Available online at http://www.journalcra.com

International Journal of Current Research
Vol. 10, Issue, 02, pp.64862-64865, February, 2018

INTERNATIONAL JOURNAL OF CURRENT RESEARCH

ISSN: 0975-833X

RESEARCH ARTICLE

THYROID HORMONES: AN IMPORTANT LINK IN DEVELOPMENT OF DIABETIC COMPLICATIONS

[1]Ms. Anmol Kohli, [2,*]Dr. Sukhraj Kaur, [3]Dr. Pashaura Singh Sandhu and [4]Dr. Mridula Mahajan

[1]M.Sc. Student, Department of Biochemistry, Government Medical College, Amritsar
[2]Assistant Prof, Department of Biochemistry, Government Medical College, Amritsar
[3]Assistant Prof, Dept. of Medicine, Guru Nanak Dev Hospital, Government Medical College
[4]Amritsar, Ex. Professor and Head, Department of Medicine, Government Medical College, Amritsar

ARTICLE INFO

Article History:
Received 28th November, 2017
Received in revised form
06th December, 2017
Accepted 10th January, 2018
Published online 18th February, 2018

Key words:
Diabetic complications,
fT_3,
fT_4,
TSH.

ABSTRACT

Background and Aim: Diabetes mellitus is one of the most common metabolic disorders with increasing prevalence. Associated thyroid dysfunction is 2.2-17% with women more frequently affected. Subclinical hypothyroidism is an important risk factor in development of complications of diabetes. The aim of the study was to evaluate thyroid profile in diabetics with and without complications and find a correlation if any amongst the complications and levels of thyroid hormones.
Design and Methods: In this study apart from the base line biochemical parameters fT_3, fT_4 and TSH were estimated in 200 diabetic individuals which included both diabetics with complications and diabetics without complications. 100 individuals were recruited to serve as controls.
Statistical analysis: Data collected is presented as mean± S.D. student t test was used to compare means and Pearson's coefficient of correlation was calculated to study the correlation between different parameters.
Results: Sub clinical hypothyroidism is prevalent in diabetic complications like Nephropathy, CAD and Hypertension. Levels of fT_3 are negatively correlated with fasting plasma glucose. Levels of fT_4 and TSH correlated positively with LDL and VLDL and negatively with HDL
Conclusions: Prevalence of sub clinical hypothyroidism is an important risk factor in development of diabetic complications. A small deviation from the normal levels of TSH should be taken into consideration and treated accordingly so as to prevent complications of diabetes.

Citation: Ms. Anmol Kohli, Dr. Sukhraj Kaur, Dr. Pashaura Singh Sandhu and Dr. Mridula Mahajan. 2018. "Thyroid hormones: An important link in development of Diabetic complications.", *International Journal of Current Research*, 10, (02), 64862-64865.

INTRODUCTION

Diabetes Mellitus is one of the most common metabolic disorder manifested by hyperglycaemia resulting due to defects in insulin secretion, insulin action or both and disturbance in the carbohydrate, lipid and protein metabolism (Tiwari, 2002). It is an important health problem affecting major populations worldwide. The incidence of Diabetes Mellitus is increasing and it is projected to grow from 415 million in year 2015 to 642 million by the year 2040. Diabetic patients have higher prevalence of thyroid disorder when compared with the normal population, with hypothyroidism being the most common disorder (Wu, 2000). Prevalence of thyroid dysfunction varied from 2.2%-17% in diabetics and women are more frequently affected than men (Papazafiropoulou *et al*., 2010). Thyroid hormones are insulin antagonists, both insulin and thyroid hormones are involved in cellular metabolism.

Corresponding author: **Dr. Sukhraj Kaur,**
Assistant Prof, Department of Biochemistry, Government Medical College, Amritsar.

Excess or deficit of any one can result in functional derangement of the other (Singh *et al*., 2011). Sub–clinical hypothyroidism is an independent risk factor for development of diabetic nephropathy (Chen *et al*., 2007). At low insulin sensitivity, relatively minor changes in TSH levels are associated with marked changes in lipid risk factors and thus cardiovascular risk (Chubb *et al*., 2005). Unrecognized thyroid dysfunction may impair metabolic controls in patients with diabetes and amplify existing cardiovascular risk. Recognition and treatment of thyroid dysfunction in diabetic patients will benefit glycemic control, attenuate cardiovascular risk, and improve general well-being. A meta-analysis reported a frequency of 11% of thyroid dysfunction in the patients with diabetes mellitus (Kadiyala *et al*., 2010). Like diabetes, diseases of the thyroid gland are also amongst the most abundant endocrine disorders in the world, second only to diabetes. Thyroid disorders can have a significant effect on blood glucose levels and, if left untreated, can affect diabetes control. The relation between type 2 diabetes mellitus and thyroid dysfunction has been a less explored arena which may behold answers to various facts of metabolic syndrome

including atherosclerosis, hypertension, and related cardiovascular disorders. Thus keeping in view the prevalence of thyroid dysfunction in diabetes and its probable role in development of different complications, the present study was planned to study thyroid dysfunction in diabetes with or without complications and to find a correlation if any between development of diabetic complications and levels of thyroid hormones.

MATERIAL AND METHODS

The present study was conducted in the Department of Biochemistry, Government medical college, Amritsar in collaboration with the Department of Medicine, Guru Nanak Dev Hospital, Amritsar. The study comprised of 200 patients suffering from Type 2 diabetes mellitus (with and without complications). The individuals diagnosed with Type 2 diabetes and visiting outpatient department and wards of GNDH were included in the study.100 age and sex matched apparently healthy asymptomatic individuals were recruited to serve as control. Written informed consent along with detailed history was taken. The individuals on drugs like Gluco-corticoids, Nicotinic acid, Thyroid hormones, β-adrenergic antagonists and Thiazide diuretics, drug addicts, patients with endocrinopathies were excluded from the study. Prior permission from Institutional Ethics Committee was taken before starting the project.

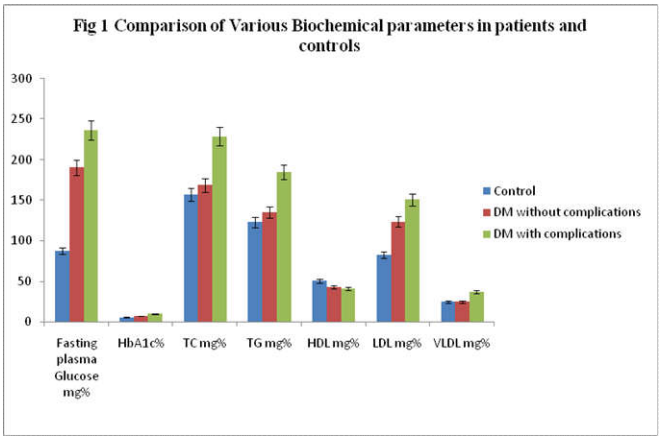
Blood glucose was estimated by glucose oxidase method as described by Trinder P (1969)[8].Glycated haemoglobin was estimated by Ion exchange resin chromatography as explained by Klen (1982) Total Cholesterol was estimated by enzymatic method as described by Charles CA (1974) using kits from Biosystems (SA Costa Brava, 30-Barcelona Spain), HDL-C was estimated by method described by Burstein (1970) using kits from Transasia Biomedicals Ltd. Serum Triglycerides was estimated by Trinder's method described by MC Gowen (1983) using kits from Transasia Biomedicals. Serum LDL was determined by using Friedwald's and Fredrickson's formula[13] LDL=TC-(HDL+ VLDL). VLDL was estimated using VLDL= Triglycerides/5 based on the average ratio of TG to cholesterol in VLDL. fT_3[14], fT_4[15] were estimated by competitive ELISA whereas TSH[16] was estimated by sandwich ELISA using diagnostic kits from MERIL diagnostic Pvt. Ltd. The data thus generated was analyzed using ANOVA (SPSS 19.0 inc. Chicago U.S.A computer software). All the values are expressed as mean±S.D. student t test was done to study the variance of mean between two groups and p value of 0.05 was taken as statistically significant.

RESULTS

The present study constituted of 200 patients of Type 2 diabetes out of which 138(69%) were having complications whereas 62 (31%) were without any complications.

Table 1. Age and sex wise distribution of controls and patients

Group	Age	Controls		DM without complications		DM with complications	
		Male	Female	Male	Female	Male	Female
I	>20-40	20	20	9	8	18	12
II	>40-60	15	10	13	11	28	22
III	>60	30	5	12	9	35	23



The mean duration of diabetes in individuals with complications was 12 years. The individuals (both diabetics and control) were divided into 3 groups depending upon their age as group I> 20-40 yr, group II>40-60 yr and group III> 60 yr. (Table 1). It was observed that maximum number of diabetics with complications belong to the age group of 60 year whereas diabetics without complications the maximum number was in the age group of > 40-60 year (both males and females). Levels of plasma glucose were more in diabetics with complications as compared to both diabetics without complications and controls. In diabetics without complications levels of Fasting plasma glucose were more as compared to controls. This increase in fasting plasma glucose was statistically significant ($p<0.05$). Levels of Glycated haemoglobin (HbA1c) correlated to the level of fasting plasma glucose in all the three groups. The mean variation was statistically significant when control group was compared with diabetics with complications and diabetics without complications. A statistically significant increase was observed when patients with and without complications were compared amongst each other (Fig 1).

Levels of Lipid profile (TC, TG, LDL, and VLDL) were more in diabetics with complications as compared to both diabetics without complications and controls. In diabetics without complications levels of Total cholesterol (TC), Triglycerides (TG) and Low density lipoproteins (LDL) were more as compared to controls. This increase in Total cholesterol, Triglycerides and LDL were statistically significant. HDL had no significant variation when the levels were compared amongst Diabetics with and without complications. The levels of HDL levels were significantly decreased in both Diabetics with and without complications as compared to controls (Fig 1) Evaluation of fT_3, fT_4 and TSH revealed significant increase ($p<0.001$) in levels of fT_3, fT_4 and TSH in diabetics with complications as compare to diabetics without complications and controls (Table 2).

Table 2. Levels of Thyroid profile in patients of Diabetes mellitus with and without complications as compared to controls

S.No.	Group	fT_3 ng/dl (Mean ±S.D)	fT_4 ng/ml (Mean ±S.D)	TSH µIU/ml (Mean ±S.D)
1	Control	1.90±0.5	1.56±0.15	0.75±0.04
2	DM without complications	1.15±0.13*	0.8±0.15*	2.4±0.14*
3	DM with complications	†2.09±0.13**	†1.79±0.15**	†5.63±0.47**

*(P<0.001) when controls were compared with diabetics without complications.
**(P< 0.001)) when controls were compared with diabetics with complications.
†(P< 0.001) when diabetics with and without complications were compared amongst each other.

Table 3. Percentage prevalence of different complications of Diabetes as per present study

S.No.	Complications	No.	% occurrence
1.	Microvascular		
	Retinopathy	9	6.53
	Neuropathy	7	5.08
	Nephropathy	30	21.74
2.	Macrovascular		
	Coronary artery disease	18	13.05
	Peripheral vascular disease	1	0.72
	Stroke	2	1.44
	Gastropathy	1	0.73
3.	Diabetic Ketoacidosis & septicaemia	8	5.80
	Hypertension	8	5.79
	Hyperthyroidism	6	4.34
	Pulmonary TB	4	2.89
3.	Others	44	31.89
	Total	138	100%

Levels of fT_3 were more in diabetics with and without complications as compared to controls, a similar trend was observed from TSH whereas levels of fT_4 were decreased in diabetics without complications as compared to controls and diabetics with complications. All the diabetics with complications were further sub divided depending on the complications into microvascular and macrovascular complications to study the %age occurrence of the various micro and macro vascular complications .In the present study it was observed that maximum number (30) 21.74% of the patients had nephropathy followed by (18) 13.05% having coronary artery disease. 6.53% patients had retinopathy whereas 5.08% had neuropathy. We encountered 1 patient of peripheral vascular disease, 1 of Gastropathy and 2 of stroke (Table 3).

Table 4. Levels of TSH in various complications as compared to normal individuals

S.No	Complication	TSH µIU/ml (Mean ±S.D)	p value as compared to controls
1	Controls	0.75±0.04	----------
2	Retinopathy	0.80±0.3	p>0.5
3	Neuropathy	0.6±0.1	p>0.5
4	Nephropathy	5.01±1.3	P<0.05*
5	Coronary artery disease	7.81±1.19	P<0.05*
6	Stroke	0.38±0.06	p<0.7
7	Diabetic Ketoacidosis and Septicaemia	0.54±0.16	P<0.6
8	Hypertension	4.38±1.77	p<0.05*
9	Hyperthyroidism	0.42±0.05	p<0.6
10	Pulmonary TB	2.97±2.2	p<0.05*

*p<0.05 statistically significant as compared to control individuals

DISCUSSION

Type 2 Diabetes is emerging as a pandemic with majority of individuals suffering in developing countries. It is a metabolic disorder involving diverse lifestyle i.e. consumption of high fat, high sodium, low dietary fibre with physical inactivity. The prevalence is expected to increase from 415 million in the year 2015 to 642 million by the year 2040 bringing along with it the burden of various complications. Keeping in view the magnitude of the disease and its expression in the form of various micro and macrovascular complications, the present study was planned to see any correlation between the levels of fT_3,fT_4 and TSH. All the individuals enrolled in the present study were classified as diabetics without complications and diabetes with complications and it was observed that the % prevalence of diabetics with complications was more as compared to diabetics without complications probably because they belonged to the age group of >40 years with a long standing period of type 2 diabetes from 5-10 years (Table1). Levels of fasting plasma glucose, complete lipid profile were statistically significantly more (Fig1) in patients with complications as compare to patients without complications. Thus indicating as the levels of fasting plasma glucose increases the levels of Glycated haemoglobin and lipid profile increases leading to the micro and macrovascular complications. The present study is in accordance with observations given in UKPDS[17] 35 prospectus observational study. Thyroid hormones are antagonist to insulin. Thus increasing the prevalence of thyroid disorders in patients with diabetics as compare to normal population. In the present study it was observed that levels of fT_3, ft_4 and TSH (Table 2) were significantly more as compare to control group. As reported in previous study[5] diabetic patients are more likely to have thyroid dysfunction as compared to normal healthy population. Serum TSH and tissue insulin sensitivity have important effect on serum lipid parameters in type 2 diabetes. Any minor change in the levels of TSH is expressed as a marked change in the lipid profile and thus cardiovascular risk. In the present study the lipid profile in diabetics with complications was significantly increased as compared to diabetes without complications thus indicating that the levels of thyroid profile affect the levels of lipid profile in diabetics (Fig1).

The metabolic control in patients of diabetics is impaired and recognition and treatment of thyroid dysfunction in diabetic patient will benefit glycemic control, attenuate cardiovascular risk and improve general values. An attempt was made to see whether there is any variation in the levels of fasting plasma glucose, Glycated haemoglobin, complete lipid profile in males and females. No significant variation of glucose and Glycated haemoglobin is seen in both males and females when compared amongst each other. As far as thyroid profile is concerned TSH levels in females were slightly higher ($P < 0.05$) as compared to males which may be an accident observation as no data regarding evaluation of TSH levels in males and females is available. In the present study out of total 138 patients of diabetics with complications 30 had nephropathy followed by coronary artery disease, retinopathy, diabetic ketoacidosis, hypertension, neuropathy, hyperthyroidism, pulmonary tuberculosis, stroke, peripheral vascular disease, gastropathy (Table 3). Increased levels of fasting plasma glucose over a prolonged period with increased lipid profile are potential cause for the development of diabetic complications. Thyroid hormones have significant effect on blood glucose and if left untreated can affect diabetes control. Increased or near normal TSH concentration is important in development of diabetic complications[6]. Diabetic nephropathy a major microvascular complication of type 2 Diabetes mellitus is an important cause of chronic kidney disease. It results from interaction between hemodynamic and metabolic factors[18]. In the present study also we encountered maximum number of patients with diabetic nephropathy (21.74%). Levels of TSH although not normal did not indicate overt hypothyroidism in cases of Nephropathy, CAD, Hypertension and Pulmonary Tuberculosis (Table 4). Iodothyronins are insulin antagonists with high levels being diabetogenic, while cessation of hormones inhibit the development of Diabetes. Failure to recognise the presence of abnormal thyroid hormones may be a primary cause of poor management of diabetes mellitus type 2. An attempt was made to study a correlation between the levels of fT_3, fT_4 and TSH with glucose, Glycated haemoglobin and complete lipid

profile. It was observed that fT_3had a negative significant correlation with fasting plasma glucose, levels of fT_4 and TSH correlated positively with LDL and VLDL and negatively with HDL thus indicating more the levels of fasting plasma glucose lesser are the levels of fT_3 leading to defective glycemic control and dyslipidemia leading on to various complications.

Conclusion

Diabetes mellitus has become a pandemic, considering the role of thyroid hormones as antagonists to Insulin, and their variation in different complications thyroid hormones should be estimated at regular intervals in diabetic patients so as to prevent the development of complications and enabling them to lead a healthy normal life.

REFERENCES

Bristow A.F., Sutcliffe, N., Ayling, C. and Bangham, D.R. 1982. Evaluation of candidate materials for replacement of international reference preparation of human thyroid stimulating hormone (TSH) for immunoassay . In hormone Drugs, Proceedings of the FDA-USP workshop on drugs, reference standards for insulins, somatropins and thyroid axis hormones . Bethaesda, MD. The U.S. Pharmacopoeial convention, inc Rockville, MD 524- 533.

Brustein, M, Scholnick, HR, Morfin, R, 1970. 'Rapid method for the isolation of lipoprotein from human serum by precipitation with polyanions, *J Lipid Res*. Vol 11, pp 583–595.

Charles, C, A' Lucy S, P, Cicely S, *et al* 1974. 'Enzymatic Determination of Total Serum Cholesterol, *Clinical Chemistry*, vol. 20, no. 4, pp 470-475.

Chen HS, Wu TEJ, Jap TS, Lu RA, Wang ML, *et al*. 2007. Subclinical Hypothyroidism is a risk factor for nephropathy and cardiovascular diseases in Type 2 diabetic patients. Diabetic Medicine. 24:1336–44.

Chubb SA, Davis WA, Davis TME. 2005. Interactions among Thyroid Function, Insulin Sensitivity, and Serum Lipid Concentrations: The Fremantle Diabetes Study. *The Journal of Endocrinology and Metabolism*. 90(9):5317–20.

Kadiyala R, Peter R, Okosieme O.E. 2010. Thyroid dysfunction in patients with diabetes: clinical implications and screening strategies. *The International journal of clinical practice*. July 64(8):1130–39.

Klenk, DC, Hermanson, GT, Krohn, RI. *et al* 1982. 'Determination of glycosylated hemoglobin by affinity chromatography: comparison with colorimetric and ion-exchange methods, and effects of common interferences, *Clinical Chemistry*, vol. 28, no. 10 pp 2088-2094.

Melmed S, Geola FL, Reed AW, Pekary AE, Park J, Hershman JM. 1982. A comparison of methods for assessing thyroid function in nonthyroidal illness. *J Clin Endocrinol Metab.,* Feb;54(2):300-6

Michael, W, Gowan, Mc, Joseph, D, *et al* 1983. 'A peroxidase coupled method for the colorimetric determination of Serum triglycerides, *Clin Chem*, vol 29/3, pp 538-542.

Nelson J.C. and Wilcox, RB. 1996. "Analytical performance of Free and Total thyroxine assays". *Clin. Chem.* Vol. 42, 146-154.

Papazafiropoulou A, Sotiropoulos A, Kokolaki A, Kardara M, Stamataki P, *et al*. 2010. Prevalence of thyroid dysfunction among Greek type 2 diabetic patients attending an outpatient clinic. J Clin Med Research.2010;2(2):75–78

Singh G, Gupta V, Sharma AK, Gupta N. 2011. Frequency of thyroid dysfunction among diabetes in Punjabi population. *Adv. Biores*. 2:3–9.

Slratton, IM, Adler, AI, Neil, HAW *et al* 2000. 'Association of glycemia with macrovascular and microvascular – complications of type 2 diabetes (UKPDS 35): Prospective observational study, '*Br Med J,* vol 321, pp405-12.

Srinidhi Rai, AshokKumar J, Prajna K, Shobith Kumar Shetty, Tirthal Rai, Shrinidhi, Mohamedi Begum, Shashikala. 2013. Thyroid function intype 2 diabetes mellitus and diabetic nephropathy. Journal of Clinical and Diagnostic Research. 2013 Aug, Vol-7(8): 1583-1585

Tiwari AK, Roa JM. 2002. Diabetes mellitus and multiple therapeutic approaches of phytochemicals: Present status and future prospectus. *Current Science*. July 83(1):30-38.

Trinder, P. 1969. 'Determination of blood glucose using an oxidase-peroxidase system with a non-carcinogenic chromogen. *J. clin. Path*, vol 22, 158-161

Udiong CEJ, Udoh AE and Etukudoh ME. 2007. Evaluation of Thyroid Function in Diabetes Mellitus in Calabar, Nigeria. *Indian Journal of Clinical Biochemistry.* 22(2): 74-78.

William, T, Friedwald, Robert, I, Levy and Donald, S, Fredrickson 1972. 'Estimation of concentration of low density lipoprotein cholesterol in plasma, without the use of preparative ultracentrifuge,' *Clinical Chemistry*, vol 18, no 6, pp 499-502.

Wu P. 2000. Thyroid disease and diabetes. *Clinical diabetes*. 18(1):1–10

****