause of iron loss in reproductive age group. In the Third National Health and Nutrition Examination 1988-1994 and more than 11% women had iron deficiency anemia.[3,4]

We will study whether elevated Hba_{1C} in Hypothyroidism has any correlation with anaemia and hypothesized that Hba1c is elevated in iron deficiency anemia and hypothesized other factors associated with HbA1c and iron deficiency including age, race/ethnicity, and waist circumference would persist after adjustment.

MATERIAL AND METHODS

Study Population

140 non diabetic hypothyroid patients of age between 18-45 years were selected from OPD and IPD of Rohilkhand Medical College and hospital, Bareilly between January 2016 to july 2016 and approval was taken by institutional research and ethics committee. After getting a informed consent patients complete blood count, iron studies, and Hba_{1C} levels were done (40 microcytic hypochromic anaemia, 40 normocytic normochromic, 60 non anaemia) and 140 age, sex, fasting glucose level and anaemia status matched controls were selected. Diabetes was excluded by doing fasting and post prandial blood sugar levels. We excluded pregnant patients, patients having haemolytic anaemia, other haemoglobinopathies, anaemia due to other chronic illnesses, renal disease that shorten erythrocyte survival may proportionately decrease Hba_{1C} levels and are also associated with iron deficiency,[5] but the degree of renal impairment at which anemia occurs is unclear.[6] CKD patients were also excluded, defined as a glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2 or GFR from 60 to 90 ml/min/1.73 m^2 with microalbuminuria[7] from the primary analysis.

Main Outcome Measures

Hba_{1C} measurements were performed by chromatographic method in the laboratory of our college.

89% sensitivity was in patients with Hba1c of 5.5% and 80% specificity when it was compared with fasting glucose, and sensitivity of 67% sensitivity was in patients with Hba1c of 6.1% and a 98% specificity when compared to fasting glucose levels ≥ 126 mg/dl to detect diabetes.[8]

Independent variables

Patients having two of the following three indices: erythrocyte protoporphyrin levels > 70 ug/dl red blood cells; ferritin ≤ 15 ug/L, and transferrin saturation levels < 16%.[3] were diagnosed as a case of iron deficiency anemia. Hemoglobin level of < 12.0 g/dl for women and < 13.5 g/dl for men.[3] was diagnosed as a case of anemia.

Several factors have served as confounders due to their associations with both Hba_{1C} and iron deficiency anemia

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including age[9,11] race[9,10] and obesity, particularly visceral adiposity.[10,11] Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared and waist circumference is reported in centimeters.

STATISTICAL ANALYSIS

We constructed several types of multivariable models. We compared and examined the distribution of Hba_{1C} between participants with and without iron deficiency.

IBM SPSS Statistics 20 was used to analyse data. Anova with Tukey's test was applied for comparison of group means and Mean ± SD was used to present data.

Correlation between two variables was done and pearson's coefficient of correlation was calculated.

$\chi 2$ test was analysed by categorical data. Logistic regression analyses was calculated for odds ratio and 95% confidence intervals (CIs). P value less than 0.05 was considered statistically significant.

To determine if the association between iron deficiency and HbA1c was independent of glycemia, we had gone for fasting glucose to exclude diabetes. Eight hours fasting was done prior appointment time.

RESULTS

Subject characteristic are as shown in Table 1. Females showed more predisposition towards being hypothyroid and anemic than males

HbA1C was around 6.52± 0.70in anemic cases as compared to 5.80 ± 0.38 of non anemic cases. HbA1C levels in different types of anaemia are as shown in Table 2. According to the table lower HbA1C levels in normocytic normochromic anaemia (6.24 ± 0.70) as compared to the microcytic hypochromic anaemia (6.52± 0.70) and differences between their respective control groups were statistically significant

As shown in Table 3 patients having HbA1C >6.5 odds were 3.154 (1.325-7.014). No significant odds ratio of patients with overt hypothyroidism (0.999 [0.111-2.013])

DISCUSSION

Results showed elevation of HbA1C in anaemia patients. Elevation was more in microcytic hypochromic anaemia. Etiology of microcytic anaemia may be iron deficiency,thalassemia and anaemia of chronic diseases. Because we had excluded anaemia due to other Haemoglobinopathies and chronic diseases, based on the ferritin levels we could ascertain that those with iron deficiency anaemia had higher levels of HbA1C when compared to anaemia of endocrine diseases.

In Indian population hypothyroidism and diabetes are the most common endocrine disorders. 10-15% of prevelance is seen with thyroid disease and diabetes.[12,13] 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.,[14] 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.[15] chronic kidney diseases and pregnancy are conditions where iron deficiency anaemia play a pivotal role in elevating HbA1C levels.[16,17] 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. HbA1C above 6.5% had more odds ratio in anemic patients. Anemic patients have more odds of being misdiagnosed as having diabetes when compared to non anemic subjects. Correlation was not significant between TSH and HbA1C levels in our study and Odds of Patients with overt hypothyroidism

Type	Microcytic Hypochromic	Normocytic Normochromic	Non-anemic
Haemoglobin (g/dl)	8.46 ± 1.32	8.84 ± 1.64	13.4 ± 1.98
Ferritin (ng/ml)	12.43 ± 3.54	173.2 ± 28.45	203.40 ± 22.8
MCV (fL)	544.6 ± 5.88	76.43 ± 6.68	86.8 ± 5.6
MCH (pg/cell)	16.4 ± 3.8	36.8 ± 5.9	32.8 ± 2.02
Plasma Glucose (mg/dl)	86.02 ± 5.1	86.1 ± 5.3	87.3 ± 7.6
TSH (µIU/ml)	45.15 ± 12.8	35.22 ± 10.15	40.55 ± 11.5
Female: Male ratio	32:8	30:10	48:12

Table-1: Females showed more predisposition towards being hypothyroid and anemic than males

	Hypothyroid			Euthyroid		
Group	Total	Female	Male	Total	Female	Male
Microcytic hypochromic	6.52± 0.70**	6.57 ± 0.79***	6.25 ± 0.40*	6.14 ± 1.87	6.17 ± 2.04	6.12 ± 0.76
Normocytic normochromic	6.24 ± 0.70*	6.30± 0.50***	6 ± 0.28*	5.76 ± 0.38	6.04 ± 0.43	5.20 ± 0.17
Non-anemic	5.80 ± 0.38	5.89 ± 0.32*	5.60 ± 0.24	5.38 ± 0.60	5.58 ± 0.50	5.36 ± 0.64

Table-2: Distribution of HbA1C (%)in hypothyroid cases and controls according to type of anemia *p <0.05, **p <0.001, ***p<0.0001

	Female (HbA1C >6.5)		Male(HbA1C >6.5)		Total (HbA1C>6.5)	
	Odds ratio	95% Confidence interval.	Odds ratio	95% Confidence interval	Odds ratio	95% Confidence interval
Anemia	3.203*	1.128-6.324	3.014	0.965-6.543	3.154*	1.325-7.014
TSH>14	1.010	0.234-1.256	0.786	0.345-4.312	0.999	0.111-2.013

Table-3: A1C>6.5 with odds ratio for anaemia and degree of hypothyroidism *p <0.05

had non significant odds ratio for HbA1C > 6.5%. Hence effect of severity of hypothyroidism on HbA1C levels could not be explained by this study. Kim et al.,[14] 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.

There was no significant correlation found between HbA1c and erythrocyte indices in case of normocytic normochromic anaemia but significant negative correlation was found between hypochromic index in microcytic hypochromic anaemia and HbA1C (MCH, r=-0.58, p= 0.05). Kim et al.,[14] found improvement in red cell indices after thyroid hormone therapy and pallavi et al.,[18] 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.[19,20] Hence, red cell survival time gives a better explanation than red cell mor [hology for HbA1c levels. We did not measure the erythrocyte lifespan, which was one of the limitations of our study.

HbA1C and TSH had no significant correlation. No significant odds ratio for HbA1C>6.5 for overt hypothyroidism. In a study done on diabetic subjects, amela et al[21] found positive correlation between HbA1C TSH and. Our subjects were non-diabetic, hence presence of diabetes could be a criteria for TSH associated with HbA1c.[21]

Plasma glucose levels and TSH has no significant correlation. Patients suffering from diabetes showed association in previous studies. Presence of diabetes could be a criteria for plasma glucose levels to be associated with TSH, as all patients were non diabetic.

We excluded pregnant patients, patients having haemolytic anaemia, other haemoglobinopathies, anaemia due to other chronic illnesses, renal disease that shorten erythrocyte survival may proportionately decrease Hba_{1C} levels and are also associated with iron deficiency

The limitations however include inability to measure the RBC life span and also the lack of knowledge of treatment. The findings of the study also need to be validated in larger cohort.

CONCLUSION

Non diabetic hypothyroid patients may show elevated Hba_{1C} of pre diabetic range with anaemia. Hence care must be taken when making a diagnosis of diabetes in such patients.

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