Double Trouble: an observational study of thyroid dysfunction in South Indian subjects with type 2 diabetes

R. Anil Kumar1, R. Lalitha2, Surekha B. Shetty3

1Dr R. Anil Kumar, Consultant Diabetologist, 2Dr R Lalitha, Consultant Diabetologist, 3Dr Surekha B. Shetty, Consultant Diabetologist; All authors are affiliated to Karnataka Institute of Endocrinology and Research Bangalore, Karnataka, India.

Address for Correspondence: Dr R. Anil Kumar, Email: r.anil_kumar@yahoo.co.in

Abstract

Objective: Studies conducted in subjects with type 2 diabetes have shown increased prevalence of overt hypothyroidism and subclinical hypothyroidism. Hence, we designed a study to find out the prevalence of thyroid dysfunction in south Indian subjects with type 2 diabetes.

Research Design and Methods: 400 subjects with type 2 diabetes attending the out-patient department of Karnataka Institute of Endocrinology and Research, Bangalore were randomly selected. 200 relatives who accompanied the subjects without diabetes were recruited as controls. BMI, waist circumference, blood pressure, fasting plasma glucose, post prandial plasma glucose, HbA1c, lipid profile, and thyroid profile of these subjects were determined. Results: 400 subjects with type 2 diabetes and 200 subjects without diabetes were included in the study. They were in the age group of 25 to 75 years. Thyroid dysfunction was present in 13% of non diabetic controls. Subclinical hypothyroidism was present in 7%, overt hypothyroidism in 5% and hyperthyroidism in 1% of the controls. Thyroid dysfunction was present in 24% of subjects with type 2 diabetes. Subclinical hypothyroidism was present in 11.25%, overt hypothyroidism in 12% and hyperthyroidism in 0.75% of the 400 subjects with type 2 diabetes.

Conclusions: Hypothyroidism especially subclinical hypothyroidism is more common in south Indian subjects with type 2 diabetes. Hence, it is indispensable to investigate for thyroid dysfunction in subjects with type 2 diabetes. Failure to recognize the presence of thyroid dysfunction may be a primary cause of poor glycemic control often encountered in some subjects with type 2 diabetes, despite appropriate anti diabetic therapy. This highlights the need for the routine evaluation of thyroid function in subjects with type 2 diabetes.

Keywords: Hypothyroidism, Diabetes, Hyperthyroidism, Insulin.

Introduction

Diabetes mellitus (DM), a common endocrine metabolic disorder, is a leading cause of death worldwide [1]. It is characterized by hyperglycemia resulting from a variable interaction of hereditary and environmental factors and is due to the combination of insulin resistance and defective secretion of insulin by pancreatic β-cells or both [2]. 415 million people worldwide have diabetes in 2015; by 2040 this will rise to 642 million. The number of people with type 2 diabetes is increasing in every country. 80% of people with diabetes live in low and middle-income countries. India has 69.2 million people with type 2 diabetes and it will increase to 123.5 million by 2040 [3]. Thyroid disorders are also very common in the general population and it is second only to diabetes as the most common endocrine disorder. As a result, it is very common for an individual to be affected by both thyroid diseases and diabetes. The first report showing the association between diabetes and thyroid dysfunction were published in 1979 [4, 5]. Since then, several studies have estimated the prevalence of thyroid dysfunction among diabetes patients to be varying from 2.2 to 17% [6, 7]. Till date, not much data is available about thyroid diseases in south Indian subjects with type 2 diabetes. The aim of the present study was to evaluate the prevalence of thyroid dysfunction in south Indian subjects with type 2 diabetes.
Both insulin and thyroid hormones are involved in cellular metabolism and excess and deficit of any one can result in functional derangement of the other [8]. Thyroid disease is a pathological state that adversely affects diabetic control and is commonly found in most forms of DM which is associated with advanced age in type 2 diabetes and autoimmune diseases in type 1 diabetes. DM appears to influence thyroid function at two sites; firstly at the level of hypothalamic control of TSH release and secondly at the conversion of T4 to T3 in the peripheral tissue.

Marked hyperglycemia causes reversible reduction of the activity and hepatic concentration of T4-5-deiodinase, low serum concentration of T3, elevated levels of reverse T3 and low, normal, or high level of T4 [9]. Since thyroid hormone regulates metabolism and diabetes can alter metabolism of food, the metabolism may be further affected by the combination of thyroid disease and diabetes.

**Research Design and Methods**

400 subjects with type 2 diabetes attending the outpatient department of Karnataka Institute of Endocrinology and Research, Bangalore were randomly selected. The 200 relatives without diabetes who accompanied diabetic subjects were selected as controls. BMI, waist circumference, blood pressure, fasting plasma glucose, post prandial plasma glucose, HBA1c, lipid profile, and thyroid profile of these subjects were determined.

**Statistical Methods**- Descriptive statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean ± SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data. Microsoft word and Excel have been used to generate graphs, tables etc.

**Results**

400 subjects with type 2 diabetes were studied and 200 subjects without diabetes accompanying the patients were used as controls. The age distribution of the type 2 diabetes subjects ranged from 25 to 75 years. Body mass index of type 2 diabetes subjects were <25 in 29.5%, 25 to 30 in 44.5% and >30 in 26%. Waist circumference of the subjects were less than 80 cms in 9.5%, 80–90 cms in 27.5%, 90-100 cms in 36% and >100 in 27% (Table 1).

Family history of the subjects with type 2 diabetes showed that in 20.3% of the subjects have a father with diabetes, and another 20.3% had mother with diabetes. Both parents had diabetes in 11.5%. Positive family history was found in 52% of the type 2 diabetes subjects. Duration of diabetes ranged from 0 to >20 years. 9% were newly diagnosed. 29.25% had duration of 0f <5 years, 22% had duration of 5 to 10 years and 39.75% had duration of >10 years. 45.8% of the diabetes subjects had hypertension in this study.

Thyroid dysfunction was present in 24% of type 2 individuals with diabetes. Subclinical hypothyroidism was present in 11.25%, overt hypothyroidism in 12% and hyperthyroidism in 0.75% of the 400 type 2 diabetes subjects (Table 3). In the overt hypothyroidism group, 70.8% were females and in the subclinical hypothyroid group, 40% were females.

Thyroid dysfunction was present in 13% of non diabetic controls. Subclinical hypothyroidism was present in 7%, overt hypothyroidism in 5% and hyperthyroidism in 1% of 200 non diabetic controls (Table 3). Thyroid dysfunction was
associated with the longer duration of diabetes more than 5 years which was statistically significant. (Table 4) There was no statistically significant difference in the plasma glucose variables and HbA1C between the thyroid groups (Table 5). A statistically significant association was found among the different thyroid variables (Table 6).

There was no statistical significant difference between total cholesterol, triglycerides, HDL, LDL levels between normal, subclinical and overt hypothyroidism in type 2 diabetes individuals in our study (Table 7).

Table-1: Presents the sex and age distribution of subjects with and without diabetes.

| Group                                | Sex     | Percentage | Mean age in years | Mean BMI     | Mean waist circumference in cms |
|--------------------------------------|---------|------------|-------------------|--------------|-------------------------------|
| Type 2 subjects with diabetes N= 400 | Male    | 59         | 55.85±9.6         | 27.2±9.6     | 93.64±11.12                   |
|                                      | Female  | 41         |                   |              |                               |
| Subjects without diabetes N=200      | Male    | 59         | 55.1±8.9          | 26.89±8.9    | 92.59±11.02                   |
|                                      | Female  | 41         |                   |              |                               |

Table-2: Age distribution of individuals studied.

| Age in years | Number of patients | % |
|--------------|--------------------|---|
| 30-40        | 23                 | 5.9 |
| 40-50        | 76                 | 19.3 |
| 50-60        | 153                | 38.5 |
| 60-70        | 111                | 28.0 |
| >70          | 29                 | 7.7 |
| Total        | 400                | 100.0 |

Table-3: Comparison of Thyroid dysfunction in type 2 diabetes individuals and controls.

| Diagnosis               | Number of diabetes patients | Percentage of diabetes patients | Number of controls | Percentage of controls |
|-------------------------|-----------------------------|---------------------------------|--------------------|------------------------|
| Euthyroid               | 304                         | 76                              | 174                | 87                     |
| Sub clinical hypothyroid| 45                          | 11.25                           | 14                 | 7                      |
| Hypo thyroid            | 48                          | 12.0                            | 10                 | 5                      |
| Hyper thyroid           | 3                           | 0.75                            | 2                  | 1                      |
| Total                   | 400                         | 100.0                           | 200                | 100                    |

Table-4: Comparison of Clinical variables in type 2 diabetic subjects.

| Clinical variables       | Diagnosis                                    | P value |
|--------------------------|----------------------------------------------|---------|
| Age in years             | Euthyroid 54.51±10.53 Sub clinical Hypothyroid 56.26±9.27 Overt Hypo thyroid 56.79±10.29 | 0.272   |
| BMI (kg/m²)              | 26.61±4.16 Sub clinical Hypothyroid 27.34±4.69 Overt Hypo thyroid 27.65±4.34 | 0.208   |
| Waist circumference (cm) | 93.41±11.04 Sub clinical Hypothyroid 93.82±11.97 Overt Hypo thyroid 93.70±11.04 | 0.969   |
| Duration of diabetes in years | 7.91±7.07 Sub clinical Hypothyroid 11.48±7.96 Overt Hypo thyroid 8.76±7.23 | 0.019*  |
Table-5: Comparison of plasma glucose parameters according to diagnosis in type 2 diabetic subjects.

| Glucose parameters | Diagnosis       | P value |
|--------------------|-----------------|---------|
|                    | Euthyroid       | Sub clinical Hypothyroid | Hypothyroid |
| FPG (mg/dl)        | 177.58±70.62    | 171.60±62.63   | 158.69±59.77 | 0.207 |
| PPPG (mg/dl)       | 280.46±99.70    | 272.94±85.06   | 248.54±85.17 | 0.104 |
| HBA1c (%)          | 9.05±2.21       | 8.95±2.17      | 8.38±1.90    | 0.140 |

Table-6: Comparison of thyroid parameters subjects with type 2 diabetes.

| Thyroid parameters | Diagnosis       | P value |
|--------------------|-----------------|---------|
|                    | Euthyroid       | Sub clinical Hypothyroid | Hypothyroid |
| T3                 | 1.77±0.38       | 1.78±0.33     | 1.59±0.33   | 0.006** |
| T4                 | 105.84±22.78    | 103.01±23.47  | 103.19±29.67 | 0.650  |
| TSH                | 2.22±1.07       | 6.53±1.24     | 8.63±13.87  | <0.001** |

Table-7: Comparison of Lipid parameters according to diagnosis.

| Lipid parameters | Diagnosis       | P value |
|------------------|-----------------|---------|
| Total cholesterol (mg/dl) | 180.57±43.09 | 175.76±47.33 | 170.47±41.36 | 0.293 |
| Triglycerides (mg/dl)     | 176.07±112.39  | 164.41±99.56 | 142.56±48.61 | 0.113 |
| HDL (mg/dl)         | 40.24±9.48     | 38.09±7.99   | 42.02±7.77   | 0.163 |
| LDL (mg/dl)         | 103.55±33.78   | 106.18±42.02 | 103.81±43.26 | 0.927 |
| VLDL (mg/dl)        | 35.22±22.67    | 32.88±19.92  | 28.38±9.87   | 0.116 |

Discussion

Type 2 diabetes mellitus is a complex metabolic disorder with multiple pathophysiologic abnormalities. Insulin resistance in muscle/liver and β-cell failure represents the core defects [11, 12]. β-Cell failure occurs much earlier in the natural history of T2DM and is more severe than previously thought [13, 14]. Subjects in the upper tertile of impaired glucose tolerance (IGT) are maximally/near-maximally insulin resistant and have lost >80% of their β-cell function. In addition to muscle, liver, and β-cells (“triumvirate”) adipocytes (accelerated lipolysis), gastrointestinal tract (incretin deficiency/resistance), α-cells (hyperglucagonemia), kidney (increased glucose reabsorption), and brain (insulin resistance and neurotransmitter dysregulation) play important roles in development of glucose intolerance in T2DM individuals [15]. Collectively, these eight players comprise the “ominous octet” and dictate that 1) multiple drugs used in combination will be required to correct the multiple pathophysiological defects, 2) treatment should be based upon reversal of known pathogenic abnormalities and not simply on reducing HbA1c, and 3) therapy must be started early to prevent/slow progressive β-cell failure that is well established in IGT subjects. A treatment paradigm shift is recommended in which combination therapy is initiated with agents that correct known pathogenic defects in T2DM and produce durable reduction in HbA1c rather than just focusing on the glucose-lowering ability of the drug.

The prevalence of hypothyroidism in India is 11%, compared with only 2% in the UK and 4.6% in the USA. Compared with coastal cities (e.g., Mumbai, Goa, and Chennai), cities located inland (e.g., Kolkata, Delhi, Ahmedabad, Bangalore, and Hyderabad) have a higher prevalence (11.7% vs. 9.5%). According to Anbhirsh Mithal, chairman of the Medanta Division of Endocrinology and Diabetes (Gurgaon, India), the reason behind the higher mean thyroid stimulating hormone concentration and range in India compared with western countries is possibly linked to long-standing iodine deficiency in the country, which has only been partly corrected over the past 20 years. The highest prevalence of
hypothyroidism (13.1%) is noted in people aged 46–54 years, with people aged 18–35 years being less affected (7.5%). In Western countries the most common cause of primary hypothyroidism is autoimmune thyroiditis. However, in many parts of the world, iodine deficiency remains an important cause [16].

Several population studies have shown higher prevalence of thyroid dysfunction in diabetes. This close link has been attributed to a common genetic background [17]. The association has clinical implication since thyroid hormones have profound effects in the regulation of glucose homeostasis. Thyroid hormones are known to modify circulating insulin levels and counter regulatory hormones, intestinal absorption, hepatic production and peripheral tissues uptake of insulin. They are also involved in stimulation of gluconeogenesis and glycogenolysis [18]. Ashok kurana et al in their study showed that there was a high prevalence (16%) of thyroid disorders in patients of type 2 diabetes mellitus. Most common thyroid disorder found was subclinical hypothyroidism (7.5%) followed by hypothyroidism (4.5%) which was followed by hyperthyroidism (2.5%) and subclinical hyperthyroidism (1.5%) [19]. Navneet Agrawal et al in their study found that 27.8% had associated thyroid dysfunction, out of that 15.2% had subclinical hypothyroidism, 10.6% had clinical hypothyroidism and 2% had hyperthyroidism [20]. Laloo Demitrost et al in their study found out of the 202 type 2 DM patients included in the study, 61 are males and 141 are females.

The mean duration of type 2 DM is 62 months (just more than 5 years). It is found that 139 (68.8%) are euthyroid, 33 (16.3%) have subclinical hypothyroidism, 23 (11.4%) have clinical hypothyroidism, 4 (2%) have subclinical hyperthyroidism and 3 (1.5%) are hyperthyroidism cases. This study showed prevalence of 31.2% thyroid dysfunction in type 2 diabetes [21]. Gurjeet Singh et al in their study found 30% thyroid dysfunction among type 2 diabetes. Hypothyroidism was present in 23.75%, (15% subclinical hypothyroidism and 8.75% Primary hypothyroidism) and hyperthyroidism was present in 6.25% (all primary hyperthyroidism) of diabetic subjects [22]. Athanasia papazafiropoulou et al, in their study showed that the prevalence of thyroid dysfunction among Greek diabetic patients attending an outpatient clinic was 12.3%. Diabetic women were more frequently affected than men [23].

Table-8: Comparison of different studies regarding prevalence of thyroid dysfunction in Indian type 2 diabetes patients.

| Study                      | Thyroid dysfunction | Subclinical hypothyroidism | Overt hypothyroidism | Hyperthyroidism |
|----------------------------|---------------------|----------------------------|----------------------|-----------------|
| Ashok khurana et al        | 16                  | 7.5                        | 4.5                  | 2.5             |
| Navneet Agrawal            | 27.8                | 15.2                       | 10.6                 | 2               |
| Laloo demitrost            | 31.2                | 16.3                       | 11.4                 | 1.5             |
| Gurjeet Singh et al        | 30                  | 15                         | 8.75                 | 6.25            |
| Present study              | 24                  | 11.25                      | 12                   | 0.75            |

We have compared the present study with other studies in the table 8 and the prevalence of thyroid dysfunction is almost similar. Overt and subclinical hypothyroidism is more common in type 2 diabetes patients. The present study reports the prevalence of thyroid dysfunction in 24%, out of which subclinical hypothyroidism in 11.25%, overt hypothyroidism in 12% and hyperthyroidism in 0.75% of 400 type 2 diabetes subjects studied.

Thyroid dysfunction was present in 13% of non diabetic controls, out of which Subclinical hypothyroidism was present in 7%, overt hypothyroidism in 5% and hyperthyroidism 1% of 200 non diabetic controls. This corresponds to the prevalence data reported in the above quoted studies. This highlights the fact that all diabetic population should be screened for thyroid dysfunction.

Conclusions

Hypothyroidism and subclinical hypothyroidism are more common in South Indian type 2 diabetes individuals and so it is necessary to investigate for thyroid dysfunction in type 2 diabetes subjects. Failure to recognize the presence of abnormal thyroid hormone level in type 2 diabetes may be a primary cause of poor
management often encountered in some treated type 2 diabetics. There is therefore need for the routine assay of thyroid hormones in type 2 diabetics.

Abbreviations
DM- Diabetes mellitus.
BMI- Body mass index
TSH- Thyroid stimulating hormone.
HDL- High density lipoprotein
LDL- Low density lipoprotein
VLDL- Very low density lipoprotein
FPG- Fasting plasma glucose
PPPG- Postprandial plasma glucose
HBA1C- Glycosylated hemoglobin

Acknowledgements- Dr. K. P. Suresh, Scientist (Biostatistics), National Institute of Animal Nutrition & Physiology, Bangalore-560030. No potential conflicts of interest relevant to the article are reported.

Funding: Nil, Conflict of interest: None.
Permission of IRB: Yes

References
1. Imani SF, Hashemipour M, Kelishadi R. Lipid profile of children with type in diabetes compared to controls. ARYA Journal. 2006; 2(1):36-8.

2. World Health Organization (1985). Diabetes mellitus: Report of a WHO study group Technical Report Series 727.

3. Nam Han Cho et al (2015). IDF Diabetes Atlas Seventh Edition.

4. Feely J, Isles TE. Screening for thyroid dysfunction in diabetics. British Medical Journal. 1979; 1(6179): 1678.

5. Gray, R.S., Irvine, W.J. and Clarke, B.F. Screening for thyroid dysfunction in diabetics. Br Med J. 1979; 2 (6 202): 1439.

6. Perros P, McCrimmon RJ, Shaw G, Frier BM. Frequency of Thyroid Dysfunction in Diabetic Patients: Value of Annual Screening. Diabet Med, 1995; 12: 622−627. doi:10.1111/j.1464-5491.1995.tb00553.x.

7. Smith MJ. Screening for thyroid dysfunction in a community population of diabetic patients. Diabet Med, 1998; 15: 148−150. doi:10.1002 / (SICI) 1096-9136 (199802) 15:2<148::AID-DIA540>3.0.CO;2-I.

8. Sugrue DD, McEvoy M, Drury MI. Thyroid disease in diabetics. Postgraduate Medical Journal. 1982; 58 (685) : 680-684.

9. Shah SN. Thyroid disease in diabetes mellitus. J Assoc Physicians India, 2007; 32(12):1057- 1059.

10. Garber JR, Cobin RH, Gharib H, Hennessey JV, Klein I, Mechanick JI, Pessah-Pollack R, Singer PA, Woebber for the American Association of Clinical Endocrinologists and American Thyroid Association Taskforce on Hypothyroidism in Adults KA. Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association. Thyroid, 2012; 22(12):1200-35.

11. DeFronzo RA. Lilly lecture 1987. The triumvirate: beta-cell, muscle, liver. A Collusion responsible for NIDDM. Diabetes 1988; 37:667−687.

12. DeFronzo RA. Pathogenesis of type 2 diabetes: metabolic and molecular implications for identifying diabetes genes. Diabetes Res 1997; 5:177−269.

13. Gastaldelli A, Ferrannini E, Miyazaki Y, Matsuda M, DeFronzo RA, San Antonio metabolism study Beta-cell dysfunction and glucose intolerance: results from the San Antonio metabolism (SAM) study. Diabetologia 2004;47:3139.

14. Abdul Ghani MA, Jenkinson CP, Richardson DK, Tripathy D, DeFronzo RA. Insulin secretion and action in subjects with impaired fasting glucose and impaired glucose tolerance: results from the Veterans Administration Genetic Epidemiology Study. Diabetes 2006; 55: 1430−1435pmid:16644701.

15. DeFronzo RA. Banting Lecture. From the triumvirate to the ominous octet: a new paradigm for the treatment of type 2 diabetes mellitus. Diabetes 2009; 58:773−795pmid:19336687

16. Sanjeeet Bagcchi Lancet diabetes and endocrinology volume 2 October 2014.
17. Wang C. The Relationship between Type 2 Diabetes Mellitus and Related Thyroid Diseases. Journal of Diabetes Research. 2013; 2013:390534. doi:10.1155 / 2013/390534.

18. Huber A, Menconi F, Corathers S, Jacobson EM, Tomer Y. Joint genetic susceptibility to type 1 diabetes and autoimmune thyroiditis: from epidemiology to mechanisms. Endocrine Reviews. 2008 Oct; 29(6): 697-725.

19. Ashok Khurana, Preeti Dhoat, Gourav Jain. Prevalence of thyroid disorders in patients of type 2 diabetes mellitus JIACM 2016; 17(1): 12-15.

20. Navneet Agrawal, Manoj Gulati. Study of prevalence of thyroid dysfunction in patients with type 2 diabetes mellitus. International Journal of Contemporary Medical Research 2016; 3 (8): 2212-2214.

21. Demitrost L, Ranabir S. Thyroid dysfunction in type 2 diabetes mellitus: A retrospective study. Indian Journal of Endocrinology and Metabolism. 2012; 16 (Suppl 2) : S334-S335. doi:10.4103/2230-8210.104080.

22. Singh G, Gupta V, Sharma AK, Gupta N. Evaluation of thyroid dysfunction among type 2 diabetic Punjabi population. Advances in bioresearch. 2011 Dec 2; 2(2):3-9.

23. Papazafiropoulou A, Sotiropoulos A, Kokolaki A, Kardara M, Stamataki P, Pappas S. Prevalence of thyroid dysfunction among Greek type 2 diabetic patients attending an outpatient clinic. Journal of clinical medicine research. 2010 Mar 25; 2(2):75-8.

How to cite this article?

R. Anil Kumar, R. Lalitha, Surekha B. Shetty. Double Trouble: an observational study of thyroid dysfunction in South Indian subjects with type 2 diabetes. Int J Med Res Rev 2017;5(02):156-162. doi:10.17511/ijmrr. 2017.i02.10.