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Research Article

HbA1c-deceptive Levels in Subclinical Hypothyroidism?

D Ponnudhali[1], S Preetha[2], Nirmal Sujitha IJ[3]

[1]Professor & HOD, Dept. of Biochemistry, [2,3]Vinayaka Mission's Kirupananda Variyar Medical College & Hospital, Salem.
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I N F O

Corresponding Author:
D Ponnudhali, Dept. of Biochemistry, Vinayaka Mission's Kirupananda Variyar Medical College & Hospital, Salem.
E-mail Id:
ponnudhalid@gmail.com
Orcid Id:
https://orcid.org/0000-0002-1444-0782
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A B S T R A C T

Background: Subclinical hypothyroidism (SH) has been known to be related to type 2 diabetes mellitus and prediabetes. The association of SH with insulin resistance and altered glycemic status has been reported in past studies. We have aimed to look for the relationship of subclinical hypothyroidism with HbA1c levels, among non-diabetic individuals.

Aim & Objectives: To compare the HbA1c levels among non-diabetic participants with subclinical hypothyroidism (SH), and healthy controls having normal thyroid function.

Materials & Methods: It is an analytical cross-sectional study carried out among 33 non-diabetic individuals with subclinical hypothyroidism and 36 euthyroid people. Mean serum HbA1c, TSH and other thyroid parameters were compared among the 2 groups, using independent "t" test. Spearman's correlations were done, along with the odds ratio for the risk of association of HbA1c levels with subclinical hypothyroidism.

Results: Serum HbA1c levels were significantly enhanced in the SH group (4.91 ± 0.88 %) compared to healthy controls (4.39 ± 0.89 %, p = 0.018). A significant positive correlation was found to exist between TSH and HbA1c levels (p = 0.002).

Conclusion: Serum HbA1c levels were increased in non-diabetic individuals with subclinical hypothyroidism. This should be taken into consideration while analysing the HbA1c values in the diagnosis of diabetes/ prediabetes.

Keywords: Subclinical Hypothyroidism, TSH, HbA1c, Non-diabetic

Introduction

Glycosylated haemoglobin (HbA1c) is a routine diagnostic test for diabetes mellitus and used to monitor the glycemic status in diabetes mellitus patients. HbA1c has been recommended for screening as well as diagnosis of diabetes by the American Diabetes Association (ADA). As per the ADA criteria, HbA1c > 6.5% is diagnostic of diabetes and HbA1c levels between 5.7% and 6.4% fall under the prediabetic category.[1]

Variations in HbA1c levels have been noticed in many clinical conditions such as chronic kidney diseases, haemoglobinopathies, and non-diabetic pregnancies.[2] HbA1c is often falsely low in some conditions like haemolysis, cirrhosis, haemorrhage, blood transfusions, and

haemoglobinopathies.[3,4] Due to the dependence of HbA1c concentration on the life span of erythrocytes (besides on prevailing glycemia), the conditions that have an effect on erythrocyte turnover/ survival may cause low/ falsely elevated levels of HbA1c.[5,6]

Subclinical hypothyroidism (SH) is a clinical condition characterised by increased serum TSH levels and normal thyroid hormone concentrations, with no clinical signs or symptoms.[7] There are some studies that have brought out the relationship between elevated HbA1c levels and subclinical hypothyroidism in non-diabetic individuals.[8-10] Increase in HbA1c levels in non-diabetic subjects was also related to the coexistence of anaemia in hypothyroid patients.[11]

In our study, we have attempted to assess the HbA1c levels among non-diabetic participants and determine its association with subclinical hypothyroidism, in a small south Indian population.

Materials and Methods

It is an analytical cross-sectional study which was carried out for a period of six months (May 2019 to October 2019). The study was conducted in a private medical college hospital in Salem, after obtaining clearance from the Institutional Ethics Committee. The sample size was calculated on the basis of already reported mean HbA1c levels among subclinical hypothyroid and euthyroid non-diabetic individuals.[12]

The participants were recruited through convenience sampling. They were adults above 20 years of age and included patients, their attenders, hospital staff and volunteers who consented to participate in the study. Information such as demographic details and medical history was collected by interviewing the participants using a structured questionnaire. Participants were informed about the purpose of the research and the possible risks/ benefits, after which written consent was obtained from all of them. Subjects who were known to have anaemia, diabetes, thyroid disorders, liver disease, renal disease, haematological malignancies, haemoglobinopathies, and those with a history of blood transfusion within the last 3 months, were excluded.

Five ml of venous blood was collected from the median cubital vein from the participants after overnight fasting, out of which, 3 ml was transferred to clot activator tubes (red top tubes), serum was separated and used to estimate FT3, FT4, T3, T4 and TSH. 2 ml of blood was collected in EDTA tubes for analysis of FBG (Fasting Blood Glucose) and HbA1c. HbA1c was estimated using EM 200 autoanalyser and FBG was estimated using semi-auto analyser. Estimation of TSH, T3, T4, FT3 and FT4 was done using MINIVIDAS analyser by immunofluorescence technique.

Participants with FBG more than 110 mg/dl along with low T3 and T4 levels were also excluded from the study, after informing them. There were 69 participants in total. Based on the TSH levels, participants were divided into 2 groups, 1 and 2. Group 1 included euthyroid individuals with fasting blood glucose less than 110 mg/dl and normal TSH (0.27 to 4.2 Mu/L), T3, T4, FT3, and FT4 levels. Group 2 included those with subclinical hypothyroidism with fasting blood glucose less than 110 mg/dl, high TSH (4.2 to 10.0 Mu/L) and normal T3, T4, FT3, and FT4 levels.

Statistical Analysis

Continuous data along with categorical data were summarised as means and proportions respectively, at 5% level of significance. Mean and standard deviations of serum HbA1c levels, FBG, TSH, T3, T4, FT3, and FT4 were compared among the 2 groups and analysed using Student's independent "t" test. Spearman's correlation coefficients were computed to identify correlations of serum TSH levels with HbA1c and FBG levels. The odds ratio was computed to establish the association of subclinical hypothyroidism with high HbA1c levels. All the above statistical analyses were done using Jamovi version 2.3.18 software.

Results

A total of 69 non-diabetic individuals were recruited for the study. Among them, 33 had subclinical hypothyroidism (Group 2) and 36 were euthyroid individuals (Group 1). The mean age of the participants was 34.6 years. The mean age in Group 1 was 30.03 ± 10.15 years and the mean age in Group 2 was 39.15 ± 10.5 years. Out of 69 participants, 94% (65) were female and 6% (4) were male. In Group 1, males comprised 5.6% (2) and females 94.4% (34), while in Group 2, 6% (2) of participants were males and 94% (34) were females (Table 1).

No difference was found in haemoglobin levels among SH and control groups. The mean difference was 0.29 and it was not statistically significant. While comparing the thyroid profile in both groups, there was a mean difference of 8.44 mU/L in TSH ($p < 0.001$). A mean serum TSH level of 2.45 ± 1.38 mU/L was seen in the control group. This value was increased in the subclinical hypothyroid group which had a mean TSH of 10.89 ± 5.62 mU/L. No significant difference was found between the means of T3, T4, FT3, and FT4 in both groups (Table 1). The mean difference in FBG levels in both groups was only marginally significant ($p = 0.046$). Group 1 had a mean FBG of 95.7 ± 6.88 mg/dl and Group 2 had a mean of 99.21 ± 7.35 mg/dl. There was a higher mean HbA1c level in Group 2 participants as compared to Group 1, the mean difference being 0.52% ($p = 0.02$). The mean HbA1c level in Group 1 was 4.394 ± 0.89 % and that in Group 2 was 4.91 ± 0.88 % (Table 1).

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Table 1.Values of Parameters of Subclinical Hypothyroid and Normal Subjects

S. No.	Parameters	Group 1 Euthyroid (Mean ± SD)	Group 2 Subclinical Hypothyroidism (Mean ± SD)	p value
1.	**Socio-demographics**			
	Age (years)	30.03 ± 10.15	39.15 ± 10.5	< 0.001
2.	**Hb (gm/dl)**	12.35 ± 0.69	12.06 ± 0.74	0.09
3.	**Thyroid function**			
	TSH (mU/L)	2.45 ± 1.38	10.89 ± 5.62	< 0.001
	T3 (nmol/L)	1.17 ± 0.37	1.31 ± 0.69	0.502
	T4 (µg/dL)	7.77 ± 2.42	7.32 ± 0.91	0.459
	FT3 (pg/dL)	2.46 ± 0.65	2.13 ± 1.026	0.245
	FT4 (ng/dL)	1.28 ± 0.47	1.14 ± 0.571	0.406
4.	**Glycemic status**			
	FBG (mg/dl)	95.7 ± 6.88	99.21 ± 7.35	0.046
	HbA1c (%)	4.394 ± 0.89	4.91 ± 0.88	0.018

p < 0.05 has been considered significant.

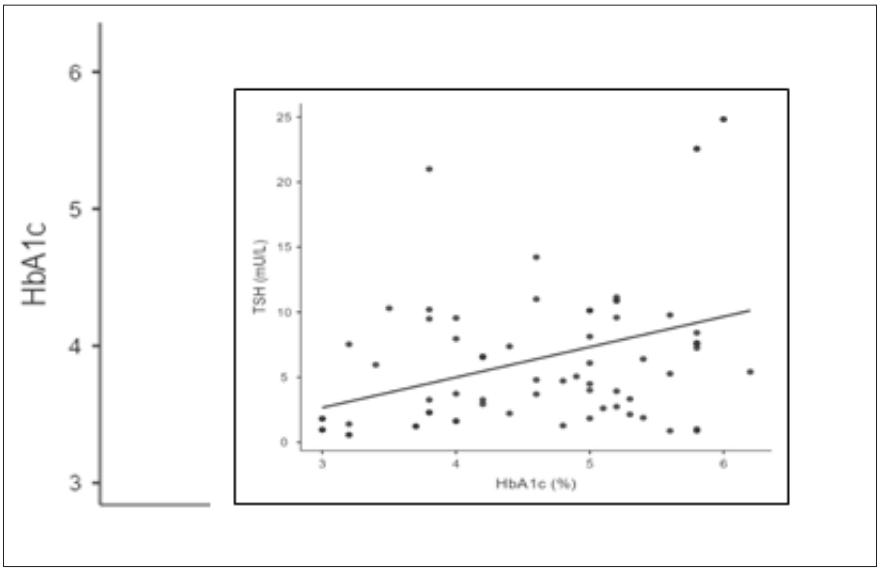

Figure 1.Median HbA1c Values

Table 2.Correlation of TSH with FBG and HbA1c

	Spearman's Correlation Coefficient	p Value	Strength of Association
FBG	0.331	0.005	Weak
HbA1c	0.363	0.002	Weak

p < 0.05 has been considered significant.

The median HbA1c levels in euthyroid and subclinical hypothyroid individuals were 4.5% and 5.0% respectively (Figure 1). There was a significant positive correlation (p = 0.002) of serum TSH with HbA1c levels with a Spearman's co-efficient of 0.363 (Figure 2). Similarly, a positive correlation (p = 0.005) of serum TSH with FBG was present, with a Spearman's co-efficient of 0.331 (Table 2).

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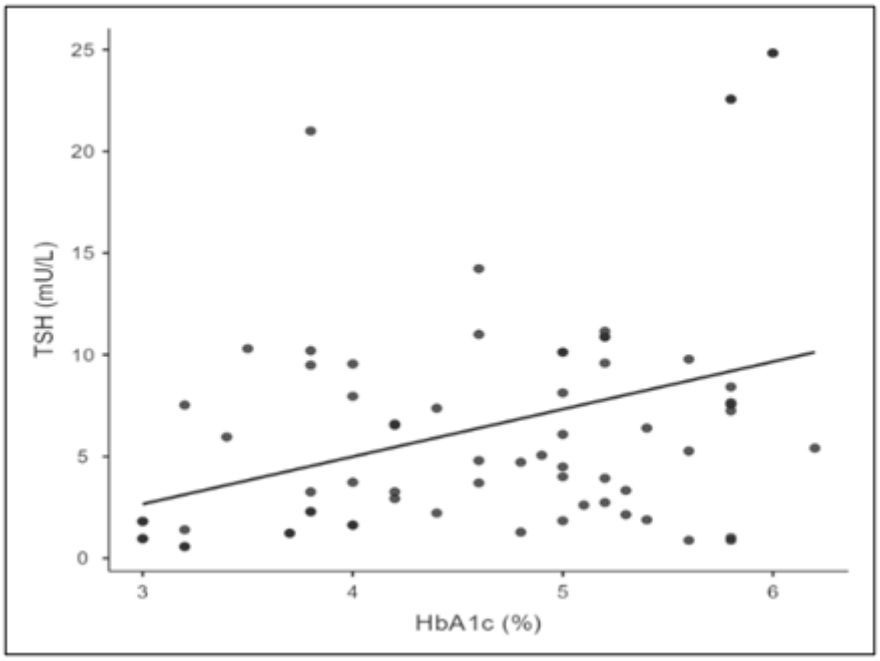

Figure 2.Correlation of Serum HBA1c with TSH Levels (r = 0.363 and p = 0.002)

Table 3.Binary Logistic Regression Analysis for Elevated HbA1c

S. No.	Variables	Crude OR with 95% CI	p Value	Adjusted OR with 95% CI	p Value
1.	Age	1.11 (1.04-1.2)	0.003	1.1 (1.02-1.18)	0.016
2.	Subclinical hypothyroidism	7.4 (1.5-36.9)	0.015	4.13 (0.76-22.56)	0.102

$p < 0.05$ has been considered significant.

Binary logistic regression was computed to establish the association between subclinical hypothyroidism and HbA1C elevation. The regression model (Table 3) was statistically significant ($\chi2(2) = 14.8$, $p \leq 0.001$) and it explained 31.9% (Nagelkerke R2) of the HbA1c elevation in non-diabetic individuals. Increasing age was associated with an increased likelihood of HbA1c elevation by a factor of 1.1 which was significant ($p = 0.016$), even after adjusting for thyroid status. Individuals with subclinical hypothyroidism had 7.4 times higher odds for HbA1c elevation than euthyroid individuals, but the significance of this association was lost after adjusting for age (Table 3).

Discussion

We carried out our study on 69 non-diabetic subjects; among them, 33 had subclinical hypothyroidism and 36 were healthy euthyroid individuals. HbA1C has been recommended by ADA as one of the criteria that can be used to diagnose diabetes mellitus. In this study, we found a significant increase in HbA1c levels in the non-diabetic SH group as compared to the euthyroid controls ($p = 0.018$), though the mean serum HbA1c levels were within the normal range. This is in accordance with other studies which had also reported similar results.[9,12-16] We had excluded those with anaemia and no significant difference was found in haemoglobin levels in both groups. Some studies have found reduced erythropoiesis/ anaemia to be related to elevated HbA1c levels.[8,16]

Vyakaranam et al. found serum insulin as well as HOMA-IR (Homeostatic Model Assessment for Insulin Resistance) to be significantly high in SH, compared to that in euthyroid state and serum TSH to be positively correlated with insulin and HOMA-IR.[13] Maratou et al. found the Insulin- resistant state to be present during fasting and also in post-prandial states.[16] El-Eshmawy et al. observed that prediabetic individuals with SH had higher fasting insulin, HOMA-IR, and TSH levels compared to healthy controls.[17] Stoica et al. were not able to identify any relationship between reduced thyroid function and insulin resistance.[18]

We identified a positive significant correlation of HbA1c levels with TSH ($p = 0.002$). Similarly, Ram et al. not only

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found HbA1c to have a positive correlation with TSH ($p < 0.0001$), but also substantiated that SH correlated with hyperinsulinaemia and insulin resistance.[9] In their study, Sharma et al. found the insulin resistance index to be positively correlated with TSH.[19] SH was found to independently increase the risk of reduced insulin sensitivity in muscle and adipose tissue, which in turn correlated with insulin resistance and hyperinsulinaemia.[9] Subclinical hypothyroidism together with insulin resistance may disrupt the glycemic homeostasis.[20]

In our study, SH was also found to be positively associated with HbA1c levels and individuals with SH had higher odds of elevation of HBA1c, compared to euthyroid people ($p = 0.015$). Christy et al. observed that hypothyroid patients with anaemia had higher odds of having HbA1c more than 6.5.[11] Both SH and clinical hypothyroidism have been described as insulin-resistant states.[18,21] This insulin-resistant state, in turn, could be responsible for the elevation of HbA1c levels in subclinical hypothyroid patients.

In a study by Roos et al., low normal levels of FT4 were associated with increased insulin resistance. Hence they reported that FT4 levels were inversely related to HOMA-IR in euthyroid individuals.[22] Kim et al. observed in their study that after thyroid hormone replacement therapy in overtly hypothyroid patients, the HbA1C levels had gone down.[23] All the above findings throw light on the effect of underlying thyroid status on serum HbA1c levels, causing its spurious elevation, in non-diabetic individuals.

Limitations

- This study has been carried out in a small population in South India.
- RBC indices, serum insulin levels, and insulin resistance have not been assessed in association with HbA1c and TSH levels.

Conclusion

As per our data, HbA1c levels are increased in non-diabetic individuals with subclinical hypothyroidism, which may be related to insulin resistance. Hence we have to consider the possibility of underlying subclinical hypothyroidism while making a diagnosis of either prediabetes/ diabetes mellitus based on elevated HbA1c levels. This finding needs to be validated by further studies in a larger population.

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Conflict of Interest: None

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