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A Comparative Study on Levels of Glycated Haemoglobin (Hba1c) In Non-Diabetic Hypothyroid and Euthyroid Patients

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ABSTRACT

Introduction: The thyroid disorders are one of the most common endocrine disorders in developing countries such as India and any derangement in thyroid hormones causes widespread pathological manifestations in human body. One such manifestation is altered RBC turnover which causes an increase in the mean age of erythrocytes, thus, causing falsely elevated glycated haemoglobin (HbA1c) levels even in non-diabetic population.

Aims and objectives: To study effect of hypothyroidism on HbA1c levels and its comparison in non-diabetic hypothyroid and euthyroid subjects.

Material and method: This cross-sectional study was done on 100 non-diabetic subjects that presented in Department of Medicine, Government Medical College, Amritsar, Punjab. They were divided into 2 groups, Group A (non-diabetic patients with newly diagnosed hypothyroidism) and Group B (non-diabetic euthyroid controls). Both groups were subjected to routine history taking, physical examination, hematological and biochemical tests. The data was analyzed using appropriate statistical methods.

Result: In our study, patients in Group A had a mean HbA1c level of 5.44±0.30% and Group B had a mean HbA1c level of 5.14±0.31%. This difference was statistically significant ($p<0.001$). There was a significant positive correlation between HbA1c and TSH levels in group A ($r=+0.565$ and $p=0.0001$) and also a significant negative correlation between HbA1c and T4 levels in group A ($r=-0.421$ and $p=0.0023$).

Conclusion: Thus, our study concluded that HbA1c levels can be falsely elevated in patients with hypothyroidism in the absence of true hyperglycemia and this can result in overestimation of HbA1c in non-diabetic patients.

Keywords: Glycated Haemoglobin (HbA1c), Thyroid Stimulating Hormone (TSH), Hypothyroidism.

INTRODUCTION

The thyroid gland is a vital endocrine gland. It plays a major role in the growth and development of the human body and also controls numerous metabolic functions of the body from birth.[1] Thyroid disorders and Diabetes mellitus (DM) are two common endocrine disorders in adult population. Presence of one disorder can influence the other. Thyroid disorders are particularly common in T1DM, involving about 1/3rd of patients. In children with T1DM, 20% may have anti thyroid antibody & 3-8% may have autoimmune hypothyroidism.[2] In hypothyroidism, glucose homeostasis is also affected although its clinical impact is less obvious. Decreased glucose disposal has been proved in hypothyroid patients by different methods including clamp studies. But it is compensated by reduced

intestinal absorption of glucose and reduced hepatic glucose output.[3] HbA1c levels are used as a diagnostic test for diagnosis of DM.[4] These can affected by a number of genetic, hematologic, medicines, and illness-related factors, one such being altered thyroid hormone levels which causes elevated HbA1c levels, even in non-diabetic population.[5]

Review of Literature

Overt Hypothyroidism is categorized by TSH >10 mIU/L with fall in unbound T4 levels and more readily apparent symptoms.[6] Iodine deficiency and autoimmune Hashimoto's disease accounts for majority of cases of primary hypothyroidism.[7] One-third of the world's population live in iodine deficient areas and the catastrophic consequences of severe iodine deficiency on fetal and child neurological and cognitive development are well recognised.[8]

Thyroid dysfunction has an intersecting underlying pathology with type 2 diabetes mellitus (T2DM). The literature is punctuated with evidence indicating a contribution of abnormalities of thyroid hormones to type 2 DM. The most probable mechanism leading to T2DM in thyroid dysfunction could be attributed to perturbed genetic expression of a constellation of genes along with physiological aberrations leading to impaired glucose utilization and disposal in muscles, overproduction of hepatic glucose output, and enhanced absorption of splanchnic glucose. A plethora of preclinical, molecular, and clinical studies have evidenced an undeniable role of thyroid malfunctioning as a comorbid disorder of T2DM. HbA1c can be affected by changes in erythrocyte lifespan, because increasing the mean age of erythrocytes will increase HbA1c. Thyroid hormones stimulate erythrocyte production, and hypothyroidism often results in hypo-proliferative erythropoiesis leading to decreased RBC turnover which causes an increase in the mean age of erythrocytes thus causing falsely elevated glycated haemoglobin levels, even in non-diabetic population.[5]

There are many studies which support the above hypothesis. In one study conducted by Kim et al, HbA1c levels were measured in 45 non-diabetic patients with overt hypothyroidism and 180 euthyroid control subjects. HbA1c levels were higher in patients with hypothyroidism compared with control subjects and these levels were decreased by thyroid hormone replacement.[9]

Similarly, a case-control study conducted by Makadia et al included 200 individuals for the study of HbA1c levels, out of which 100 were hypothyroid cases and 100 were euthyroid controls. The mean HbA1c levels were 5.70 ± 0.35 % and 5.26 ± 0.17 % in the case and control groups respectively. The levels were significantly higher in case group ($p<0.0001$).[10]

In another study done by Billic-Komarica E et al, the sample consisted of 100 patients with Subclinical Hypothyroidism (SH). 20 patients with SH had prediabetes and 38 patients had DM. After 6 months of treatment with L-thyroxine, the patients had significantly reduced HbA1c (6.74±1.01 vs. 6.26±1.12). The correlation between TSH and HbA1c was positive and significant ($r=0.46$).[11]

Christy AL et al in a study assessed HbA1c levels of 120 non-diabetic hypothyroid patients (30 microcytic hypochromic anaemia, 30 normocytic normochromic anaemia and 60 non anaemic patients) with 120 controls. Non-diabetic hypothyroid individuals with anaemia showed elevated A1C levels in pre-diabetes range. Hence care should be exercised while using HbA1c as a diagnostic tool for diabetes in such patients.[12]

In a prospective longitudinal study carried out by Anantarapu S et al, adult non-diabetic patients with overt hypothyroidism were rendered euthyroid on thyroxine. HbA1c fell from 5.8 ± 0.7% to 5.6 ± 0.5% ($p = 0.009$) at 3 months following the correction of hypothyroidism. The number of patients with dysglycemia diagnosed by HbA1c (i.e HbA1c ≥ 5.7%) fell from 25 to 17 after treatment. Thus the study revealed that HbA1c is not a reliable diagnostic test for diabetes in the presence of hypothyroidism.[13]

Aims and objectives

1. To study the effect of hypothyroidism on glycated hemoglobin levels.
2. To compare the HbA1c levels in non-diabetic hypothyroid and euthyroid patients.

Materials and Methods

This was a cross-sectional study which was done on 100 non diabetic subjects, 50 of which were included in "Group A" and were newly diagnosed with hypothyroidism who presented to the Medicine department (indoor/outdoor department) of Guru Nanak Dev Hospital Amritsar and fulfilled the

Volume 4, Issue 2; March-April 2021; Page No 698-704

inclusion criteria of the study and 50 were euthyroid, included in "Group B" serving as controls. The study was conducted after approval from Institutional Ethics Committee, Govt. Medical College Amritsar. The patients were explained in their vernacular language about the procedure to be adopted in the study and their informed consent was taken.

INCLUSION CRITERIA:

1. Age between 18 to 60 years of both the genders.
2. Recently diagnosed overt primary hypothyroidism.

EXCLUSION CRITERIA:

1. Patients with diabetes, Impaired glucose tolerance (IGT) or Impaired fasting glucose (IFG)
2. Hemoglobin <10 gm/dl
3. Renal dysfunction (B. Urea >50mg/dl or S. Creatinine >1.5mg/dl)
4. Hepatic dysfunction (increased bilirubin, reduced albumin [<3.5mg/dl], SGOT and SGPT 3 times upper limit of normal)
5. Acute or subacute thyroiditis
6. Known hemoglobinopathies
7. Pregnancy

A detailed history and clinical examination were recorded in the patient proforma. Complete blood count was done using automated cell counter.

HbA1c was measured by fully automated serum analyzer (Cobas c311 by Roche) and serum thyroid hormone profile was measured by Enzyme linked immunosorbent assay (ELISA) technique on serum concentration.

Plasma glucose, urea, creatinine, bilirubin, SGPT, SGOT, Albumin and Globulin were estimated by standard protocols on Semi-auto analyzer.

Data Analysis

Descriptive statistics was calculated using Excel 2010 (Microsoft, Redmond, WA, USA). Statistical analysis was performed using SPSS 21.0 statistical package (SPSS, Chicago, IL). Student's t test and Chi square test were used. Association between variables was assessed by Pearson's coefficient of correlation. Data was presented as mean ± standard deviation (SD). p value of <0.05 was considered significant and p value of <0.001 as highly significant and p value of >0.05 was considered as non-significant.

Observations and Results

The present study entitled glycated haemoglobin levels in non-diabetic hypothyroid and euthyroid patients was conducted in Guru Nanak Dev Hospital attached to Govt. Medical College, Amritsar. This was a cross sectional study on 100 Non Diabetic patients. Out of these, 50 patients were Hypothyroid and were included in Group A (Case Group), and rest 50 patients were Euthyroid and were included in Group B (Control Group).

The patients in Group A had a mean age of 41.16 ± 10.807 years and Group B had 42.56 ± 11.718 years. The difference was statistically not significant (p=0.54). In Group A, males were 9 (18%) and females were 41 (82%). In Group B, males were 8 (16%) and females were 42 (84%). The sex distribution in two groups was statistically not significant (p=0.79).

In our study, there was no statistically significant difference of hemoglobin, total leukocyte count, mean corpuscular volume, mean corpuscular haemoglobin, mean corpuscular haemoglobin concentration, red cell count, blood urea, serum creatinine, serum bilirubin, serum transaminases and serum proteins between both groups. There was a statistically significant difference between thyroid function tests between both groups.

There was no significant difference between mean fasting blood sugar (FBS) and 2 hour oral glucose tolerance test (2hr OGTT) levels between both groups. The patients in Group A had a mean HbA1c level of 5.444 ± 0.301 and Group B had a mean HbA1c level of 5.144 ± 0.311. The difference was statistically very significant (p<0.0001).

Volume 4, Issue 2; March-April 2021; Page No 698-704

Table 1: COMPARISON OF MEAN HbA1c LEVELS IN BOTH GROUPS

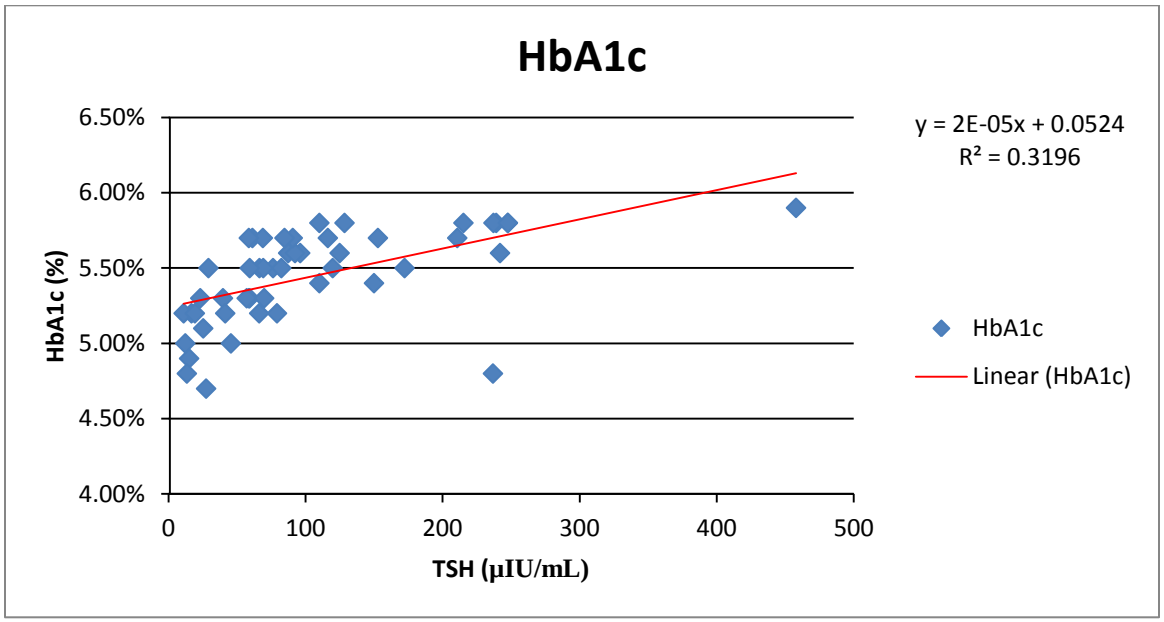
HbA1c (%)	Group A	Group B	P Value
Mean ± SD	5.444 ± 0.301	5.144 ± 0.311	<0.0001*

*Significant

Among 50 patients of Group A, 16 patients (32%) had an HbA1c level more than 5.6% and 3 patients (6%) of Group B had an HbA1c level more than 5.6%. The difference was statistically significant (p=0.0009)

The HbA1c levels and serum TSH levels in patients of group A were found to have a positive correlation with Pearson's correlation coefficient (r) = 0.565 with a statistical significant p value = <0.0001.

Chart 1: SCATTER PLOT SHOWING CORRELATION OF HBA1C WITH SERUM TSH LEVELS IN GROUP A (HYPOTHYROID PATIENTS)

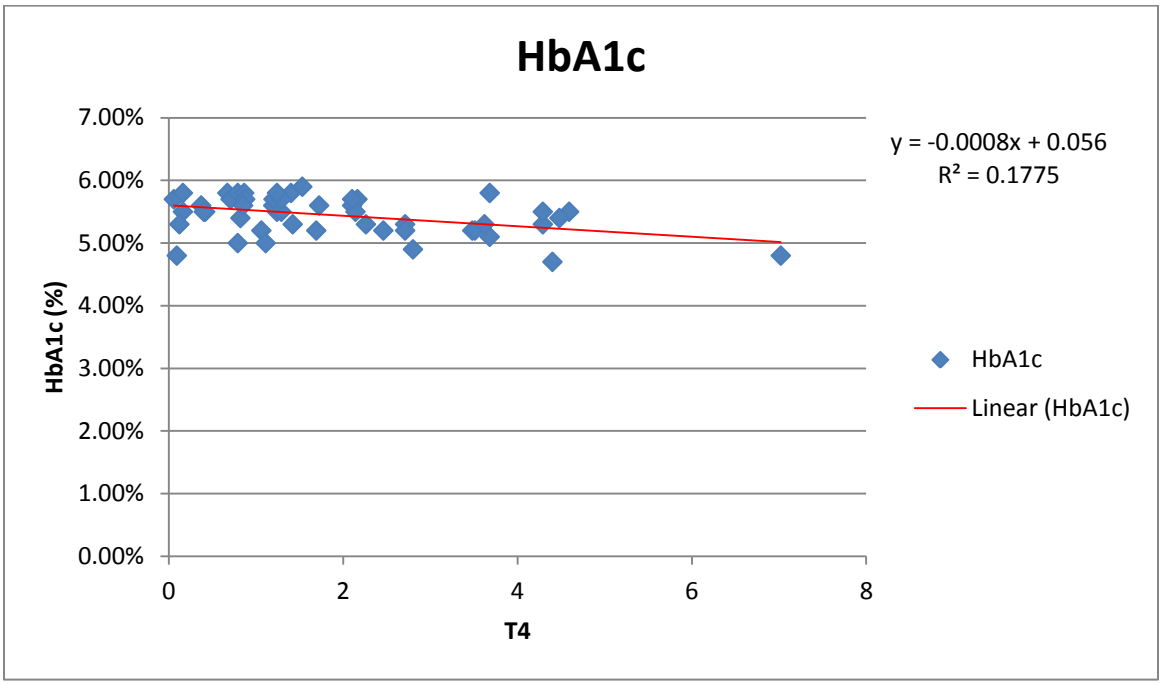


The HbA1c levels and serum T3 levels in patients of group A are found to have no significant correlation (r=-0.117, p=0.417).

The HbA1c levels and serum T4 levels in patients of group A are found to have a significant negative correlation (r=-0.421, p=0.0023).

Volume 4, Issue 2; March-April 2021; Page No 698-704

Chart 2: SCATTER PLOT SHOWING CORRELATION OF HBA1C WITH SERUM T4 LEVELS IN GROUP A (HYPOTHYROID PATIENTS)



The FBS levels were also compared with TSH, T3 and T4 levels and no significant correlation was found between these entities. The HbA1c was also compared with FBS and 2hr OGTT levels and no significant correlation was found.

Discussion

Hypothyroidism is approximately 10 times more common in women than men.[14] There is also a growing appreciation in India that hypothyroidism represents a substantial health problem, despite extensive universal salt iodisation.[15] In this study a total of 100 non diabetic subjects were taken, 50 of which were included in "Group A" and were newly diagnosed with hypothyroidism and 50 were euthyroid, included in "Group B" serving as controls. Christy AL et al conducted a study on 120 non diabetic hypothyroid patients to investigate elevation of HbA1c levels in these patients.[12]

In the present study, the mean age of group A was 41.16 ± 10.807 years and Group B was 42.56 ± 11.718 years. It was observed that there was no statistically significant difference between the two groups. In study conducted by Makadia et al, the mean age of cases was 49.45 ± 101.03 years and controls was 48.28 ± 11.27 years.[10]

In the present study the ratio of male to female patients was 0.22 in group A and 0.19 in group B. It was observed that there was no statistically significant difference between the two groups. A study conducted by Kim MK et al had a male to female ratio of 0.3 in case group which is comparable to our study.[9]

There was a statistically significant difference between thyroid function tests between both groups.

In the present study, the patients in Group A had a mean HbA1c level of 5.44±0.30% and Group B had 5.14±0.31%. The difference was statistically significant (p value<0.001). In study by Kim MK et al, the mean HbA1c levels in hypothyroid cases was 5.57 ± 0.26% and in euthyroid controls was 5.37 ± 0.32%. The difference between the two groups was statistically significant.[9] Similarly, Makadia et al found mean HbA1c levels of 5.7 ± 0.35% in hypothyroid patients compared to 5.26 ± 0.17% in euthyroid control group. The difference was statistically significant.[10] In another study conducted by Christy AL et al, the hypothyroid group had a mean HbA1c level of 5.91 ± 0.31% and control group had a mean HbA1c level of 5.46 ± 0.62%. The difference was significant statistically.[12]

In the present study, 16 out of 50 patients (32%) in the hypothyroid group had HbA1c ≥5.7% compared to 3 out of 50 patients (6%) in the euthyroid group. This difference was also found to be statistically

Volume 4, Issue 2; March-April 2021; Page No 698-704

significant (p value=0.0009). In a study conducted by Anantarapu S et al, 25 out of 38 patients (65.78%) had HbA1c ≥5.7% irrespective of blood sugar levels and 16 out of 38 patients (42.1%) had HbA1c ≥5.7% with normal FBS and normal PPBS levels.[13]

The HbA1c levels and serum TSH levels in patients of group A were found to have a positive correlation with Pearson's correlation coefficient (r) = 0.565 with a statistical significant p value = <0.0001. This explains the elevation of HbA1c in group A hypothyroid patients when compared to group B euthyroid patients. Makadia et al found significant positive correlation between HbA1c and serum TSH levels (r=0.51, p<0.0001).[10] Similar findings were also found by Billic-Komarica E et al with Pearson's correlation coefficient (r) = 0.46 and a statistical significant p value <0.05.[11] Similarly, studies conducted by Kim MK et al[9] and Anantarapu S et al[13] also found a positive correlation between HbA1c and serum TSH levels.

The HbA1c levels and serum T3 levels in patients of group A were found to have no significant correlation (r=-0.117, p=0.417). The HbA1c levels and serum T4 levels in patients of group A were found to have a significant negative correlation (r=-0.421, p=0.0023). In a study conducted by Karar T et al, no significant correlation was found between HbA1c levels and serum T4 levels with Pearson's correlation coefficient (r) = -0.018 and a statistically non significant p value = 0.855.[16] A study conducted by Ogbonna SU et al found a significant negative correlation of HbA1c with free T3 levels.[17] Both these studies showed findings in contrast to our study. The possible explanation for this could be explained by the fact that both these studies were done on diabetic patients, and thyroid disorders are much more common in these patients, compared to general population. The state-of-art evidence suggests a pivotal role of insulin resistance in underlining the relation between T2DM and thyroid dysfunction. A plethora of preclinical, molecular, and clinical studies have evidenced an undeniable role of thyroid malfunctioning as a comorbid disorder of T2DM.

In the present study, we also studied correlation of HbA1c with FBS and 2hr OGTT in Group A (non diabetic hypothyroid) patients. No significant correlation was found which showed that, even though diabetic population has a direct relationship between blood sugar levels and HbA1c levels, the elevation of HbA1c levels in hypothyroid patients of our study were independent of blood sugar levels and affected by complex metabolic and pathophysiological effects of thyroid hormone dysfunction on the human body and not due to the effect of hyperglycemia.

Conclusion

Our study showed that in hypothyroid patients, due to complex metabolic and pathophysiological effects of thyroid hormone dysfunction on the human body, the bone marrow and further RBC survival and turnover are disturbed which could be a possible cause of elevation of HbA1c levels in hypothyroid patients of our study and this elevation was independent of blood sugar levels, suggesting that caution should be exercised when using HbA1c as a diagnostic tool in patients with thyroid dysfunction.

Thus, in the present study we conclude that HbA1c levels can be falsely elevated in patients with hypothyroidism in the absence of true hyperglycemia and this can result in overestimation of HbA1c and further prediabetes or diabetes in patients who do not have a chronic hyperglycemic state.

Bibliography

1. InformedHealth.org [Internet]. Cologne, Germany: Institute for Quality and Efficiency in Health Care (IQWiG); 2006-. How does the thyroid gland work? 2010 Nov 17 [Updated 2018 Apr 19].
2. Kordonouri O, Maguire AM, Knip M. Schober E, Lorini R, Holl RW, Donaghue KC. Other complications and associated conditions with diabetes in children and adolescents. Pediatric Diabetes 2009; 10: 204-10
3. Rochon C, Tauveron I, Dejax C et al. Response of glucose disposal to hyperinsulinemia in human hypothyroidism and hyperthyroidism. Clin Sci 2003; 104:7-15.
4. American Diabetes Association. Standards of Medical Care in Diabetes. Diabetes Care. 2012;35(1):S11-S63.
5. Fein HG, Rivlin RS. Anemia in thyroid diseases. Med Clin North Am. 1975 Sep;59(5):1133-45.

Volume 4, Issue 2; March-April 2021; Page No 698-704

6. Jameson JL, Kasper DL, Longo DL, Fauci AS, Hauser AL, Loscalzo J. Harrisons Principles of Internal Medicine. 18th Edition McGraw-Hill Publishers;2018;Vol 2:2918
7. Chaker L, Bianco AC, Jonklaas J, Peeters RP. Hypothyroidism. Lancet. 2017 Sep 23;390(10101):1550-1562.
8. Zimmermann MB. Iodine deficiency. Endocr Rev. 2009 Jun;30(4):376-408.
9. Kim MK, Kwon HS, Baek KH, Lee JH, Park WC, Sohn HS, Lee KW, Song KH. Effects of thyroid hormone on A1C and glycated albumin levels in nondiabetic subjects with overt hypothyroidism. Diabetes Care. 2010;33(12):2546–8.
10. Makadia MG, Patel VI, Patel KP, Shah AD, Chaudhari KS, Shah HN, Nilayangode HN. Study of Glycated Haemoglobin (HbA1c) In Non-Diabetic Subjects with Subclinical Hypothyroidism. J Clin Diagn Res. 2017 Apr; 11(4):BC01-4.
11. Billic-Komarica E, Beciragic A, Junuzovic D. The Importance of HbA1c Control in Patients with Subclinical Hypothyroidism. Mater Sociomed. 2012;24(4):212-9.
12. Christy AL, Manjrekar P, Babu RP, M S R, Hegde A. Elevation of HbA1C in Non-diabetic Hypothyroid Individuals: Is Anaemia the Connecting Link? -A Preliminary Study. J Clin Diagn Res. 2013 Nov;7(11):2442-4.
13. Anantarapu S, Vaikkakara S, Sachan A, Phaneendra BV, Suchitra MM, Reddy AP, Epuri S, Mukka A, Vemvakam D. Effects of thyroid hormone replacement on glycated hemoglobin levels in non diabetic subjects with overt hypothyroidism. Arch Endocrinol Metab. 2015 Dec;59(6):495-500.
14. Vanderpump MP. The epidemiology of thyroid disease. Br Med Bull. 2011;99:39-51.
15. Bagcchi S. Hypothyroidism in India: more to be done. Lancet Diabetes Endocrinol. 2014 Oct;2(10):778.
16. Karar T, Alhammad RI, Fattah MA, Alanazi A, Qureshi S. Relation between glycosylated hemoglobin and lipid and thyroid hormone among patients with type 2 diabetes mellitus at King Abdulaziz Medical City, Riyadh. J Nat Sci Biol Med. 2015 Aug;6(1):S75-9.
17. SU Ogbonna, IU Ezeani, CI Okafor, S Chinenye. Association between glycemic status and thyroid dysfunction in patients with type 2 diabetes mellitus. Diabetes Metab Syndr Obes. 2019;12:1113–22.

Volume 4, Issue 2; March-April 2021; Page No 698-704