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Screening For Thyroid Disorders In Patients Of Diabetes Mellitus

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Abstract

Background: Diabetes mellitus is an endocrinal disorder and is associated with other endocrine disorders in various ways. Same is the case with thyroid gland. Endocrinopathies are seen in adult population of both the glands. Insulin and thyroid hormones are intimately involved in cellular metabolism and so excess or deficit of both either of these hormones could result in functional derangement of the other.

Methods: A case-control study was carried out among 50 newly diagnosed type 2 diabetic patients. Thyroid-stimulating hormone (TSH), free triiodothyronine, free thyroxine, and blood glucose levels were measured in sample of fasting serum sample. Homeostasis model assessment for IR was calculated as per formula.

Result: Among 50 diabetic patients, 16 were hypothyroid, 5 were hyperthyroid, and 19 were found to be in normal euthyroid. Blood glucose was found to be significantly higher in hypothyroid when related with euthyroid patients. A positive association was found between TSH and blood glucose (r =- 0.281) among hypothyroid patients though association was not significant. In hyperthyroid patients, a strong negative correlation (r = −0.514) was found between TSH and blood glucose levels, but no association was found among euthyroid patients.

Conclusion: Ignoring the presence of thyroid hormone dysfunction is one of the important causes of poor treatment of DM. Therefore, in routine, thyroid hormones in diabetic patients must be done to improve the morbidity from either of these two causes.

Keywords: Diabetes mellitus, insulin resistance, thyroid hormones, thyroid-stimulating hormone

Introduction

Thyroid is highly vascular ductless gland that claps the upper part of trachea. It extends from 5th or 6th tracheal ring to oblique line on the tracheal cartilage. Thyroid gland produces two hormones thyroxin (T3) and triiodothyronine (T4). They act through nuclear receptor and play an important role in cell differentiation during development and help to maintain thermogenic and metabolic homeostasis in the adult. These hormones require a rare element Iodine for bioactivity. They are utilized as part of very large precursor molecule (thyroglobulin) and stored in an intracellular reservoir (Colloid)[6].There is peripheral conversion of T4 to T3, which is more active hormone. In various foothills Iodine is scarce, so it is given as supplementation in food stuffs like salt. Conversion of thyronine from tyrosine and this synthesis takes place in thyroglobulin. About 70% of the iodide in thyroglobulin exists in the inactive precursor, mono-iodotyrosine (MIT) and di-iodotyrosine (DIT). When iodine supplies are sufficient, T3:T4 ratio is about 7:1. In iodine deficiency, this ratio decreases as does DIT: MIT ratio. Various acid protease and peptidases hydrolyze to thyroglobulin into its constituent amino acids including T3 and T4 which are discharged from the basal portion of the cell. TSH, secreted by thyrotrope cells of anterior pituitary plays a pivotal role in control of thyroid axis and serves as the most useful physiological marker of thyroid gland hormones. Thyroid axis is a classic example of an endocrine feedback loop. Hypothalamic TRH stimulates

pituitary production of TSH, which, in turn, stimulates thyroid hormone synthesis and secretion. Thyroid hormones give feedback negatively to inhibit TSH and TRH production[8]. In metabolically stable diabetic patients, basal TSH levels and TSH response to thyrotropin-releasing hormone (TRH) are essentially normal. However, poorly controlled diabetic patients may show poor TSH responses to TRH or loss of the normal nocturnal TSH peak. TSH secretion normalizes when Euglycaemia is achieved. Hyperthyroidism is defined as hyper metabolic condition caused by excessive production of thyroid hormones. This disorder is caused by a number of conditions resulting from excess availability of thyroid hormone. Thyrotoxicosis is defined as the state of thyroid hormone excess thyroid function. In primary hyperthyroidism there is an increase in T3 and T4 with a TSH suppressed to undetectable cases except in those cases in which hyperthyroidism is mediated by TSH itself[14]. In subclinical hyperthyroidism there is persistently suppressed serum TSH itself. In subclinical hyperthyroidism there is persistently suppressed serum TSH concentration with normal values of serumT3 and T4. Subclinical hyperthyroidism is found in approximately 2% of the population. A serum TSH level of less than 0.1 micro U/ mL is associated with progression to overt hyperthyroidism, atrial fibrillation, reduced bone mineral density and cardiac dysfunction[5]. There is little evidence that early treatment alters the clinical course. T3 and T4 hormones and insulin both are antagonistic to each other in cell metabolism. According to Mouradian et al (1983), hypothyroidism is found in about 3% of patients with insulin-dependent diabetes mellitus (IDDM). Moreover, 13-20% of IDDM patients have elevated blood thyrotropin levels and anti-thyroid antibodies. Type 1 DM is an autoimmune disorder. Patients of type 1 DM are at a risk of developing other autoimmune diseases, thyroid disorders being one of them. Up to 30% of type 1 female diabetic patient has thyroid disease. In one of the study it is shown that Hypothyroidism was more common in females (41%) than in males (19%) subjects and in patients with positive TPO antibodies (Type 1 DM)[16]. Annual laboratory determinations of anti-TPO antibodies and level of TSH should be part of routine tests in the diabetic population, especially in girls, children with DM for > 9 years, patients above 12 years of age and those in whom DM is associated with another autoimmune disease. Anti-thyroid antibody positivity may indicate the necessity for thyroid function testing at shorter intervals. So any type of rise and fall in one causes derangement in the other. Recently, it has been investigated that if blood glucose is persistently raised it influences thyroid hormone action on insulin levels. But this correlation of glucose levels causes thyroid dysfunction. The development of diabetes may also lead to many metabolic abnormalities[15]. It has been found that studies have revealed recently the rates of prevalence of thyroid hormone disorders in type 2 diabetes[1]. Compared to normal diabetic patients have higher incidence of thyroid disorder. As a whole hypothyroidism has been found to be the most commonly detected. In cases of endemic goiter, iodine deficiency is the major cause of hypothyroidism. Since the prevalence rate of hypo- or hyperthyroidism in various parts of the world different, the prevalence rates of thyroid dysfunction in diabetes still remain controversial. Unidentified disorder of thyroid may lose the metabolic controls in patients with diabetes and may also exaggerate already existing CVA risk. Diagnosis and treatment of thyroid disorder in diabetic patients may better glycemic control, decrease cardiovascular risk, and maintains the better health status[2]. With this background, we intended to do a study to look for thyroid dysfunction in diabetic patients and to find the correlation between thyroid hormones and Insulin Resistance, if any.

Material & Methods

The study was carried out in Clinical laboratory of Department of Medical Biochemistry, Govt. Medical College & Hospital, Amritsar. A total of fifty patients were taken attending the OPD & Indoor of Guru Nanak Dev Hospital, Amritsar suffering from diabetes mellitus (Type 1, Type 2) which served as test group and another 50 persons living in the same socioeconomic strata, most of the times attendants of the patients were taken as control group (age and sex matched from the same population with normal blood sugar). Exclusion criteria Patients with the following history were excluded from the study. Total/Subtotal thyroidectomy, Patients on I131 treatment, lithium, antithyroid drugs, Graves disease, toxic multi nodular goiter, toxic adenoma and carcinoma patients, Radiation exposure, Gestational hyperthyroidism

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Collection and processing of blood sample 7ml of fasting venous blood sample was drawn from each subject under aseptic conditions. 2 ml of the Sample was dispensed in to fluoride oxalate bottles for plasma glucose estimation.

Exclusion criteria:

Patients with the following history were excluded from the study:-

Total/Subtotal thyroidectomy, Patients on I^{131} treatment, lithium, antithyroid drugs. Graves disease, toxic multinodular goiter, toxic adenoma and carcinoma patients, Radiation exposure, Gestational hyperthyroidism, chronic renal failure

Collection And Processing Of Blood Sample:-

5 ml of fasting venous blood sample was drawn from each subject under aseptic conditions.2 ml of the Sample was dispensed in to EDTA vials. Sample was send to the hematology laboratory. The rest of the sample was discharged into a plain vial and allowed to clot. The serum was separated and used for various investigations.

Following investigations were carried out in all the patients:-

Fasting blood glucose: - glucose oxidase method, Serum T_3 estimation: - Immunoenzymometeric assay, Serum T_4 estimation: - Immunoenzymometeric assay, Serum TSH estimation: - Immunoenzymometeric assay, Hb estimation:- Acid haematin method using Sahli's haemoglobinometer, TLC: - Thoma-Zeiss haemocytometer with improved Neubar counting chamber, Blood urea estimation:- Diacetyl monoxime method, Serum creatinine estimation: - Method of Brod and Sirota.

Observations

Table-I Distribution Of Cases According To Age In Study And Control Groups

AGE GROUPS(IN YEARS)	STUDY GROUP		CONTROL GROUP	
	NO. OF CASES	PERCENTAGE (%)	NO OF CASES	PERCENTAGE (%)
15-30	10	20	9	18
31-45	15	30	14	28
46-60	25	50	27	54

Table-I shows that in study group, 10 patients (20%) were in the age group of 15-30 years, 15 patients (30%) were in age group of 31-45 years, 25 patients (50%) were in age group of 46-60 years. In the control group 9 subjects (18%) were in the age group of 15-30 years, 14 subjects (28%) were in age group of 31-45 years, 27 subjects (54%) were in age group of 46-60 years.

Table-II Mean Age Of Subjects In Study And Control Groups

	STUDY GROUP		CONTROL GROUP		P VALUE
	MEAN	±SD	MEAN	±SD	
MEAN AGE (YEARS)	42.68	11.9	42.24	12.7	0.429
Range (years)	17-59		18-60		

The mean age in the study group was 42.68±11.9 years and range is 17-59 years. The mean age in the control group was 42.24±12.7 years and range is 18-60 years. This table shows that both the groups were similar statistically with respect to the mean values of age.

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Table-III Distribution Of Cases According To Gender

	STUDY GROUP		CONTROL GROUP	
	NO OF CASES	PERCENTAGE (%)	NO OF CASES	PERCENTAGE (%)
MALE	21	42	19	38
FEMALE	29	58	31	62

In the study group there were 21 males and 29 females whereas in the control group there were 19 males and 31 females. The difference between the two groups was not statistically significant.

Table-IV Distribution Of Patients According To Gender In Type1, Type2 Diabetes Mellitus

	TYPE1 DIABETES MELLITUS (TOTAL NO-7)	TYPE2 DIABETES MELLITUS (TOTAL NO-43)
MALE	3	18
FEMALE	4	25

In Type1 diabetes mellitus there were 3 males and 4 females (Total 7 patients). In Type 2 diabetes mellitus there were 18 males and 25 females (Total 43 patients).

Table-V Routine Hematological And Biochemical Investigations In Study And Control Groups

	Study group		**Control groups**		**p value**	**Significance**
	MEAN	**±SD**	**Mean**	**±SD**		
HB (GM%)	10.93	1.37	11.25	1.81	0.161	NS
TLC (CUMM)	7553	966	7448	1122	0.277	NS
BLOOD UREA (MG%)	26.76	5.63	27.78	5.55	0.182	NS
SERUM CREATININE (MG%)	1.5	0.28	1.47	0.29	0.255	NS

The above table shows that these investigations (Hb, TLC, Blood urea, Serum creatinine) of both the groups were comparable and all were within the normal range.

Table-VI Comparison Of Thyroid Hormones (T3, T4, Tsh) And Fbs Levels In Study And Control Groups

	Study group		Control group		p value	Significance
	Mean	±SD	Mean	±SD		
SerumT3 (ng/ml)	0.814	0.40	1.22	0.38	<.0001	HS
SerumT4 (µg/dl)	6.30	1.95	7.85	2.09	<.05	S
SerumTSH (µIU/ml)	6.40	5.96	3.35	2.26	<.05	S

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FBS (mg %)	159.1	16.17	85.4	11.0	<.0001	HS

The mean level of serum T3 was 0.814±0.40 ng/ml and 1.22±0.38 ng/ml in patients of study and control group respectively. T3 values were highly significant when compared between two groups (p<0.0001). The mean level of serum T4 was 6.30±1.95 µg/dl and 7.85±2.09 µg/dl in patients of study and control group respectively. T4 values were significant when compared between two groups (p<0.05). The mean level of serum TSH was 6.40±5.96 µIU/ml and 3.35±2.26 µIU/ml in patients of study and control group respectively. TSH values were significant when compared between two groups (p<0.05). The mean levels of FBS were 159.1±16.17 mg% and 85.4±11.0 mg% in patients of study and control group respectively. FBS values were highly significant when compared between two groups (p<0.0001).

Table-VII Comparison Of Thyroid Hormones (T3, T4, Tsh) Level Between Type 1, Type 2 Diabetic Mellitus Patients

	TYPES OF DIABETES MELLITUS				P VALUE	SIGNIFICANCE
	TYPE 1		TYPE 2			
	MEAN	±SD	MEAN	±SD		
SERUMT3 (NG/ML)	0.68	0.52	0.83	0.38	>.05	NS
SERUMT4 (µG/DL)	5.52	3.0	6.43	1.74	>.05	NS
SERUMTSH (µIU/ML)	10.76	9.93	5.69	4.86	<.05	S

The mean level of serum T3 was 0.68±0.52 ng/ml and 0.83±0.38 ng/ml in patients of diabetes mellitus Type1 and diabetes mellitus Type2 respectively. T3 values were not significant when compared between two groups (p>0.05). The mean level of serum T4 was 5.52±3.0 µg/dl and 6.43±1.74 µg/dl in patients of diabetes mellitus Type1 and diabetes mellitus Type2 respectively. T4 values were not significant when compared between two groups (p>0.05). The mean level of serum TSH was 10.76±9.93 µIU/ml and 5.69±4.86 µIU/ml in patients of diabetes mellitus Type1 and diabetes mellitus Type2 respectively. TSH values were significant when compared between two groups (p<0.05).

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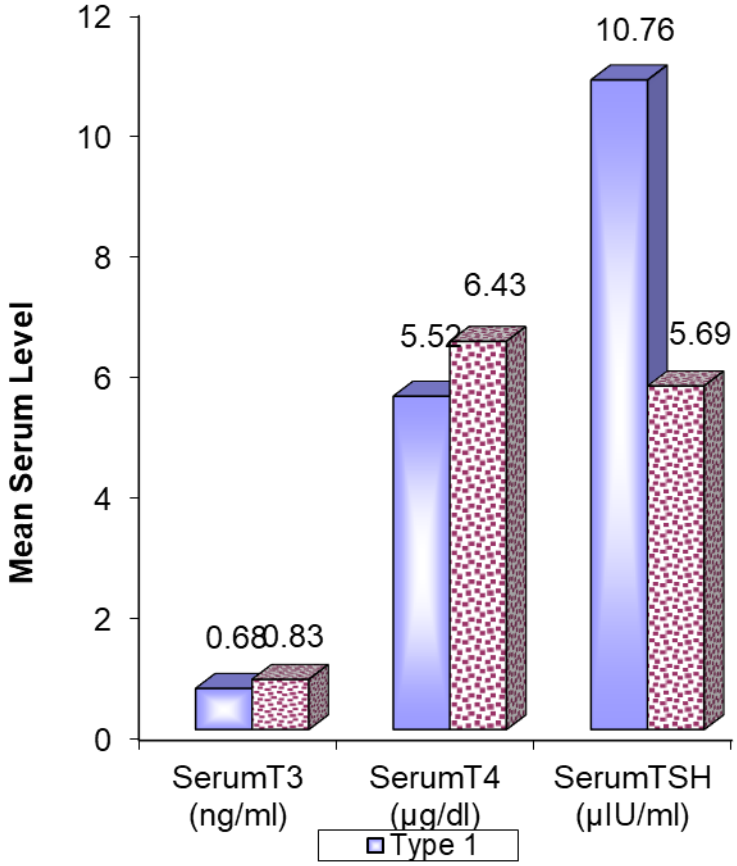
GRAPH 1: COMPARISON OF THYROID HORMONES (T3,T4,TSH) LEVEL IN PATIENTS OF DIABETES MELLITUS (TYPE 1, TYPE 2).



Discussion

Various studies have found that diabetes and thyroid disorders tend to co-occur in patients. Almost one third of people with type 1 diabetes have been found to have thyroid disease. This is because type 1 diabetes and the most common thyroid disorders are1 autoimmune diseases, which are diseases in which the immune system attacks a gland or organ of the body[3]. People with an autoimmune disease are more likely than the general population to develop other autoimmune diseases, such as Addison disease, pernicious anemia, rheumatoid arthritis, or lupus. Our study was planned to assess correlation between thyroid disorders and diabetes mellitus (Type 1, Type) The study was carried out in 50 adult cases of type 1, type 2 diabetes mellitus who reported to Guru Nanak Dev Hospital, Amritsar. Fifty adults of same age group and normal sugar levels acted as controls. Patients with history of total/subtotal thyroidectomy, patients on I^{131} treatment, lithium, antithyroid drugs, diagnosed cases of Graves ' disease, toxic multinodular goiter, toxic adenoma and carcinoma patients, gestational hyperthyroidism were excluded from the study[11]. Patients with chronic renal failure and history of radiation exposure were also not included in the study. In the present study it was seen that the levels of thyroid hormone i.e. T3, T4 and TSH affected in diabetes mellitus both type 1 and type 2[11]. On one hand the levels of serum T3 and T4 were not significantly change in type 1 when compared with type 2 DM, because in type 1 DM there were cases of Primary hypothyroidism but the prevalence of this type of diabetes is very low in population whereas prevalence of type 2 DM were very high in normal population as compared to type 1 DM, and in this type of DM there were patients of both Primary and Subclinical hypothyroidism and Hyperthyroidism so the levels of serum T3 and T4 does not decrease significantly in type 1 DM when compared with type 2 DM[9].On the other hand the levels of serum TSH was significantly raised in type

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1 DM when compared with type 2 DM. From this study it was clear that:-

1. Thyroid hormones levels i.e. T3, T4 and TSH significantly changes in diabetes mellitus (type 1, type 2) due to Occurrence of cases of Primary hypothyroidism in type 1 and type 2 diabetes mellitus and cases of Primary and Subclinical hypothyroidism and Primary and Subclinical hyperthyroidism in type 2 DM.
2. Serum TSH is the sensitive marker in case of Thyroid hormones in diabetes mellitus as its levels were always changes in cases of Primary or Subclinical Hypothyroidism or Hyperthyroidism. So it is justified that T3, T4 and TSH levels should be screened in DM (type 1, type 2).

The thyroid hormones, triiodothyronine and tetraiodothynine are insulin antagonists that potentiate the action of insulin indirectly[4]. TRH synthesis decreases in diabetes mellitus. These facts could be responsible for the occurrences of low thyroid hormone levels in some diabetics. In euthyroid individuals with diabetes mellitus, the serum T3 levels, basal TSH levels and TSH response to thyrotropin releasing hormone (TRH) may all be strongly influenced by the glycemic status. Low serum T3 is due to reduced peripheral conversion of thyroxine (T4) to tri-iodothyronine (T3) via 5' monodeiodination synthesis decreases in diabetes mellitus. These facts could be responsible for the occurrences of low thyroid hormone levels in some diabetics[5]. Our observation that thyroid disorders are more common in females is consistent with the studies done by various authors (Gray et al, Smithson, Udiong et al)[2]. The finding is probably associated with the higher prevalence of obesity recorded in female diabetics (Sacks, 1999)[12]. The various studies by Celani et al, Smithson, Bal et al, Rajan et al, Radaideh et al, Pimenta et al, Udiong et al suggests higher prevalence of thyroid disorders in diabetic patients. But in a study by Alagia Nambi et al there is a higher prevalence of thyroid disorders in non diabetic (27.6% as compared to diabetics (14.29%). The abnormal thyroid hormones levels may be the outcome of the various medications the diabetics were receiving. It is known that insulin, an anabolic hormone enhances the levels of FT4 while it suppresses the levels of T3 by inhibiting hepatic conversion of T4 to T3.[3] On the other hand some of the oral hypoglycemic agents such as the phenylthioureas are known to suppress the levels of FT4 and T4, while causing raised levels of TSH.[4]

Many studies have shown that type 1 DM is caused by autoimmune destruction of the pancreatic ß-cells, which is characterized by the presence of circulating islet autoantibodies, and has a strong association with endocrine autoimmunity. There are now reports emerging from various parts of the world about the risk for autoimmunity in subjects with type 2 DM. In our study majority of the type 2 diabetic (78%) were on oral hypoglycemic agents alone and 12% were on both insulin injections and oral hypoglycemic agents and type 1 diabetic patients were on insulin injections. Our study is being supported by the above studies showing the maximum prevalence of hypothyroidism as thyroid disorder in type 1 and type 2. Diabetics (Moghetli et al, Celani ct al, Wu. Rajan et al, Udiong ct al). The presence of both raised and low levels of thyroid hormones levels in diabetics in this study may also be due to modified TRH synthesis and release.[7] TRH synthesis decreases in diabetes mellitus (Suzuki, 1994).[76] It also depends on the on the glycemic status of the diabetics studied. Glycemic status is influenced by insulin, which is known to modulate TRH and TSH levels (Reusch et al, 1999).[6] The thyroid hormones, tri-iodothyronine and tetra -iodothyronine are insulin antagonists that also potentiate the action of insulin indirectly (Granner, 2000).

These facts could be responsible for the occurrences of low thyroid hormone levels in some diabetics.

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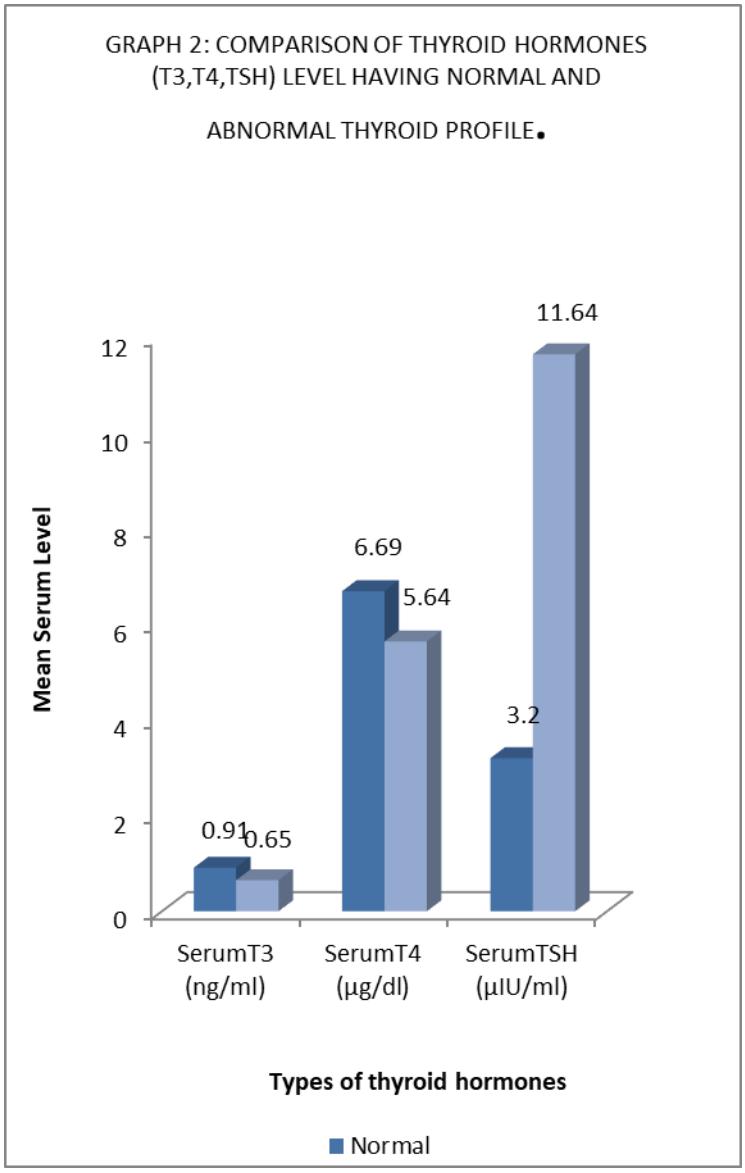

Summary And Conclusion

Thus to conclude, there is high prevalence of thyroid disorders in diabetes mellitus (Type 1, Type 2). The thyroid disorders are more common in females[9]. The most common thyroid disorders are hypothyroidism. In Type1 diabetes mellitus there are chances of Primary hypothyroidism in females as well as in males. In Type2 diabetes mellitus there are chances of Subclinical hypothyroidism in females and hyperthyroidism in males. The association of thyroid disorders is more frequent in diabetics who have deranged metabolic control. From the above study it is also shown that the TSH is more sensitive marker when we compared the thyroid hormones level between Type 1 and Type 2 diabetic patients. Thus biochemical screening for thyroid disease is justified in patients of diabetes mellitus (Type 1, Type 2) in view of high yield demonstrated in this study and the likelihood of symptoms of thyroid disease being masked by diabetes mellitus.

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