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Original Research Article

Association of subclinical hypothyroidism and HbA1c levels in non-diabetic subjects attending rural tertiary care centre in central India

Vidya Sagar Ram, Granth Kumar*, Manoj Kumar, Vivek Kumar Verma, Dheeraj Kela, Kasim Ali

Department of Medicine, Uttar Pradesh University of Medical Sciences, Saifai, Uttar Pradesh, India

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***Correspondence:**
Dr. Granth Kumar,
E-mail: drgranth@gmail.com

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 haemoglobin 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 ($r=0.35$, $p < 0.0001$).
Conclusions: 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 pre-diabetes in the subclinical hypothyroid patients.

Keywords: Subclinical Hypothyroidism, Glycosylated Haemoglobin, Serum TSH

NTRODUCTION

Thyroid disorders are very common in the general population and is second most common condition affecting the endocrine system after diabetes mellitus. Decreased production of thyroid hormone is the key feature of hypothyroidism.[2] Subclinical hypothyroidism is defined as an elevated serum TSH level and normal concentrations of free T3 (FT3), free T4 (FT4), T3 and T4.[1] It is often complicated by conditions such as dilutional hyponatremia, anaemia and hyperlipidemia.[3] Subclinical hypothyroidism is more common in the elderly and is more prevalent in women than in men.[4,5]

The American Diabetes Association (ADA) have approved the use of HbA1c for the screening and the diagnosis of diabetes.[6] The HbA1c concentration not only depends on prevailing glycaemia but also the life span of the erythrocytes and so, the conditions which affect the erythrocyte turnover or survival may lead to falsely elevate or lower the HbA1C levels.[7-11] 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. Recent studies have shown its spurious elevation in hypothyroidism in the absence of diabetes.[1,2] Present study was planned to assess

correlation between subclinical hypothyroidism and glycosylated haemoglobin levels in non-diabetic patients.

METHODS

This study was a case-control study, conducted in the Medicine Department at UPUMS, Saifai, during November 2016 to April 2017. Total 209 individuals were considered for the study, 109 each in case and 100 in control groups. Controls were relatives and friends of patients who were matched for age and sex.

Inclusion criteria

- Non-diabetics
- Subclinical hypothyroidism
- Patients who consent to the participation.

Exclusion criteria

- Diabetes
- Anaemia
- Renal insufficiency
- Liver dysfunction.
- Severe hypertriglyceridemia
- Hypothyroid patients already on thyroid hormone replacement
- Abnormal haemoglobinopathy
- Hemolytic disorder
- Recent (< 3 months) blood transfusion.

Haemoglobin, FBS, Serum T3, T4, TSH, HbA1c, CBC, fasting lipid profile, LFT, KFT were measured. All data were collected and analysed statistically to determine the significance of different parameters. All values were given as mean±SD. Comparison between the case and the control groups were made using Student's t-test (unpaired), and the p-value of less than 0.05 was considered statistically significant. Box and Whisker Plot and regression graph were presented for correlation between serum TSH and HbA1c.

RESULTS

This study enrolled total 209 subjects, out of which 109 subjects were in the case group and 100 subjects were in the control group. Table 1 shows the details of demographic data of the study.

Table 1: Comparison of the various parameters in the case and the control groups.

Parameters	Case (mean±SD)	Control (mean±SD)	p value
Age (years)	46.90±12.84	47.41±14.56	0.78
Sex (M:F)	0.84	0.88	0.86
FBS (mg/dl)	101.30±4.74	101.23±5.04	0.92
Haemoglobin (gm/dl)	12.75±1.08	13.02±1.14	0.85
S. T3 (ng/ml)	1.09±0.28	1.11±0.29	0.76
S. T4 (µg/dl)	7.07±1.07	7.31±1.01	0.09
S. TSH (µIU/ml)	7.10±1.34	2.49±0.72	<0.0001
HbA1c (%)	5.65±0.34	5.13±0.31	<0.0001

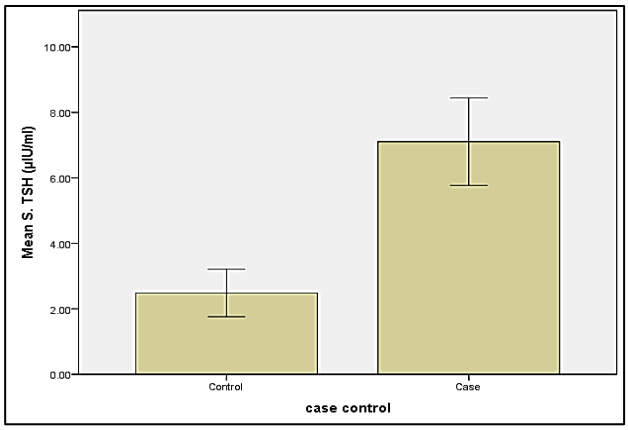

Figure 1: Box and whisker plot showing levels of serum TSH (µIU/ml) in the case and the control groups.

The mean age of the case group and the control group were 46.90±12.84 and 47.41±14.56 respectively. Male:female ratio was 0.84 in case group and 0.88 in control group with p value of 0.86. Details of various characteristics of the case and the control groups are given in (Table 1). Fasting blood sugar levels for control group was 101.23±5.04 and for case group was 101.30±4.74 respectively. There was no statistically significant difference between the case and the control groups. Similarly, haemoglobin levels were 12.75±1.08 and 13.02±1.14 in case and control groups respectively with p value 0.85. The mean serum TSH level was 7.10±1.34 µU/L and 2.49±0.72 µU/L in the case and the control groups, respectively. There was statistically significant difference with the p-value of < 0.0001 and the levels of S. TSH (µU/L) were significantly higher in the case group compared with the control group as shown in the Box and Whisker Plot (Figure 1). The mean

HbA1c levels were 5.65±0.34% and 5.13±0.31 % in the case and the control groups respectively. There was statistically significant difference with the p-value of <0.0001. The levels of HbA1c (%) were significantly higher in the case group compared with the control group as shown in the Box and Whisker plot (Figure 2).

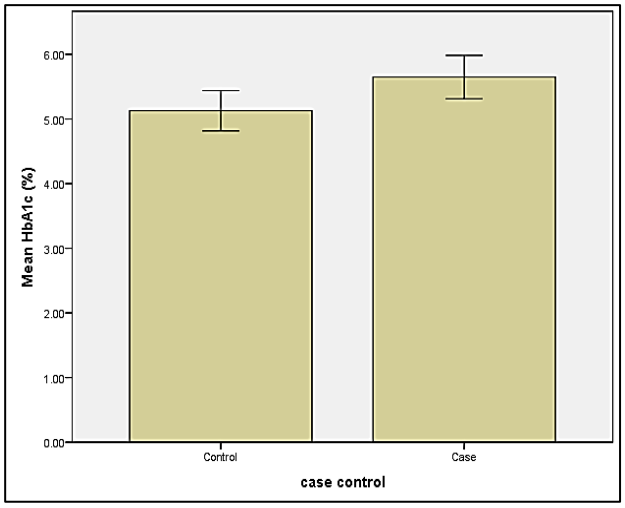

Figure 2: Box and Whisker plot of HbA1c (%) levels in the case and the control groups.

We also 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) (Figure 3).

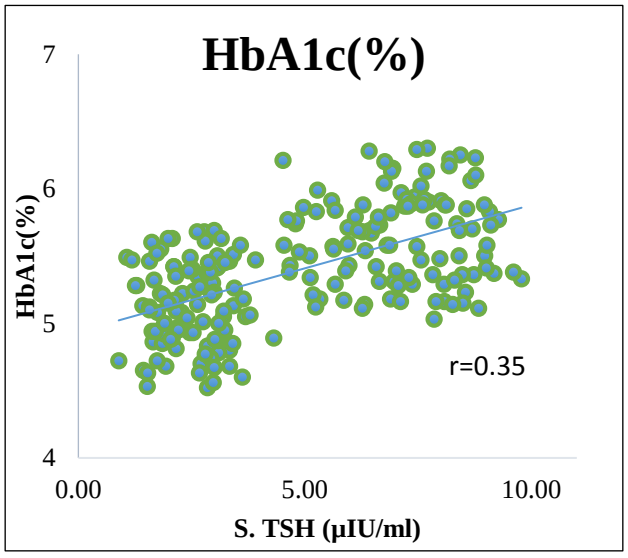

Figure 3: The correlation between the levels of serum TSH (µU/L) and HbA1c in all the subjects of the study by Pearson's correlation coefficient (r = 0.35, p < 0.0001).

DISCUSSION

Subclinical Hypothyroidism is a commonly encountered endocrine disorder in present days. This study was aimed to determine the effect of thyroid hormone on the levels of glycosylated haemoglobin in both deficient and normal states. It is important to study the effects of thyroid hormones on HbA1c, so as to help us in better interpretation of its levels in patients with thyroid dysfunction. Keeping in mind the various other non-glycaemic factors affecting glycosylated haemoglobin, the inclusion and exclusion criterion were formulated. Some confounding medical conditions include acute and chronic blood loss, haemolytic anaemia, other anaemias, haemoglobin variants, blood urea and serum creatinine were excluded.[13] The mean serum TSH level in the case group with Subclinical hypothyroidism and the control group were statistically significantly different (p < 0.0001). The levels of serum TSH were significantly higher in the case group which consists of subjects of Subclinical hypothyroidism compared with the control group comprising of normal healthy individuals. The mean HbA1c level in the case group and the control group was statistically significant (p < 0.0001). The levels of HbA1c (%) were significantly higher in the case group compared with the control group. As there was no statistically significant difference between the case group with Subclinical hypothyroidism and the control group with normal healthy individuals for the age, sex, FBS, haemoglobin, serum T3 and serum T4 levels, the only difference in the case and the control groups were the levels of serum TSH. Also, the levels of serum T3, serum T4 and Haemoglobin were normal in both the groups. So, we can say that the levels of HbA1c in both the groups were not affected by age, sex, and the levels of FBS, serum T3 and serum T4.

Serum TSH levels were significantly higher in the cases with subclinical hypothyroidism than normal healthy individuals and the study result also showed that HbA1c levels were significantly higher in the cases than the controls. In this study, we also found that there was statistically significant correlation between the levels of serum TSH and HbA1c in all the study subjects by Pearson's correlation coefficient (r=0.35, p<0.0001). Kim MK et al, conducted a study to determine the effects of thyroid hormones on glycosylated haemoglobin which showed a strong positive correlation between TSH and glycosylated haemoglobin in 45 cases that were studied by them. A comparison was held between mean TSH and mean HbA1c levels. Both were found to be higher in cases when compared to the controls.

The mean TSH in cases was 89.6 versus controls 2.28 (p=0.001), and the mean HbA1c in cases was 5.58% versus controls 5.44% (p=0.061). The above observation infers that glycosylated haemoglobin levels are higher in hypothyroid individuals as compared to those of same age and sex matched euthyroid individuals, in accordance with previously reported studies.[12] Billic-Komarica E et al, also found a positive and statistically significant (r=0.46) correlation between the level of serum TSH and HbA1c levels. Subclinical hypothyroidism independently increases the risk for decreased insulin sensitivity. There

is an apparent correlation between the subclinical hypothyroidism and hyperinsulinemia and insulin resistance. Subclinical hypothyroidism and insulin resistance via its numerous mechanisms involved in the disruption of glycaemic control.[14] In Kuwaiti a study done by Al-Sayed A et al, on women to investigate the correlation between Subclinical hypothyroidism and insulin resistance. They found that the insulin levels were significantly higher in the Subclinical hypothyroidism group comparable to the normal control.[15] Another study by Christy et al selected 30 hypothyroid, non-diabetic patients with normocytic normochromic anaemia and compared these patients with 30 euthyroid non-diabetic patients also with normocytic normochromic anaemia. HbA1c in the hypothyroid patients was 6.32±0.75% versus 5.87±0.46% in the euthyroid group, the difference being statistically significant.[16] Edina Bilic-Komarica et al also conducted a study which significantly correlated TSH and HbA1c ($r = 0.46$, $p < 0.05$) as found in this study.[17]

The prevalence of thyroid disease in patients with diabetes mellitus is approximately 10-15%.[18,19] Studies done in hypothyroid patients showed elevated HbA1C not only in the presence of diabetes but also in non-diabetic subjects. Hence the role of HbA1C as a marker of diabetes was questioned in such conditions especially when American Diabetes Association has endorsed it as diagnostic criteria for diabetes mellitus. Hypothyroidism is mainly complicated by normocytic normochromic anaemia which may be early iron deficiency anaemia due to nutritional deficiency or it may be secondary to hypothyroidism itself.[20] The aetiology of anaemia in hypothyroidism can be related to the nutritional iron deficiency or to the endocrine disorder itself where the lowered thyroid hormone levels represses the bone marrow often resulting in decreased erythrocyte production which may affect the life span of erythrocytes. Altered erythrocyte life span may be partially responsible for spurious elevation in HbA1C levels.[21-23]

CONCLUSION

From the present study, it is concluded that HbA1c levels are increased in Subclinical hypothyroid patients. Our data suggest that non-diabetic subjects with the Subclinical hypothyroidism show high levels of HbA1c. The reasons for this might be due to the association of insulin resistance in the subjects with Subclinical hypothyroidism or effect of thyroid hormones on altered erythropoiesis. Elevated HbA1C in hypothyroidism can be attributed to anaemia also. Hence it is recommended to consider it before diagnosing diabetes solely on the basis of HbA1C. 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 pre-diabetes in the subclinical hypothyroid patients. However, to find out the exact mechanism further studies are required on larger cohort.

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REFERENCES

1. Vij V, Chitnis P, Gupta VK. Evalution of thyroid dysfunction among type 2 diabetic patients. Int J Pharm Bio Sci. 2012;2:150-5.
2. Joseph L. Radioisotopic evaluation of the thyroid and the parathyroids. In: Kronenberg H, Melmed S, Polonsky K, Larsen P, Price D, editors. Williams Textbook of Endocrinology. 11th ed. Philadelphia. Saunders, An Imprint of Elsevier; 2008:377-78.
3. Antonijevi N, Nesovi M, Trbojevi B, Milosevi R. Anaemia in hypothyroidism. Med Pregl. 1999;52(3-5):136-40.
4. Cooper DS. Subclinical hypothyroidism. N Engl J Med. 2001;345(4):260-5.
5. Hueston WJ, Pearson WS. Subclinical hypothyroidism and the risk of hypercholesterolemia. annals of family medicine. Ann Fam Med. 2004;2(4):351-5.
6. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care. 2011;34(Suppl. 1):S62-69.
7. World Health Organization Prevention and Control of Iron Deficiency Anaemia in Women and Children: Report of the UNICEF/ WHO Regional Consultation February 1999. Geneva, World Health Org; 2001.
8. Fitzgibbons JF, Koler RD, Jones RT. Red cell age-related changes of Haemoglobins A1a, A1b and A1C in normal and diabetic case. J Clin Invest. 1976;58:820-4.
9. McGill JB, Bell DS. Anaemia and the role of erythropoietin in diabetes. J Diabet Complicat. 2006;20:262-72.
10. Gram-Hansen P, Eriksen J, Mourits-Andersen T, Olesen L. Glycosylated Haemoglobin (HbA1c) in iron and vitamin B12 deficiency. J Int Med. 1990;227:133-6.
11. Hashimoto K, Noguchi S, Morimoto Y, Hamada S, Wasada K, Imai S, et al. A1C but not serum glycated albumin is elevated in late pregnancy owing to iron deficiency. Diabetes Care. 2008;31(10):1945-8.
12. Kim MK, Kwon HS, Baek KH, Lee JH, Park WC, Sohn HS, et al. Effects of thyroid hormone on A1C and glycated albumin levels in nondiabetic subjects with overt hypothyroidism. Diabetes Care. 2010;33(12):2546-8.
13. Bernstein RE. Glycosylated hemoglobins: hematologic considerations determine which assay

for glycohemoglobin is advisable. Clin Chem 1980;26(1):174-5.
14. Billic-Komarica E, Beciragic A, Junuzovic D. The importance of HbA1c control in patients with subclinical hypothyroidism. Mater Sociomed. 2012;24(4):212-9.
15. Al Sayed A, Al Ali N, Bo Abbas Y, Alfadhli E. Subclinical hypothyroidism is associated with early insulin resistance in Kuwaiti women. Endocr J. 2006;53(5):653-7.
16. Christy AL, Manjrekar P, Babu RP, Rukmini MS, Hegde A. Elevation of HbA1C in non-diabetic hypothyroid individuals: is anaemia the connecting link? A preliminary study. J Clin Diagnostic Res. 2013;7(11): 2442-4.
17. Billic-Komarica E, Beciragic A, Junuzovic D. The importance of HbA1c control in patients with subclinical hypothyroidism. Materia Socio-medica. 2012;24(4):212.
18. Trbojevi B. Tiroidna žlezda: Pathophysiological basics and clinical approach. Beograd. 1998:305-10.
19. Diez JJ, Iglesias P, Burman KD, Spontaneous normalization of thyrotropin concentrations in patients with subclinical hypothyroidism. J Clin Endocrinol Metab. 2005;90:4124-7.
20. Hardikar PS, Joshi SM, Bhat DS, Raut DA, Katre PA, et al. Spuriously high prevalence of prediabetes diagnosed by HbA1c in young Indians partly explained by haematological factors and iron deficiency anemia. Diabetes Care. 2012;35(4):797-802.
21. Horton L, Coburn RJ, England JM, Himsworth RL. The hematology of hypothyroidism Q J Med 1976;45(177): 101-23.
22. Das KC, Mukherjee M, Sarkar TK, Dash RJ, Rastogi GK. Erythropoiesis and erythropoietin in hypoand hyperthyroidism. J Clin Endocrinol Metab. 1975;40:211-20.
23. Fein HG, Rivlin RS. Anaemia in thyroid diseases. Med Clin North Am. 1975;59:1133-45.

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