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Original Article

Screening of Subclinical Hypothyroidism and Glycosylated Hemoglobin Levels in Healthy Subjects Attending Rural Tertiary Care Centre in Western U.P. (Hapur)

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ABSTRACT

Background: *Subclinical hypothyroidism is defined as an elevated serum TSH level and normal concentrations of free T3 (FT3), free T4 (FT4), T3 and T4. A positive association between thyroid and diabetes mellitus is well recognized but to study the effect of thyroid disorders on glucose metabolism in non-diabetic patients is an area for extensive research. Present study was planned to assess correlation between subclinical hypothyroidism and glycosylated hemoglobin levels in non-diabetic patients.*

Methods: *A case-control study was conducted on total 209 subjects. 109 patients were allotted in case group and 100 in control group. Controls were relatives and friends of patients who were matched for age and sex. Comparison between the case and the control groups were made using Student's t-test (unpaired) and Box and Whisker Plot and regression graph were presented for correlation between serum TSH and HbA1c.*

Results: *It was found that there was a positive correlation between the levels of serum TSH (μU/L) and HbA1c (%) in all the participants of the study by Pearson's correlation coefficient ($r=0.35$, $p < 0.0001$).*

Conclusion*: HbA1c levels are increased in subclinical hypothyroid patients. The effects of the elevated levels of Serum TSH on the HbA1c must be considered when interpreting the HbA1c for the diagnosis of diabetes or prediabetes in the subclinical hypothyroid patients.*

Keywords: *Subclinical Hypothyroidism, Glycosylated Haemoglobin, Serum TSH.*

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INTRODUCTION

People with diabetes had an increased risk of developing thyroid disorder. Around 6% of general population had some form of thyroid disorder. However, the prevalence of thyroid disorder increases to above 10% in people with diabetes. Studies suggest that people with one form of autoimmune disorder had an increased chance of developing other autoimmune disorders; people with T1DM had a higher risk of autoimmune thyroid disorder. Up to 30% of women with T1DM had some form of autoimmune thyroid disease. 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 HbA1c 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]

METHODS

Study Population

140 non-diabetic hypothyroid patients of age between 18-45 years were selected from OPD and IPD of Saraswathi institute of medical sciences, Hapur between January 2017

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to July 2018 and approval was taken by institutional research and ethics committee. After getting an informed consent patients complete blood count, iron studies, and Hba1c levels were done. Total 140 patients in which 40 were microcytic hypochromic anemia, 40 were normocytic normochromic and 60 were non-anemia. 140 age, sex, fasting glucose level and anemia status matched controls were selected. Diabetes was excluded by doing fasting and post prandial blood sugar levels. We excluded pregnant patients, patients having hemolytic anemia, other hemoglobinopathies, anemia due to other chronic illnesses, renal disease that shorten erythrocyte survival may proportionately decrease Hba1c 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 microalbuminuria7 from the primary analysis.

Main Outcome Measures

HbA1c 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 Hba1c and iron deficiency anemia

STATISTICAL ANALYSIS

We constructed several types of multivariable models. We compared and examined the distribution of Hba1c 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. χ^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.

RESULTS

Subject characteristic is as shown in Table 1. Females showed more predisposition towards being hypothyroid and anemic than males. HbA1C was around 6.52± 0.70 in 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])

Table 1: Distribution of the both type Diabetes Patients based on Hba1c status

S.No.	HbA1c level	Type of Diabetes Mellitus (DM)		
		Type 1 (%)	Type 2 (%)	Total (%)
1	< 6.0	0	9 (7.3)	9 (6.9)
2	6.0 – 7.0	0	29 (23.6)	29 (22.3)
3	7.1 – 8.0	0	20 (16.3)	20 (15.4)
4	>8.1	7 (100)	65 (52.8)	72 (55.4)
	Total	7 (100)	123 (100)	130 (100)

Table 2: Distribution of Patients based on Thyroid Condition and Type of DM

S.No.	Thyroid Condition	Type of Diabetes Mellitus (DM)		
		Type 1 (%)	Type 2 (%)	Total (%)
1	No Deformity	5 (71.4)	77 (62.6)	82 (63.1)
2	Hyperthyroidism	1 (14.3)	14 (11.4)	15 (11.5)
3	Hypothyroidism	1 (14.3)	32 (26.0)	33 (25.4)
	Total	7 (100)	123 (100)	130 (100)

Chi Square test = 0.489; df = 2; p value = 0.783

Table 3: Distribution of both Type of DM with level of TSH (Thyroid Stimulating Hormone)

S.No.	TSH Level (µIU/mL)	Type of Diabetes Mellitus (DM)		
		Type 1 (%)	Type 2 (%)	Total (%)
1	<0.28	2 (28.6)	14 (11.4)	16 (12.3)
2	0.28 – 6.82	5 (71.4)	98 (79.7)	103 (79.2)
3	>6.82	0	11 (8.9)	11 (8.5)
	Total	7 (100)	123 (100)	130 (100)

Chi Square test = 2.273; df = 2; p value = 0.321

Table 4: Distribution of all Patients based on Thyroid condition and Anemia

S.No.	Anemia Classification	Thyroid Condition			Total (%)
		No Deformity (%)	Hyperthyroidism (%)	Hypothyroidism (%)	
1	No Anemia	31 (37.8)	9 (60.0)	10 (30.3)	50 (38.5)
2	Mild Anemia	19 (23.2)	2 (13.3)	9 (27.3)	30 (23.1)
3	Moderate Anemia	22 (26.8)	3 (20.0)	11 (33.3)	36 (27.7)
4	Severe Anemia	10 (12.2)	1 (6.70)	3 (9.1)	14 (10.8)
	Total	82 (100)	15 (100)	33 (100)	130 (100)

Chi Square test = 4.456; df = 6; p value = 0.615

Table 5: Distribution of Patients based on relation of Thyroid gland Condition with HbA1c level

S.No.	HbA1c level	Thyroid Condition			
		No Deformity (%)	Hyperthyroidism (%)	Hypothyroidism (%)	Total (%)
1	< 6.0	4 (04.9)	1 (06.7)	4 (12.1)	9 (06.9)
2	6.0 – 7.0	12 (14.6)	8 (53.3)	9 (27.3)	29 (22.3)
3	7.1 – 8.0	15 (18.3)	0	5 (15.2)	20 (15.4)
4	>8.1	51 (62.2)	6 (40.0)	15 (45.5)	72 (55.4)
	Total	82 (100)	15 (100)	33 (100)	130 (100)

Chi Square test = 15.461; df = 6; p value = 0.017

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 are 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 prevalence 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. All patients (100%) in Type 1 DM had HbA1c level above eight, it show poor glycemic control in Type 1 DM. while more than half (52.8%) patients in type 2 DM had HbA1c level above eight, followed by 23.6% patients who had HbA1c in between 6 – 7, 16.3% patients had HbA1c in between 7.1 – 8. Only few Type 2 DM patients (7.3%) had good glycemic control. All patients (100%) (Table 2) in Type 1 DM had HbA1c level above eight, it show poor glycemic control in Type 1 DM. while more than half (52.8%) patients in type 2 DM had HbA1c level above eight, followed by 23.6% patients who had HbA1c in between 6 – 7, 16.3% patients had HbA1c in between 7.1 – 8. Only few Type 2 DM patients (7.3%) had good glycemic control. Majority (Table 4) of the patients (71.4%) in Type 1 DM had no deformity in Thyroid gland, while 62.6% patients in Type 2 DM were normal for the thyroid glands. Hyperthyroidism was present in 14.3% cases in Type 1 DM and 11.4% cases in Type 2 DM, whereas Hypothyroidism was present in 14.3% cases in Type 1 DM and 26% cases in Type 2 DM. Chi square test was apply to check the statistical relation the type of DM with Thyroid gland condition. There was statistically no significant relationship (p>0.05). (Table 8). Majority (Table 4) of the patients (71.4%) in Type 1 DM had no deformity in Thyroid gland, while 62.6% patients in Type 2 DM were normal for the thyroid glands. Hyperthyroidism was present in 14.3% cases in Type 1 DM and 11.4% cases in Type 2 DM, whereas Hypothyroidism was present in 14.3% cases in Type 1 DM and 26% cases in Type 2 DM. Chi square test was apply to check the statistical relation the type of DM with Thyroid gland condition. There was statistically no significant relationship (p>0.05). Only few patients (28.6%) (Table 5) in Type 1 DM had TSH level below 0.28 µIU/mL, while in Type 2 DM, only 11.4% patients had TSH level 0.28 µIU/mL and 8.9% patients had TSH level above 6.82 µIU/mL. Chi square test was apply to check the statistical relation the type of DM with level of TSH hormone. There was statistically no significant relationship (p>0.05). More than one-third patients with normal thyroid function (39%) had moderate to severe anemia. While near to one-quarter patients (26.7%) with Hyperthyroidism and more than one-third patients (42.4%) with Hypothyroidism had moderate to severe anemia. To check the statistical relation between Thyroid condition and Anemia chi square test applied. There was statistically no significant relation seen (p>0.05). (Table 06). More than half of the patients (62.2%) with normal thyroid condition had poor glycemic control (HbA1c >8), while 40 % patients with Hyperthyroidism and 45.5% patients with Hypothyroidism had poor glycemic control. Very few patients with Hyperthyroidism and Hypothyroidism had good glycemic control (6.7% and 12.1% respectively). Chi square test was apply to check the statistical relation of thyroid deformity in Diabetic patients with level of HbA1c. There was statistically significant relationship (p < 0.05). (Table07) More than half of the patients (56.2%) with below normal TSH hormone level (<0.28) had poor glycemic control (HbA1c >7) and 74.8% patients with normal TSH hormone level had poor glycemic control. while only 54.6% patients with above normal TSH hormone level had poor glycemic control. Chi square test was applying to check the statistical relation of HbA1c level in Diabetic patients with TSH hormone. There was statistically no significant relationship (p>0.05). (Table 07)

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 anemia but significant negative correlation was found between hypochromic index in microcytic hypochromic anemia 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 HbA1c levels.[19,20] Hence, red cell survival time gives a better explanation than red cell morphology 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, amelaetal[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 criterion for plasma glucose levels to be associated with TSH, as all patients were non-diabetic. We excluded pregnant patients, patients having hemolytic anaemia, other hemoglobinopathies, anemia due to other chronic illnesses, renal disease that shorten erythrocyte survival may proportionately decrease HbA1C 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 HbA1C of pre-diabetic range with anemia. Hence care must be taken when making a diagnosis of diabetes in such patients.

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