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ORIGINAL ARTICLE

ASSOCIATION OF HYPOTHYROIDISM WITH TYPE 2 DIABETES MELLITUS: A HOSPITAL BASED EXPERIENCE IN A TERTIARY CARE CENTRE

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Abstract:

Background:*Thyroid diseases and diabetes mellitus are the two most common endocrine disorders encountered in clinical practice. Type 2 diabetes mellitus (T2DM) has an intersecting underlying pathology with thyroid dysfunction. Insulin and thyroid hormones are intimately involved in cellular metabolism and thus excess or deficit of either of these hormones result in the functional derangement of the other.Despite the absence of definite guidelines regarding screening for thyroid dysfunction in diabetic patients, in the view of this incidence together with the mutual effect of the common two endocrinopathies on each other and the increased risk of complications in diabetic patients in the setting of abnormal thyroid dysfunction, a systematic approach to thyroid testing in diabetic patients is favorable.* ***Methods:****A Cross sectional descriptive observational study was performed at a tertiary care centre.Patients of 30 years and older with known type 2 DM without thyroid disorders between March 2018 to September 2018 were included in this study by purposive sampling technique.A total of 100 patients were included in the study.* ***Results:****Among the study patients, 13(26%) had thyroid abnormalities, 8 cases were male and 5 cases were female. Thyroid abnormality was associated with duration of DM. The mean duration of disease was 6.28±2.57 years in patients with normal thyroid profile group and 10.92±8.13 years in patients with abnormal thyroid profile (hypothyroidism or hyperthyroidism) group. Patients with poor glycemic control prone to develop endocrinopathies like thyroid abnormality. HbA1c also shows the positive correlation with thyroid abnormality in type 2 diabetes patients. Regarding the definition of thyroid abnormality, 7% patients had Primary hypothyroidism, 2% Subclinical hypothyroidism and 3% primary hyperthyroidism and single case subclinical hyperthyroidism.* ***Conclusion:*** *Our results demonstrate that hypothyroidism is the common thyroid disorder in type 2 DM patient. It seems that unidentified thyroid dysfunction could positively impact diabetes and its complications. The ability to diagnose and treat unsuspected thyroid dysfunction in these patients may greatly enhance the quality of life. Hence the need to detect such cases where thyroid dysfunction contributes to morbidity and where it is the cause for poor control of the associated conditions.*

Keywords: *Hypothyroidism, Type 2 Diabetes Mellitus,Thyroid dysfunction.*

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Introduction:

Diabetes mellitus is a leading cause of death and disability worldwide. Bangladesh has shown diabetes as a silent killer in adults[1] .According to statement of IDF (2015), diabetes prevalence of Bangladesh in the year 2015 is 7.4%[2,3]. Diabetes is one of the largest health emergencies of the 21st century. In 2015, IDF estimates that: one in 11adults has diabetes, one in two adults with diabetes is undiagnosed and 12% of global health expenditure is spent on diabetes. Globally 415 million adults have diabetes. By 2040 this will rise to 642 million. In high-income countries, approximately 87% to 91% of all people with diabetes are estimated to have type 2 diabetes. In South-East Asia Region estimates in 2015 indicate that 8.5% (6.8-10.8%) of the adult population has diabetes. This is equivalent to 78.3 (62.9 to 100.4) million people living with diabetes.[3]

Thyroid disorders are also common, andit is second only to diabetes mellitus as the most common condition to affect the endocrine system[4]. Abnormal thyroid hormone levels can also be found in individuals with diabetes. Thyroid hormones are insulin antagonists, both insulin and thyroid hormones are involved in cellular metabolism and excess and deficit of either one can result in functional derangement of the other[5]. Greater the duration of uncontrolled T2DM in a patient, higher is the chance of thyroid dysfunction. HbA1c can be used as a test to decide if screening for thyroid dysfunction is needed in T2DM patients or not[6].

Studies have shown that hypothyroidism (Hashimoto's thyroiditis) or hyperthyroidisms (Grave's disease) are associated with diabetes. A meta-analysis reported a prevalence of thyroid dysfunction in patients with diabetes of 11%[7]. Another study in Bangladesh revealed that 10% of the patients had hypothyroidism and another 9.5% had sub-clinical conditions.Among hypothyroidism group, around 35% of the patients were in between 41-50 years of age group, whereas the lowest age group was 51-60 years (8.7%). 52% of the patients of hypothyroidism group had diabetes for more than five years[8].

Insulin resistance is a key pathological feature of type 2 diabetes and also occurs in both hypothyroidism and hyperthyroidism[9]. Study reported that in type 2 diabetic patients the prevalence of hypothyroidism and subclinical hypothyroidism was found to be 10.00% and 15.00% respectively, while the no case found in subclinical hyperthyroidism and prevalence of and hyperthyroidism was found 2.5%. The prevalence of thyroid dysfunction was found to be higher in type 2 diabetes mellitus subjects as compared to non-diabetic subjects[10].

A cross-sectional study showed a high prevalence of thyroid dysfunction in the diabetic population which indicates that screening for thyroid disease among patients with diabetes should be routinely performed. The prevalence of new cases of thyroid dysfunction diagnosed and the possible aggravation of classical risk factors such as hypertension and dyslipidemia, arising from an undiagnosed thyroid dysfunction can lead to an increased cardiovascular risk in these patients[11].

Suzuki et al in their study attributed the abnormal thyroid hormone levels found in diabetic patients to the presence of thyroid hormone binding inhibitor (THBI), an inhibitor of the extra thyroidal conversion enzyme (5-deiodinase) of T4 to T3, and dysfunction of the hypothalamo-pituitary-thyroid axis[12]. These features were observed to be aggravated by stress and poorly controlled diabetes.

The use of oral hypoglycaemic medications in the treatment of patients with type 2 diabetes also has varying effects on thyroid hormone homeostasis. Cappelli et al. in their study evaluated thyroid hormone profiles by studying the interaction between metformin and circulating thyroid function parameters in patients who were started on metformin. This study concluded that the TSHlowering effect of metformin is only seen in untreated hypothyroid patients and with L-T4replacement therapy irrespective of thyroid function test[13-14].

Altered thyroid hormones have been described in patients with diabetes especially those with poor glycaemic control. In diabetic patients, the nocturnal TSH peak is blunted or abolished, and the TSH response to TRH is impaired[15]. Reduced T3 levels have been observed in uncontrolled diabetic patients. This "low T3 state" could be explained by impairment in peripheral conversion of T4 to T3 that normalizes with improvement in glycaemic control. The abnormal thyroid hormone level may be the outcome of various medications that the diabetic patients were receiving.

Since then a number of studies have estimated the prevalence of thyroid dysfunction among diabetes patients to be varying from 2.2 to 17 %, the most common disorder being subclinical hypothyroidism[1,5-8,10,16-32]. To conclude, there is a high prevalence of thyroid disorders in patients of type 2 diabetes mellitus which was further found to be more in females, elderly patients, patients with uncontrolled diabetes. So regular screening of thyroid function in all type 2 diabetic patients should be done, especially in those with uncontrolled diabetes[33]

Methods:

This cross sectional observational study was performrd in indoor and outdoor patients of Sir Salimullah Medical College Mitford Hospital.Patients of 30 years and older with known type 2 DM without thyroid disorders who attended indoor and outpatient department (OPD) of medicine and outpatient department (OPD) of Endocrinology between March 2018 to September 2018 were included in this study by purposive sampling technique.

Patients with Type 1 DM, H/O thyroid disease (thyroid carcinoma,hypothyroidism, and goiter etc.),acute illness (sepsis, acute MI, severe heart failure, recent admission in intensive care unit),hepatic dysfunction,H/O smoking , pregnancy,H/O bronchial asthma on steroids and patients on treatment with drugs interfering with thyroid function(amiodarone , lithium) were excluded from this study.

The following standard formula is widely used in determining sample size. It was used in this study

$$n = \frac{z^2 pq}{d^2}$$

n= the desired sample size
z= Standard normal deviate usually set at 1.96
p= Proportion in the population will be 0.5 (0.01-0.99), due to unknown prevalence.
q= 1-p
d= Degree of accuracy which is considered as 0.1

According to this formula the targeted sample will be 96. Therefore 100 samples were taken in this study for convenience.

Subjects or their relatives were briefed about the objectives of the study, risk and benefits, freedom for participating in the study and confidentiality. Informed consent was obtained accordingly. Present and past history of each case record evaluated in detail regarding their general & clinical information. The pre-structured Case Record Form (CRF) was filled up by the study physician herself. The case definitions of operational variable were described. After taking informed written consent 5 cc of venous blood was collected from each patient. After getting the value of free T3, free T4, and TSH level that recorded in data sheet. Patient data such as age, sex, clinical presentation, etc were noted. This questionnaire was used for collection of information by interviewing patients. All the collected data questionnaire were checked very carefully to identify errors in collecting data.

Statistical Analysis:

After collection of all information, these data were checked, verified for consistency and edited for finalized result. After editing and coding, the coded data was directly entered into the computer by using SPSS version 24. Data cleaning validation and analysis was performed using the SPSS/PC software and graph and chart by MS excel. The result was presented in tables. A "*p*" value of <0.5 is considered as significant.

Operational definition:

Normal ranges of thyroid function test in adults are as follows[34]:

- Free Tri-iodothyronine (FT3): 3.50-8.56 pmol/L
- Free Thyroxine (FT4): 8.56-25.60 pmol/L
- Thyroid Stimulating Hormone(TSH): 0.3-5.0 m IU/L

Depending on the free T3, free T4 and TSH level, the results of thyroid function tests can be classified as follows:

1. **Euthyroid:** When FT3, FT4, TSH are within normal range.
2. **Primary hypothyroidism:** When FT4, FT3 are less than normal value and TSH more than 5.0 m IU/L.
3. **Primary hyperthyroidism**: When FT3, FT4 more than normal and TSH is more than 5.0 m IU/L.
4. **Subclinical hypothyroidism**: When TSH is more than 5.0 mIU/L and FT3, FT4 are within normal range.
5. **Subclinical hyperthyroidism**: When TSH is less than 0.3mIU/L and FT3, FT4 are within normal range.

Results:

In this study 100 patients were included who fulfilled the selection criteria. Out of them 62 were male and 38 were female.Male and female ratio was 1.63:1.Large numbers of respondents came from urban area 68.0%, followed by rural area 32.0%. The *p*-value is 0.565. So the result is not statistically significant.

Socioeconomically patients are grouped into three classes,middle class 42% comprising the major percentage of the patients, which is followed by poor class 38% and remaining are upper class 20%.Highest numbers of patients were in primary level of education (46%), illiterate was 24% , secondary passed 22%, higher secondary passed 8% and none was graduate

Demographic characteristics of the patients are shown in Table I.

Table I

Demographic characteristics of the patients (n=100)

Age (years)	Frequency		Total
	Male (n= 62)	*Female (n= 38)*	
30-40	4(6.45%)	6(15.78%)	10(10.0)
41-50	30(48.38%)	14(36.84%)	44(44.0)
51-60	22(35.48%)	10(26.31%)	32(32.0)
>60	6(9.67%)	8(21.05%	14(14.0)
Mean ± SD		49.7 ± 8.23	

In the study, the maximum incidence was seen in the 4th decade 44.0%, next to it was the 5th decade 32.0%. Highest incidence of male and female patients was in age group between 41-50 years, 48.38% and 36.84% respectively. Mean age of the patient was 49.7 ± 8.23 years.

Majority of diabetic patients were suffering for more than 6 year 62%. Only 12% of patient had history of DM <1 years. This is shown in table II.

Table II

Duration of diabetes mellitus (n=100)

Duration of DM	Number of patients	Percentage (%)
<1 years	12	12.0
1-5 years	26	26.0
6-9 years	38	38.0
>10 years	24	24.0

Assessment of serum tri-iodothyronine (T_3) level, serum thyroxine (T_4) level and serum Thyroid Stimulating Hormone (TSH) level in study subject are shown respectively in Table III, Table IV and Table V.

Table III

Assessment of serum tri-iodothyronine (T_3) levels in study subject (n=100)

Serum FT_3	Male (n=62)		Female (n=38)		P
(pmol/L)	No.	%	No.	%	value
<1.86	8	12.9	6	15.7	
1.86–6.43	49	79.0	30	78.9	
>6.43	5	8.0	2	5.2	0.086
Total	62	100.0	38	100.0	
Mean±SD	4.86	±1.3	4.62	±1.8	

Table IV

Serum thyroxine (T_4) levels in study subject (n=100)

Serum FT_4	Male(n=62)		Female (n=38)		P
(pmol/L)	No.	%	No.	%	value
<9.14	10	16.1	6	15.7	
9.14–23.18	48	77.4	29	76.3	
>23.18	4	6.4	3	7.8	0.044[s]
Total	62	100.0	38	100.0	
Mean±SD	17.25 ±1.5		18.57 ±1.82		

Table V

Study of serum thyroid-stimulating hormone (TSH) levels in study subject (n=100)

Serum TSH	Male(n=62)		Female (n=38)		P
(uIU/ml)	No.	%	No.	%	value
<0.47	4	6.4	4	10.5	
0.47–5.01	46	74.1	28	73.6	
>5.01	12	19.3	6	15.7	0.026
Total	62	100.0	38	100.0	
Mean±SD	3.68 ±1.4		3.12 ±1.1		

Status of thyroid function test in the study subject was depicted in figure I

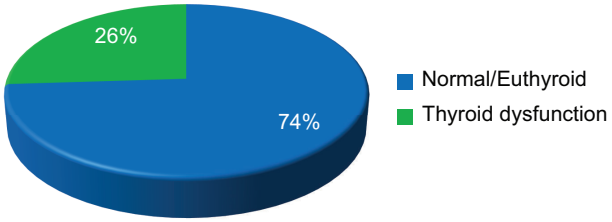

Fig.-1: *Status of thyroid function test amongst the study subject (n=100)*

Association of thyroid abnormality with duration of DM was presented in Table VI

Table VI

Association of thyroid abnormality with duration of DM

Duration of DM	Number of patients		p-value
	Euthyroid state (n=74)	*Hypo/hyper thyroid (n=26)*	
<1 years	12(16.21%)	0	
1-5 years	24(32.43%)	2(7.69%)	
6-9 years	28(37.83%)	10(38.46%)	0.012
>10 years	10(13.51%)	14(53.84%)	
Mean ± SD	6.28±2.57 yr	10.92±8.13 yr	

Figure 2 represented the relationship between HbA1C and thyroid status in study subject.

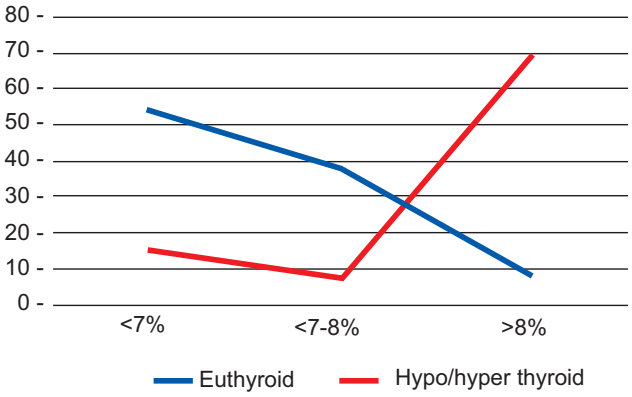

Fig.-2: *Relationship between HbA1C and thyroid status in study subject (n=100)*

Association of Hypothyroidism with Type 2 Diabetes Mellitus among 26 patients with thyroid dysfunction was depicted in Figure 3

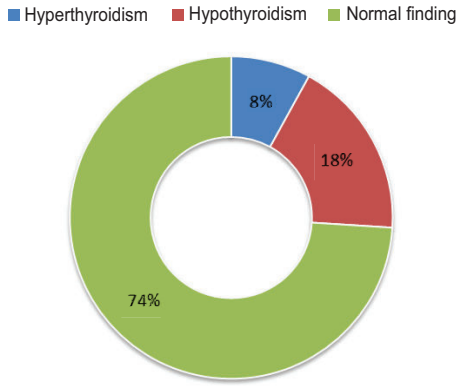

Fig.-3: *Association of Hypothyroidism with Type 2 Diabetes Mellitus (n=26)*

The pattern of thyroid abnormality among the 26 patients with thyroid dysfunction was shown in Table VII

Table VII

Pattern of thyroid abnormality in the study population (n=26)

Variable	Number of patients			p-value
	M (n= 16)	*F (n= 10)*	*Total*	
Primary hypothyroidism	8(50.0%)	6(60.0%)	14	0.400
Subclinical hypothyroidism	4(25.0%)	0	4	
Primary hyperthyroidism	4(25.0%)	2(20.0%)	6	
Subclinical hyperthyroidism	0	2(20.0%)	2	
Total	26			

Discussion:

A total 100 patients of type 2 diabetes mellitus in department of medicine and department of endocrinology, SSMC Mitford Hospital were selected. Maximum incidence was seen in the 4th decade 44.0%, next to it was the 5th decade 32.0%. Highest incidence of male and female patients was in age group between 41-50 years, 48.38% and 36.84% respectively. Mean age of the patient was 49.7 ± 8.23 years. Out of 50 cases (62%) cases were male and (38%) were female. Male and female ratio was 1.63:1.

Findings are consistent with result of other studies, e.g. Study in Bangladesh by Akter S; et al. reported that diabetes and prediabetes are highly prevalent among individuals aged 35 years or more in Bangladesh[2]. The risk of both diabetes and prediabetes was increased in older[35]. WHO listed 10 countries to have the highest numbers of people with diabetes in 2000 and 2030. According to this report, Bangladesh has 3.2 million of diabetic subjects in 2000 and the number is expected to increase to a staggering 11.1 million by 2030 placing her among the top 10 countries with diabetes[36]. Vij V et al reported that Type-2 diabetes mellitus is commonly associated with altered thyroid function. Mean age of the patients was 43.45 ± 3.18 year[4]. In a study both the diabetic and the control group are age and sex matched. The mean age (in years) of diabetic group is 55.75±8.45 and for the control group it is 54.47±9.24[37].

Large numbers of respondents came from urban area (68.0%), followed by rural area (32.0%). Socio-economically patients are grouped into three classes. Among the patients the middle class (42%) comprising the major percentage of the patients. Maximum numbers of patients were in primary level of education (46%) and illiterate was 24% patients.

Present study shows 26% of patients had thyroid abnormalities. Among them 8 cases were male and 5 cases were female. Findings are accordance with other study findings. In a study, maximum number of T2DM patients with thyroid dysfunction belonged to the age group of more than 60 years i.e. 19 out of 40 abnormal cases (47.50%) and 5 out of 9 abnormal controls (55.56%). The percentage of thyroid dysfunction was greater in male T2DM patients (M:F1.3:1). Sub-clinical hyperthyroidism was predominant in both sexes of cases as well as controls[19].

Our study demonstrated that majority of diabetic patients were suffering for more than 6 year (62%). In this series only 12% of patient had history of DM <1 years. Thyroid abnormality is associated with duration of DM. The mean duration of disease (DM) was 6.28±2.57 years in patients with normal thyroid profile and 10.92±8.13 years in patients with abnormal thyroid profile (hypothyroidism or hyperthyroidism). The mean duration of disease was highly significant when both the patient subgroups were compared. The p-value is .012312. The result is statistically significant.

All these findings are similar with the result of other study[4]. In a study, Out of the 80 type 2 diabetic subjects studied, 28.75% showed abnormal thyroid function (22.50% had hypothyroidism and 6.25% had hyperthyroidism) and 71.25% showed normal thyroid hormone level. The incidence of hypothyroidism was more in females as compared to the males in type 2 diabetes (Males 12.5 %, Females 32.50 %). Hypothyroidism was present in 22.50% patients, of which 13.75% had subclinical hypothyroidism and 8.75% had primary hypothyroidism. The ability to diagnose and treat unsuspected hypothyroidism in type 2 diabetic patients may result in better control of the diabetic state, thereby greatly enhancing the quality of life[4]. FPG and HbA1c were significantly higher in diabetic patients as compared to the non-diabetic subjects. The serum levels of T3, T4, FT3 and FT4 were significantly lower in diabetic subjects as compared to the non-diabetic subjects while level of serum TSH was significantly higher in diabetic subjects as compared to the non-diabetic subjects[4].

This study demonstrated that, 54.05 % of subjects with normal thyroid profile in the study group had glycosylated haemoglobin of less than 7% (good glycemic status). This is in contrast to the fact that 69.23% subjects diagnosed with abnormal thyroid profile had glycosylated haemoglobin of more than or equal to 8% (poor glycemic control). Patients with poor glycemic control prone to development of endocrinopathies like thyroid abnormality. HbA1c also predicts the positively correlated with thyroid abnormality in type 2 diabetes patients. Findings are consistent with result of other study. Vikhe V et al[38] The prevalence of thyroid dysfunction among type 2 DM patients is very high (30%) with subclinical hypothyroidism being the most common. The level of T3 and T4 were significantly lower while the level of TSH was significantly higher in type 2 diabetics as compared to non-diabetics. From the 50 diabetic subjects studied, 30% showed abnormal thyroid hormone levels (22 % had hypothyroidism and 8% had hyperthyroidism).

Another study[37] reported that low serum T3 level in diabetic subjects as compared to the control group. The mean levels of serum T4 and TSH levels were comparable between the two groups. Fifty one percent of subjects with normal thyroid profile in the study group had glycosylated haemoglobin of less than 7 %. The mean duration of disease (DM) was 5.98±4.23 years in patients with normal thyroid profile and 12.92±5.48 years in patients with abnormal thyroid profile (hypothyroidism or hyperthyroidism). The mean duration of disease was highly significant when both the patient subgroups in the diabetic group were compared[37]. Present study demonstrated that, prevalence of hypothyroidism is common among overall thyroid dysfunction, 18.0% of patients. Hypothyroidisms were present in 8.0% of patients.

The reported prevalence of thyroid disorders in the diabetic population varies with the characteristics of the study population. A study was carried out among diabetic patients in Calabar, Nigeria reported a high incidence (46.5%) of abnormal thyroid hormone levels among diabetic patients; the prevalence of hypothyroidism was higher in women than in men, while the prevalence of hyperthyroidism was higher in males[39]. Similarly, Radaideh et al. in Jordan, reported a prevalence of thyroid dysfunction in type 2 diabetic patients of 12.5%[40]. Bal et al. in India also found a prevalence of thyroid diseases of 40.4% among 184 type 2 diabetic patients, with a positive correlation with age of patient in the thyroid dysfunction group[41].

Pasupathi et al. investigated the effect of diabetes on thyroid hormone levels and other biochemical variables. In their study, it was found that the levels of TSH were significantly decreased, whereas the levels of T4 and free T4 (FT4) were significantly increased, in diabetic patients compared with control subjects. However, the T3 and FT4 levels did not differ significantly between groups[42]. Islam et al. investigated thyroid hormone levels in 52 uncontrolled

diabetic patients and 50 controlled subjects. They reported that patients with type 2 diabetes had significantly lower serum FT4 levels compared with the control and study subjects[43]. Bazrafshan et al. in their study of 210 type 2 diabetic patients assessed the relationship between thyroid dysfunction and diabetes. The observed disorders included goiter (30%), sub-clinical hypothyroidism (13%), clinical hypothyroidism (4%), and clinical hyperthyroidism (0.5%). A significant positive correlation was observed between haemoglobin (HbA1c) concentration and TSH levels among the subjects[44].

A cross sectional study in Bangladesh shows prevalence rate of thyroid dysfunction was 10%. Females were found with higher rate of thyroid dysfunction (78.3%) with male (21.7%). The majority of the patients had diabetes for more than a five-year duration (52%). Patients aged between 41-50 years were found to be more affected with thyroid dysfunction (34.8%)[45].

Conclusion:

There is higher prevalence of thyroid disorders in type 2 diabetics. This finding is more common in diabetic females. The most common thyroid disorder is hypothyroidism. The association of thyroid disorder with diabetes is more frequent in diabetics who have deranged metabolic control. Thyroid also influences the glycosylated haemoglobin levels. Thus, biochemical screening for thyroid disease is justified in diabetic patients in view of high yield demonstrated in this study and the likelihood of symptoms of thyroid disease being masked by the diabetic state and thyroid aggravating the diabetic picture. The approach of using a screen test to explore thyroid disorders was not effective, rather routine screening is recommended for all type 2 diabetes patients to reduce the burden of the disease.

Limitations:

This study was not without limitation. One of the limitations of the study was small sample size. Also it was a single centre study. Only patients of Sir Salimullah Medical College Mitford Hospital were taken for the study. So this will not reflect the overall picture of the country. A large scale study needs to be conducted to reach to a definitive conclusion. Study was conducted in a tertiary care hospital which may not represent the real scenario of primary or secondary care centre.

Conflict of Interest:

The authors stated that there is no conflict of interest in this study.

Funding:

No specific funding was received for this study.

Ethical consideration:

The study was conducted after approval from the ethical review committee. The confidentiality and anonymity of the study participants were maintained

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