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Glycated Haemoglobin (HbA1c) Level in Non-Diabetic Overt Hypothyroid Patient in Comparison to Control Attending in a Tertiary Care Hospital

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Abstract

Background: Glycated haemoglobin (HbA1C) is widely used to assess glycemic status of the diabetic patients. The major form of glycated haemoglobin is haemoglobinA1c (HbA1c). The use of HbA1c for the screening and the diagnosis of diabetes has been recently approved by the American Diabetes Association (ADA) and World Health Organization (WHO). Aim of the study: To observe the glycated haemoglobin (HbA1c) level in non-diabetic overt hypothyroid patient. **Methods:** This hospital-based case-control study was conducted in the Department of Medicine, Dhaka Medical College Hospital from the period of November 2018 to October 2019. Total 170 patients were included for the study. Among them 85 patients were in case group having overt hypothyroidism and 85 patients were in control group with no thyroid dysfunction. Sampling method was convenient sampling. Data were analyzed by the SPSS 20 Windows version (Chicago, Illinois, USA). The protocol was presented and approved by Research Review Committee (RRC) of department of medicine of Dhaka Medical College Hospital.**Results:**The mean age of the overt hypothyroid cases was 45.79±11.26 years. In case group 12.94%,22.35%, 31.76%, 25.88%, and 7.05% were in 18-30 years, 31-40 years, 41-50 years, 51-60 years and >60 years age group respectively. Among the hypothyroid cases 34.11% were male and 65.88% were female. In case group mean BMI was 26.46±2.84 Kg/m2 and in control group mean BMI was 23.15± 2.72 Kg/m2. In case group mean HbA1c level was 5.80±0.28% and in control group mean HbA1c level was 5.26±0.39%. HbA1c level was statistically significantly more in case group than control group ($p<0.001$).The mean serum TSH level was 19.32±6.36 and 3.78±0.50 in the case and the control group respectively. There was positive correlation between the level of serum TSH and HbA1c by Pearson correlation coefficient ($r=0.414$, $p<0.05$). **Conclusion:** As the hypothesis is proved, so from the study it is concluded that HbA1c level were significantly higher in hypothyroid patients compared to control individual despite normal glucose level.

Keywords: Hypothyroidism, Diabetes, HbA1C, Glycemic, Thyroid.

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INTRODUCTION

Glycated haemoglobin (HbA1C) is widely used to assess glycemic status of the diabetic patients. The major form of glycated haemoglobin is haemoglobinA1c (HbA1c). The use of HbA1c for the screening and the diagnosis of diabetes has been recently approved by the American Diabetes Association (ADA) and World Health Organization (WHO).[1] Both organizations have suggested that the level of HbA1c ≥ 6.5% is considered as diabetes and the ADA has also suggested that the level of HbA1c between 5.7 to 6.4% is diagnostic of pre-diabetes.[2] The major form of glycated haemoglobin is HbA1c. It develops when haemoglobin, a protein within red blood cells that carries oxygen throughout our body, joins with glucose in the blood, becoming 'glycated'. Clinicians get an overall picture of the average blood sugar levels over a period of weeks/months from the value of HbA1c. Several factors influence HbA1c. Among them, glucose is the most important one3. Thyroid hormone exerts both insulin agonistic and antagonistic actions in different organs. But, for normal glucose metabolism fine balance occurs between these effects. Deficit or excess of thyroid hormone break the equilibrium leading to alteration of glucose metabolism. It also have been observed that thyroid hormone exerts some of their actions synergically with insulin. For assessment of glycemic control glycated hemoglobin (HbA1C) is widely used. But, its concentration depends on prevailing glycaemia and also on the life span of the erythrocytes. So, the conditions which affect the erythrocyte turnover or survival may lead to falsely elevate or lower the HbA1C levels.[3] Recent studies have shown its spurious elevation in hypothyroidism in the absence of diabetes. Variation in HbA1C levels in different conditions like haemoglobinopathies, chronic kidney diseases, pregnancy even in the absence of diabetes mellitus has been observed in various studies.[4] Thyroid disorders are very common among the general population and is the second most common condition affecting the endocrine system after diabetes mellitus.[5] Thyroid hormones affect glucose metabolism via several mechanisms. Some theories have been put forward to explain the increased levels of HbA1c in hypothyroid patients.[6] One of those theories suggested dysglycemia to be the cause of increased HbA1c levels.[7] Another suggested Insulin resistance is the cause of increased glucose levels in hypothyroidism8. Unfortunately there is very limited data exist in our context regarding HbA1c levels in non-diabetic hypothyroid disorders. Therefore, the purpose of the study was to evaluate the glycated haemoglobin (HbA1c) level in non-diabetic hypothyroid patient. The result of the study will help the physician whether impaired glycaemia in patient with overt-hypothyroidism should be considered for intervention or not and thus will be helpful in public health awareness and health planning in future.

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Objectives

General objective:

- To observe the glycated haemoglobin (HbA1c) level in non-diabetic overt hypothyroid patient.

Specific Objectives:

- To measure the HbA1c level in both case and control groups.
- To find out correlation between TSH and HbA1c level.
- To describe the clinical pattern of hypothyroidism.
- To describe the socio-demographic characteristics of both case and control population.

MATERIALS AND METHODS

This hospital-based case-control study was conducted in the Department of Medicine, Dhaka Medical College Hospital from the period of November 2018 to October 2019. Total 170 patients were included for the study according to following inclusion and exclusion criteria. Among them 85 patients were in case group having overt hypothyroidism and 85 patients were in control group with no thyroid dysfunction. Sampling method was convenient sampling. Case- control ratio was 1:1. Fasting blood samples were collected with an aseptic blood collection technique by the use of sterile gloves and thorough disinfection of venipuncture site with 70% ethyl alcohol. Samples were centrifuged within one hour at 1500 rpm for 15 minutes. These were processed to obtain serum/plasma for the estimations of Thyroid function tests (TSH, FT4,), FBS, HbA1c, and haemoglobin level. HbA1c was measured by Immunoturbidimetry method by clinical chemistry analyzer, while serum TSH and FT4 were measured by radioimmune assay. Chi-squared Test (2) was performed to compare between two groups. Unpaired t-test was performed to compare the mean between the groups. Data were analyzed by the SPSS 20 Windows version (Chicago, Illinois, USA). The protocol was presented and approved by Research Review Committee (RRC) of department of medicine of Dhaka Medical College Hospital.

Inclusion Criteria

Case:

- Age ≥18 years
- Diagnosed overt hypothyroidism
- Haemoglobin: Male≥13 gm/dl, Female≥12 gm/dl (WHO)
- Provided informed written consent

Control:

- Age and sex matched healthy individual
- Provide informed written consent

Exclusion Criteria

For case and control:

- Known case of diabetes
- Patient on thyroxin replacement
- Pregnancy
- Known co-morbid disease that may hamper the glucose level like CLD, CKD etc.
- Known Hematological malignancies

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Page no- 171-178 | Section- Research Article (Medicine)

- Patients with history of haemoglobinopathy and
- Recent blood transfusion
- Drug that can modify or affects HbA1C level like ribavirin, dapsone, trimethoprim-sulphamethoxazole, and hydroxyurea etc.

RESULTS

The mean age of the overt hypothyroid cases was 45.79±11.26 years. In case group 12.94%,22.35%, 31.76%, 25.88%, and 7.05% were in 18-30 years, 31-40 years, 41-50 years, 51-60 years and >60 years age group respectively [Table 1]. Among the hypothyroid cases 34.11% were male and 65.88% were female [Table 2]. Among the study cases 68.45% were from urban community and 31.55% were from rural community [Figure 1]. Mean weight and BMI was statistically significantly more in case group than control group (p=0.002 and 0.001 respectively). In case group mean weight was 62.67±7.03 kg and in control group mean weight was 59.56±6.86 kg. In case group mean BMI was 26.46±2.84 Kg/m2 and in control group mean BMI was 23.15± 2.72 Kg/m2. Mean height statistically matched between two groups (p=0.767). In case group mean height was 1.60±0.05 m and in control group mean height was 1.61±0.05 m [Table 3]. Among the 85 hypothyroid study cases fatigue was present in 81.17% cases, cold intolerance was present in 47.05% cases, menorrhagia present in 29.41% cases, constipation present in 30.58% cases, depression was present in 43.52% cases, weight gain was present in 70.58% cases, puffy face present in 37.64% cases, hoarseness of voice present in 52.94% cases, eye brow loss was present in 24.70% cases and non-pitting edema was present in 32.94% cases [Table 4]. In case group mean HbA1c level was 5.80±0.28% and in control group mean HbA1c level was 5.26±0.39%. HbA1c level was statistically significantly more in case group than control group (p<0.001).The mean serum TSH level was 19.32±6.36 and 3.78±0.50 in the case and the control group respectively. There was statistically significant difference with the p value <0.0001 and the levels of TSH were significantly higher in the case group compared with the control group. The mean FT4 level was also statistically significantly different between case and control (4.93±1.13 vs 12.08±2.87) with the p value <0.001.Fasting blood sugar for case group was 5.05±0.81 and for control group was 4.87±0.66 respectively. There was no statistically significance difference between the case and control group. Similarly, hemoglobin levels were 12.44±1.06 and 13.69±1.54 in case and control group respectively with p value 0.183 [Table 5]. There was positive correlation between the level of serum TSH and HbA1c by Pearson correlation coefficient (r=0.414, p<0.05) [Figure 2].

Table 1: Age distribution of cases (N=85)

Age	Cases (n=85) No. (%)
18-30	11 (12.94)
31-40	19 (22.35)
41-50	27(31.76)

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Vol-7, Issue-3 | May-June, 2021
Page no- 171-178 | Section- Research Article (Medicine)

51-60	22 (25.88)
>60	06 (7.05)
Mean age	45.79±11.26

Table 2: Sex distribution of cases (N=85)

Sex	Cases(n=85) No. (%)
Female	56 (65.88)
Male	29 (34.11)

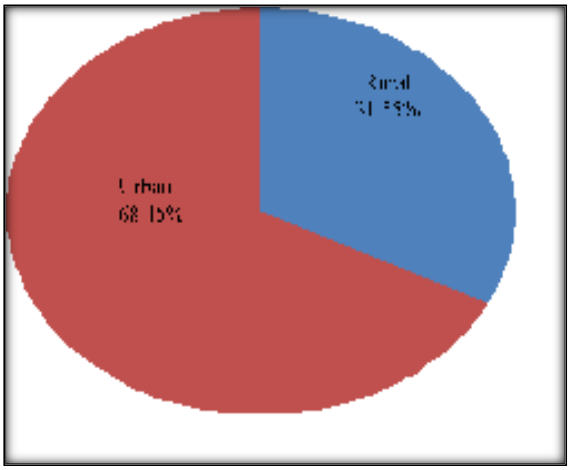

Figure 1: Community of patients (N=170)

Table 3: Mean height, weight and BMI of the patients (N=170)

Variable	Case	Control	P-value
Mean weight(kg)	62.67±7.03	59.56±6.86	0.002
Mean height(m)	1.60±0.05	1.61±0.05	0.767
Mean BMI(Kg/**m 2**)	26.46±2.84	23.15±2.72	0.001

Table 4: Clinical features of the Hypothyroid patients (N=85)

Clinical features	Frequency	Percentage(%)
Fatigue	69	81.17
Weight gain	60	70.58
Hoarseness of voice	45	52.94
Cold intolerance	40	47.05
Depression	37	43.52
Puffy face	32	37.64
Non pitting edema	28	32.94
Constipation	26	30.58
Menorrhagia	25	29.41
Loss of lateral eyebrow	21	24.70

Table 5: Investigation profile of the patients (N=170)

Variable	Case (Mean ±SD)N = 85	Control (Mean ±SD)N = 85	P value
FT4(pmol/l)	4.93±1.13	12.08±2.87	<0.001
TSH(mIU/l)	19.32±6.36	3.78±0.50	<0.0001
HbA1c (%)	5.80±0.28	5.26±0.39	<0.0001
FBS(mmol/l)	5.05±0.81	4.87±0.66	0.075
Hb (gm/dl)	12.44±1.06	13.69±1.54	0.183

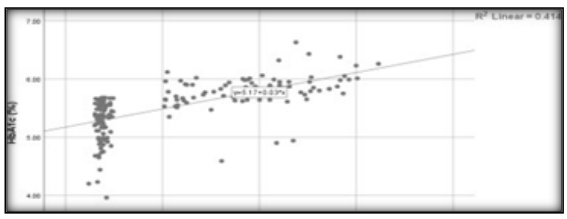

Figure 2: Correlation between TSH and HbA1c levels (r=0.414, p<0.05)

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DISCUSSION

In this study it was observed that most (31.76%) of the patients were in the age group of 41-50 years & the mean ± SD of age was 45.79 ±11.26 years. Meng and associates9 found the mean age of their hypothyroidism cases 48.61± 10.75 years and another study conducted by Nair and associates found the mean age 53.30±11.2 years which is consistent to the finding of this study. Among the hypothyroidism cases 65.88% were female and 34.11% were male. Maximum 68.45% were urban resident and rest 31.55% were rural resident. The mean weight and BMI were statistically significantly more in case group than control group (p=0.002 and 0.001 respectively). Mean weight of the cases was 62.67±7.03 kg and mean weight of the control was 59.56±6.86 kg. The mean BMI of the cases was 26.46±2.84 Kg/m2 and mean BMI of the control was 23.15±2.72 Kg/m2. This finding is similar to the findings of Verma and co-researchers.[10] Among their 548 overt hypothyroidism cases 46% cases had BMI >25 Kg/m2 which is consistent to the findings of this study. The most frequently found clinical symptoms were fatigue (81.17%), weight gain (70.58%), cold intolerance (47.05%), menorrhagia (29.41%), constipation (30.58%), depression (43.52%), and puffy face (37.64%). The mean serum TSH level in the case group with hypothyroidism and the control group was statistically significantly different ($p < 0.0001$) and the mean TSH level in the case group was 19.32 ± 6.36 and in the control group it was 3.78 ± .50. The levels of HbA1c (%) were significantly higher in the case group (5.80±.28%) compared with the control group (5.26±.38%) ($p<.0001$). This finding was consistent with a study where 48.9% of non-diabetic hypothyroid patients showed HbA1c level ≥ 5.7% Bhattachajee et al.[11] Another study also 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 Anantarapu et al, Kim et al.[12,13] Several studies have proved the association between insulin resistance in overt and subclinical hypothyroidism Sings et al, Annemieke et al and they found low normal FT4 was significantly associated with increase insulin resistance.[14,15] This study reveals statistically significant correlation between TSH levels and HbA1c levels ($r=0.414$, $p<0.05$). Study conducted by Billic-Komarica et al,[16] found statistically significant positive correlation between TSH level and HbA1c level ($r=0.46$, $p<0.05$). Another study conducted by Makadia et al,[1] also found statistically significant correlation between TSH and HbA1c levels ($r=0.51$, $p<0.0001$) which is consistent to the findings of this study.

Limitations of the study:

This was a single-center study. FT_3 and thyroid auto-antibody were not measured. HbA1c after post-thyroid

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Page no- 171-178 | Section- Research Article (Medicine)

hormone replacement was not assessed.

CONCLUSION

As the hypothesis is proved, so from the study it is concluded that HbA1c level were significantly higher in hypothyroid patients compared to control individual despite normal glucose level. As HbA1C level spuriously elevates in hypothyroid patients the effects of the elevated level of Serum TSH on the HbA1c must be considered before using HbA1c for the diagnosis of pre-diabetes in the hypothyroid patients. Though our result is significant as the result of other studies, further large scale muti- center studies should be carried out.

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