Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/18297
DOI URL: http://dx.doi.org/10.21474/IJAR01/18297

RESEARCH ARTICLE

ASSOCIATION OF EUTHYROID TYPE 2 DIABETES MELLITUS WITH HEMOGLOBIN AND SERUM BILIRUBIN LEVELS RELATING TO GLYCEMIC CONTROL - A RETROSPECTIVE STUDY

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Manuscript Info

Manuscript History
Received: 15 December 2023
Final Accepted: 18 January 2024
Published: February 2024

Key words:-
Euthyroid, Type 2 Diabetics, Hemoglobin, Bilirubin, Glycemic Control

Abstract

Background: Diabetes, along with its comorbidities, may increase the risk of anaemia by lowering iron absorption. In diabetic patients, thyroid illness was 14.7% prevalent. In 13% of T2DM patients, subclinical hypothyroidism was the most common thyroid condition. Diabetes glucose metabolism may be impacted by thyroid dysfunction, and variations in blood TSH have been linked to variations in glycatedhaemoglobin.

Methodology: Retrospective study analysis of euthyroid type 2 diabetic patients who had attended the OPD in the department of General Medicine. The hospital records (case history from MRD) were used as the sources of information by following proper procedure in obtaining the same. Collection of data for a period of four years with Type 2 diabetes (FBS>126) and who did not possess any obvious clinical manifestations of thyroid disease was included for the study group.

Results: PBS, HbA1C, LDL, TSH are highly significant with Fasting blood sugar with(p=0.00). FBS, RBC are highly significant with HbA1C (p=0.00). Uric acid, cholesterol,directbilirubin,haemoglobinishighlysignificantwithbilirubin(p=0.00).whereascholesterol, total billirubin are highly significant with haemoglobin (p=0.00). Hb showedpositive association with FT4. TAG, VLDL, Globulin showed negative association with FBS.HbisnegativelyassociatedwithTotalbilirubin.Cholesterolexhibitsstrongnegativeassociation with Hemoglobin (HbA1c ≥7). TSHwere associated with FBS. Direct bilirubinexhibits positive association with FBS and TotalCholesterol(HbA1c ≤7).

Conclusion: Our study results outcome could be concluded that the thyroid status, haemoglobinandCBCcouldbeusefultoolforT2DMpatients.

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Introduction:-

Worldwide prevalence of diabetes mellitus is 8.3% affecting approximately 382 million people. The disease can be classified into two predominant types, as type 1 T1DM defined by the destruction of pancreatic β-cells and the absence of endogenous insulin and T2DM as well as insulin resistance, both types are featured by hyperglycemia. Insulin resistance reduces glucose tolerance especially in muscle cells and adipocytes, whereas glucose uptake is insulin dependent. This causes glucose accumulation in the circulation and consequently a hyperglycemic state, generating homeostatic and systemic imbalance. (1,2) Approximately 40% of diabetic patients were affected by kidney diseases. The decreased renal function and proinflammatory cytokines are the most important factors in determining reduction of hemoglobin levels in those patients. The inflammatory situation created by kidney disease also interferes with intestinal iron absorption and mobilization of inventories. Therefore, diabetic patients with kidney disease have the highest risk of developing anemia.(3) The prevalence of anemia is significantly greater in diabetic females (38.5%) than in diabetic males (21.6%) as well as in poorly controlled diabetic (33.46%) than those with glycemic status under control (27.9%). Diabetes can contribute to anemia through reducing absorption of iron along with diabetic complications. The prevalence of thyroid diseases in all diabetes patients was 14.7%. The most frequently occurring thyroid diseases was subclinical hypothyroidism in 13% of patients with T2DM. Thyroid dysfunction may turn affect the glucose metabolism in diabetes, changes in serum TSH were found to be associated with changes in glycated hemoglobin (HbA1c). Anemia is a common complication and is more prevalent in diabetic than the non-diabetic individuals, also anemia develops earlier and more severe in patients with renal diseases or due to any other causes. (4) Further good glycemic control in diabetes mellitus is associated with better hemoglobin levels, presence of anemia in diabetes mellitus leads to progression of small and large complications of diabetes mellitus. (5) Anemia can lead to progression of falsely low HbA1C value which may result in under treatment of hyperglycemia which in turn further lead to some complication. (3) For assessing long-term glycemic control in people with diabetes, HbA1c is the standard and preferred test. In addition to its use for diagnosis, world health organization (WHO) has endorsed the use of HbA1c as a screening test for persons at high risk of diabetes, and more importantly as a test for prediction of the risk of microvascular complications. It is formed by non-enzymatic bonding of adult haemoglobin with glucose in the blood, i.e. irreversible glycation of adult hemoglobin. If hyperglycemia stays for long, it leads to glycation of large number of HbA1c. This glycated HbA1c circulates for about 120 days which is equal to the lifespans of erythrocyte. Consequently, its value reflects long-term glycemic exposure, representing the average glucose concentration over the last 8–12 weeks. (7) Insulin resistance is also associated with thyroid dysfunction. In hypothyroidism there is a reduction in glucose-induced insulin secretion by beta cells, and the response of beta cells to glucose is increased in hyperthyroidism due to increased beta cell mass which has been reported to be the major cause of impaired glucose metabolism in T2DM. (8,9) Anaemia is a common finding in type 2 diabetes mellitus when compared with general population, further good glycaemic control in diabetic patients would be desirable to evaluate the Hb level often. (10,11) patients with type 2 diabetes mellitus are twice more likely to the anemia than the patients without diabetics. Decreased hemoglobin concentration can impair the ability of RBCs to change their shapes so as to adapt themselves to the tissue microenvironments. (12) Identified anemia as a risk factor of cardio vascular and end stage of renal diseases in diabetes is a highly disabling diseases which can causes blindness, amputations, kidney diseases, anemia, cardiovascular and brain complication among others impairing the functional capacity and autonomy and individual quality of life (13,14) Further proved that reduced Hb levels identifies diabetic patients at increased risk for premature death, despite these facts anemia is 25% in diabetic patients (15) Anemia remains unidentified in most of the diabetic patients hence it is important to identify anemia by hemoglobin concentration in T2DM patients. (16) As a byproduct of normal hemoglobin breakdown was bilirubin which act as an ant oxidative and antiinflammatory properties and may effectively protect peripheral nerves against free radicals induced damage (17) Glycated hemoglobin (HbA1c) is widely used as an important indicator of chronic glycemic control. However, the level of HbA1c is not influenced by glucose levels. There are multiple conditions that also can increase the HbA1c level regardless of glycemic status like, iron deficiency and hemolytic anemia, alcohol consumption, chronic blood loss, gestation and uremia [18,19]. Anemia was a major health problem among T2DM patients in therefore, routine screening of anemia for all T2DM patients aiding in early identification and improved management of diabetes will lead to improved quality of life in this population (20,21). Our findings highlight the need for incorporating anemia screening by evaluvating hemoglobin levels into routine diabetes care to enable early detection and treatment of anemia and thus hence improve the overall care of T2DM patients.

Subjects and Methodology:-

The study was a retrospective analysis of euthyroid type 2 diabetic patients who had attended the clinics in the department of General Medicine namely diabetic clinic. The hospital records (case history from MRD) were used as the sources of information by following proper procedure in obtaining the same. Collection of data for a period of

four years with Type 2 diabetes (FBS>126) and who did not possess any obvious clinical manifestations of thyroid disease was included for the study group. Patients with previous history of thyroid, cardiac, liver, nerve, muscle diseases, renal diseases, alcoholics, gestational diabetes was excluded.
Collection of data approximately 1100 following analyses in patient's data for a period of four years with Type 2 diabetes (FBS≥126) and who did not possess any obvious clinical manifestations of thyroid disease will be included for the study group. From each case record the information will be collected under the following headings Age, Sex,Fasting blood glucose,postprandial,HbA1C, Lipid profile, Urea , creatinine, Liver function tests,Thyroid profile (T3,T4,TSH) &Hemogram.

Statistical Analysis
The data were described as mean ± standard deviation. Correlation between biochemical parameters was studied using Spearman's rank correlation test. Multivariate regression analysis was performed to find out the association between the parameters. Analysis was carried out at 5% level of significance and $P< 0.05$ was considered as statistically significant. Statistical analysis was performed using IBM SPSS statistics version 20 for Windows.

Results:-

From a total population of 931 study patients sHbA1c>7 was 279 and HbA1c<=7 was 652 (FIGURE 1). In total number of patients 392 females and 539 males.Age between 28 and 60 years. Data were divided into three groups with correlation coefficient of biochemical parameters in T2DM (Table 1), Duration of glycatedhaemoglobin in T2DM , correlation coefficient of Biochemical and Hematological parameters comparing those with HbA1c > 7 (Table 2) , Duration of glycatedhaemoglobin in T2DM , correlation coefficient of Biochemical and Hematological parameters comparing those with HbA1c ≤ 7 (Table 3). Regression for TSH with biochemical and hematogical parameters (Table 4)

Table 1:- Correlation Coefficient of biochemicalparametersin T2dm.

Parameters		**r value**	**p value**
FBS	PBS	0.444**	0.00
	HbA1C	0.133**	0.00
	LDL	0.138**	0.00
	TSH	0.182**	0.00
HbA1C	FBS	0.133**	0.00
	PBS	0.265**	0.00
	RBC	0.268**	0.00
	MCV	0.069*	0.05
Bilrubin	Uricacid	0.126**	0.00
	Cholesterol	0.133**	0.00
	Directbilirubin	0.111**	0.001
	Hemoglobin	0.091**	0.005
Hemoglobin	Cholesterol	0.111**	0.001
	Totalbilirubin	0.091**	0.005
	Indirectbilirubin	0.070*	0.032

HbA1c-Glycated haemoglobin; TAG-Triglycerides; LDL-low density lipoprotein; TSH- Thyroid stimulatinghormone;FBS-fastingbloodsugar;PBS-Postprandialbloodsugar;RBC-Redbloodcells;MCV-meancorpusucular volume.
(Correlationcoefficientat0.01,*Correlationcoefficientat0.05)**

In (Table 1) PBS, HbA1C, LDL, TSH are highly significant with Fasting blood sugar with(p=0.00). FBS, RBC are highly significant with HbA1C (p=0.00). Uric acid, cholesterol,directbilirubin,haemoglobinarehighlysignificantwithbilirubin(p=0.00).whereascholesterol, total billirubin are highly significant with haemoglobin (p=0.00). Siginificantresultwas observedbetween MCV &HbA1cfollowed byHb& Indirectbilirubin.

Table 2:- Correlation analyses of Biochemical Parameters with HbA1c >7durationin T2DM.

Parameters		**r value**	**P value**
FBS	PBS	0.310**	0.000
	TAG	-0.080*	0.042
	VLDL	-0.090*	0.022
	Globulin	-0.081*	0.037

HbA1c	PBS	0.122**	0.002
	LDL	0.114**	0.003
TotalBillirubin	Uricacid	0.130**	0.001
	Cholesterol	0.169**	0.000
	Direct bilirubin	-0.124**	0.001
	Hb	-0.093*	0.017
Hemoglobin	Cholesterol	-0.055**	0.00
	Totalprotein	0.082*	0.035
	Total Bilirubin	-0.093*	0.019
	FT4	0.138**	0.00
	WBC	0.081*	0.039

TAG-Triglycerides; VLDL-very low-density lipoprotein; HbA1c-glycated haemoglobin; PBS-post prandialblood sugar; LDL-Low density lipoprotein; Hb-Hemoglobin; FT4- free thyroxine; WBC-white blood cells.
(Correlationcoefficientat0.01, *Correlationcoefficientat0.05)**

In (Table 2) In total of 279 patients with HbA1c >7 was included for correlation analyses.PBSandLDLwerepositively associatedwithHbA1c.UricacidandCholesterolwerepositively associated with Total bilirubin with p value of (0.001) respectively. Hb showedpositive associate with FT4. TAG, VLDL, Globulin showed negative association with FBS.HbisnegativelyassociatedwithTotalbilirubin.Cholesterolexhibitsstrongnegativeassociate with Hemoglobin.

Table 3:-Correlation analyses of Biochemical Parameters with HbA1c≤7durationin T2DM.

Parameters		**r value**	**Pvalue**
FBS	PBS	0.522**	0.00
	Urea	-0.145*	0.015
	HbA1c	0.198**	0.001
	LDL	0.217**	0.00
	Directbilirubin	0.157**	0.008
	TSH	0.246**	0.00
HbA1c	FBS	0.198**	0.00
	PBS	0.221**	0.00
Bilirubin(D)	FBS	0.157**	0.004
	Cholesterol	0.218**	0.00

PBS-post prandial blood sugar; HbA1c-glycated haemoglobin; TSH-Thyroid stimulating hormone;LDL-Lowdensity lipoprotein; HDL-high density lipoprotein.
(Correlation coefficient at 0.01, *Correlation coefficient at0.05)**

(Table 3) shows that PBS, HbA1C, LDL, TSH are highly significant (p = 0.00) with fastingbloodsugar.FBSandPBSarehighlysignificantwithHbA1C(p=0.00).FBSandcholesterol are highly significant with direct bilirubin. HbA1c, LDL, Direct bilirubin, TSHwere associated with FBS. HbA1c showed association with FBS and PBS. Direct bilirubinexhibits positive association with FBS and TotalCholesterol.

Table 4:- Multivariate Binary Logistic Regression analyses of BiochemicalandHematologicalParameters (Dependent Variable TSH).

	UnstandardizedCoefficients		**StandardizedCoefficients**		
Model	**B**	**Std.Error**	**Beta**	**t**	**Sig.**
1 (Constant)	2.234	0.541		4.126	0.000
Age	-0.012	0.005	-0.077	-2.337	0.020
Glu fasting	0.000	00.002	-0.019	-0.566	0.572
Uric acid	0.041	0.033	0.041	1.249	0.212
VLDL	-0.003	0.003	-0.033	-0.998	0.318
ALP	0.000	0.002	-0.014	-0.429	0.668
HB	0.047	0.021	0.073	2.215	0.027
Platelet	2.160	0.000	0.003	0.100	0.920

Monocytes	.017	0.020	0.027	0.815	0.416

HB-Hemoglobin;VLDL-verylow-density lipoprotein.

In(Table4)MultivariateBinaryLogisticRegressionanalysesshowedAgeandHbstronglyassociatedwith TSHand p'value(0.000and0.027)respectively.

Discussion:-

Thyroid issues and diabetes mellitus interact in a complex manner. In the current study, out of 120 diabetic participants, 20 (or 17%) had hypothyroidism and 9 (or 7.5%) had hyperthyroidism. Therefore, a total of 24.5% of the patients had thyroid disease. Six of the control participants, or 5% of the group, also showed aberrant thyroid function. These findings, which are corroborated by other research[22–26], demonstrate a significant prevalence of aberrant thyroid hormone levels in the diabetic community. 89% of the patients in a study by Moghetti et al. [27] had hypothyroidism, while 11% had hyperthyroidism. Maximum prevalence of subclinical hypothyroidism was found by Celani et al. [28], followed by hypothyroidism (23.1%). In type 2 diabetics, hypothyroidism has been demonstrated to be a more common thyroid disease.

Diabetes mellitus is one of the most common multisystemic disorders with microangiopathic and macroangiopathic effects. When paired with other recognised risk factors, hyperglycemia in T2DM affects haematological indices and may cause the degenerative effects of the disease. [29] T2DM reduces thyroid-stimulating hormone levels and impairs T4 to T3 conversion in peripheral tissues. When T2DM is not properly managed, insulin resistance and hyperinsulinemia can develop. These conditions encourage the growth of thyroid tissue and expand nodules and goitres. Another study found that persons frequently have both thyroid problems and diabetes. Both diseases involve disruption of the endocrine system and can significantly impact patients' glucose regulation and uncontrolled diabetes. Thyroid function and glucose metabolism must be carefully balanced.

Inourstudy therewascorrelationbetweenWBC,HbA1c,TSH,FBSMCH,LDLandparameters of glycoregulation. However, other studies have shown association between WBCand impaired glucose control. Chronic inflammatory state in DM due to insulin action on theadiposetissue,musclesandliverpromotedifferentiationandmaturationofWBCviaproinflammatory cytokines.[30] Yet another study showed association between WBC andimpaired glucose control chronic inflammatory state in DM due to insulin action on theadiposetissue,musclesandliverpromotedifferentiationandmaturationofWBCviaproinflammatorycytokines.[31]

AccordingtoMalandrinoNetal,hemoglobin,hematocrit and whole blood viscosity were significantly lower in subjects with retinopathy comparedwithsubjectswithoutmicrovascularcomplication,retinopathy.Possiblemechanismsfordecreased RBC indices in T2DM are structural modifications of erythrocytes membrane,changes of surface electric charge, erythrocyte aggregation, that could lead to the shorterlifespanof RBC.[32] However, previous study reported that there was an elevation in the patients with macro andmicrovascular complications in diabetes. Studies of Jindal et al showed Insulin resistance iscommonly present in T2DM and associated with a disorder of platelet functiondue to insulinaction. The complete coagulation cascade is dysfunctional in T2DM [33] In HbA1c≤7%groupthereisacorrelationbetweenfastingglucoseandplatelets.AdditionalyPCTisassociated with WBC, neutrophils, lymphocytes and monocytes. Similar results were alsoobtained in theLeventDemirtasstudy[34]

According to Ximenes et al. anemia is a prevalent comorbidity in patients with hypertensionand when present, patients have more severe symptoms and worse functional capacity as wellas increased mortality. The knowledge that anemia worsens the symptoms of hypertension isnot new, but, in recent years, the magnitude of the anemia associated with this disease hasbecomemoreevident.Themaincausesthatcontributetoanemiainpatientswithhypertension are nutritional deficiencies especially iron deficiency and chronic inflammation[35,36]

Ahigherprevalenceofdiabeticretinopathyandnephropathywasrelatedtolowerconcentrationsofhemoglobin.Furthermore,study demonstratedthathemoglobinconcentrations were independently associated with postprandial C peptide response, Lowhemoglobin concentrations are common findings in patients with diabetes. Ishimura et alshowedthathemoglobinlevelswerelowerindiabeticpatientsthaninnon-diabeticsubjects(37)

Further, 13% in hyperglycemic states, haemoglobin concentrations decreased with increaseddiabetes duration, suggesting an ongoing decline of hemoglobin levels over time in type 2diabeticpatients, consistent with previous studies. [38]

Ranil et al, also reported that patients with diabetes durations of more than 5 years have abouta 1.5-fold higher risk of developing anemia than those with diabetes durations of less than 5years. Similar study showed that haemoglobin concentrations were associated with BMI,serum total cholesterol, and triglyceride concentrations in patients with type 2 diabetes. Thesefindings reports that hemoglobin levels areassociated with nutritionalstatus. [39]

Several studies have suggested that diabetic patients showed a negative correlation betweenhaemoglobinlevelandtheurinaryalbumincreatinineratioindiabeticpatients,andanincreasedprevalenceofanemiai nmicroalbuminuriacomparedwithnormoalbuminuria,despitethere beingno significant difference in glomerularfiltration rate. [40]

Uedaetal.reportedthatindiabeticpatientswithchronicrenalinsufficiency(serumcreatinine>1.5 mg/dL), a low haemoglobin level was a significant predictor of progression torenal failure [41]. In a prospective observation study, Rossing et al, demonstrated that a lowerhemoglobinconcentrationwasassociatedwithamorerapiddeclineinglomerularfiltration [42]. In a cross-sectional study of [43] subjects with diabetes, Qiao et al reported the presence ofdiabetic retinopathy in subjects with hemoglobin levels below 120 g/L. [44]. Davis et al,showed that the hematocrit was associated with retinopathy and, in the lowest hematocritgroup, the OR for the development of highrisk proliferative diabetic retinopathy was 1.52during a 5-year follow-up. In some cases, anemia treatment was related to an improvement indiabetic retinopathy [45]

In Turkey, Coban et al, conducted a study which included 50contributors and compared HbA1c level in both those who suffered from IDA and non-anemic.ThelevelofHbA1cinthecaseofIDAwas7.4%and5.2%inthosehealthier,andthe level decreased when the IDA treated from 7.4% to 6.2%. The relationship between theHbA1c and the lifespan of RBCs is a positive one. The level of HbA1c increased when thelifespan of RBCs increased like in IDA and in some diseases related to Hb. In IDA, thereduction in the iron led to raise the level of Hbglycation which cause elevation of HbA1c.On the other hand, when HbA1c increases, it prevents the cell turnover and production,contributing to IDA occurrence. Additionally, a study published in 2016, the results showedthatthelevelofHbA1cincreasedsignificantlywiththepresenceofirondeficiency,andas the level of Hb falls asthe HbA1c level becomes high [46]. Accroding to F.Ishibashipossible mechanism underlying the association between Hb and increased risk of diabeticperipheral neuropathy and it reduces the production of bilirubin, a by-product of normalhaemoglobin breakdown with antioxidant and anti-inflammatory effects on neural tissue. Anassociation between serum total bilirubin and the morphology of corneal nerve fibers wasfoundin patients with uncontrolledT2DM [47]

Whereasourstudyshowsassociationwithtotalcholesterol,glucose,uricacidandhaemoglobin thus it indicates the importance of Hb in T2DM patients as a routine screeningparameter in future.

Conclusion:-

Based on our study result outcome it could be concluded that the thyroid status, haemoglobinandCBCcouldbeusefultoolforT2DMpatients.Thus,ourfindingssuggestthathaematologicalindicesareacce ssible,useful,simple,inexpensivelaboratoryparameterswhichcould be utilised in healthcarecentres.

Conflict of Interest:
The authors declare that there is no conflict of interest.

Acknowledgement:-

The authors thank Prof. SeetheshGhosh, Dean, Mahathma Gandhi Medical College and Research Institute, a constituent teaching unit of Sri BalajiVidhyapeeth, Dr. S.R. Rao, Vice-President (Research, innovation & Development), Sri BalajiVidypeeth and Prof.(Dr) NiharRanjanBiswas Vice-Chancellor, Sri BalajiVidyapeeth for enabling this communication.

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