

Correlation between Diabetes Mellitus and Thyroid Dysfunction: Genetic Basis and Literature Review

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Abstract

Background: Co-existence of both thyroid dysfunction and diabetes mellitus is increasing in prevalence and is seen among many patients. The reason for this co-existence is not well known. Many different studies have been performed globally to ascertain this relationship. **Aim:** The aim of this study was to access the correlation between thyroid dysfunction and Type 1 and 2 diabetes mellitus. **Method:** Using internet search, a comprehensive literature review was done and words such as diabetes mellitus, thyroid, hypothyroidism, hyperthyroidism, thyroid antibodies, and thyroid problems were searched from Google scholar, Yahoo, PubMed, Medline, Web MD, and Scopus to check for various articles published on any probable link. The references of the relevant articles on this subject were also searched for further information. **Results:** Analyses of results of various studies from various parts of the world were considered and their prevalence was noted to access the correlation between thyroid dysfunction and diabetes mellitus. Subclinical hypothyroidism is seen as the commonest thyroid problem among female type 1 diabetes. **Conclusion:** There is a strong relationship between thyroid dysfunction and Type 1 and 2 diabetes mellitus.

KEYWORDS: Thyroid; Type 1 diabetes; Antibodies; Type 2 diabetes; Dysfunction

Introduction

Thyroid problems/dysfunctions and Diabetes Mellitus (DM) are common endocrine problems encountered by physicians globally (1). It is established repeatedly that there is a deep association and correlation between thyroid dysfunction and DM (2). These findings are consistent from the studies of many

researchers done globally. In this regard, thyroid dysfunction comprises hypothyroidism and hyperthyroidism. Historically, as far back as 1927, Coller and Huggins proved that there was a link between hyperthyroidism and aggravating diabetes mellitus, especially when the DM became complicated. Accordingly,

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surgical removal of the affected thyroid gland had an improved effect on the hyperthyroid patients who had co-existing DM (3). In many studies, it has been shown that DM and thyroid disorders have been noted to occur simultaneously in some patients (4). Both conditions (diabetes mellitus and thyroid dysfunction) involve a dysfunction of the endocrine system (4). Again, thyroid disorders have a major effect on body glucose regulation and control; and untreated thyroid disorders affect the management of DM patients (4). It is generally reported that DM patients are at an increased risk of thyroid diseases and vice versa. The frequency of thyroid dysfunction in DM patients is higher than in the general population and up to 33% of patients with Type 2 DM eventually develop thyroid dysfunctions (5). The prevalence of thyroid diseases in DM patients is 2-3 times higher than non-diabetic subjects. Thyroid disorders are known to increase with age and are strongly influenced by female gender, and autoimmune diabetes⁶.

Epidemiology

In the general population, about 6% of people have some forms of thyroid disorders (7). However, the prevalence of thyroid disorders increase to over 10% or more in people with DM. This is commoner in women as most women with type 1 DM have a 30% chance of developing auto-immune thyroid diseases (7). Although Type 2 DM is not an autoimmune problem, there have been reports of a higher occurrence of thyroid disease, especially hyperthyroidism among people with Type 2 DM (7). The Wickham survey reveals that the prevalence of thyroid dysfunction in male adults in England was 6.6% (8). According to the National Health and Nutrition Examination Survey (NHANES 111 Study), hypothyroidism and hyperthyroidism were reported to have prevalence of 4.6% and 1.3% of the total participants, respectively (9). A prevalence of 12.3% for thyroid dysfunction in

DM patients was reported in Greece and 16% in Saudi-Arabia (10). The frequency of thyroid disorder is higher with advancing age. Reports have it that the prevalence of thyroid disorders in diabetic population was reported to be 13.4% with higher prevalence (13.4%) in female Type 1 DM as compared to 6.9% in male Type 2 DM (11).

Materials and Methods: This study involved a comprehensive literature search from various journals online. This involved search engines as Google Scholar, PubMed, Yahoo, etc. Various journals were searched to include information from various parts of the world. References included in the main articles were also searched for relevant information and data. Data collected were analyzed for relevant information on thyroid dysfunction and diabetes mellitus.

Literature Review

Sanchez-Lugo reported a total of 78 patients who had Type 1 DM and were confirmed to have thyroid dysfunction. 15% had thyroid auto-immunity while 40% had goiter ($p < 0.001$) and more than 75% were females. This was the lowest prevalence of thyroid autoimmunity in diabetic children among the Hispanic group in USA (12). Radaideh et al. conducted an investigation into the prevalence of thyroid dysfunction and autoimmunity in Type 2 DM in Jordan and recruited students over a 6 month period. 5.9% of the DM patients had thyroid disorders before this study. However, this study was able to diagnose 6.67% fresh cases of thyroid disorders among the diabetics. Thus, the total prevalence of thyroid disorder was 12.5%, with subclinical hypothyroidism being the most common presentation. Positive thyroid peroxidase antibody (TPO) was detected in 8.3% of Type 2 DM patients versus 10.3% in the control group. Positivity for both TPO antibodies and thyroglobulin antibodies (Tg ab) was found to be 2.5% in Type 2 DM (13). Cardoso et al. carried out a study on the





prevalence of thyroid antibodies in the African diabetic population with both type 1 and type 2 DM. 46% of the Type 1 DM patients had significant levels of serum thyroid auto antibodies. 8.3% of patients had subclinical hypothyroidism in Type 2 DM, while 21% had subclinical hypothyroidism in Type 1 DM patients (14). Akbar et al. investigated the observation between thyroid dysfunction in Type 2 DM patients of Saudi origin. They concluded that thyroid dysfunction autoimmunity is common in type 2 diabetes. Thyroid dysfunction was 16% with GAD65 antibodies in 20% of Type 2 DM patients. Rodrigues studied a group of individuals to study the prevalence of thyroid dysfunction and anti-thyroid antibodies in Type 1 DM and their first degree relatives. They found that the prevalence of autoimmune thyroid diseases (AITD) among diabetic patients was 35.5% which was higher among the first degree relatives of diabetics than among relative of diabetics without auto immune thyroid disease (AITD) (15). Similarly, Ghawil et al. defined the prevalence of thyroid autoimmune disease among the patients with type 1 DM in Libya. They found that the major thyroid pathology was subclinical hypothyroidism (2.3%). About 23.4% of their patients had positive thyroid peroxidase (TPO) antibodies, while 7.8% had Tg antibodies. Most of the affected patients were females and 57% of these patients had type 1 DM for more than 5 years (16). In the literature, three cases of diabetic ketoacidosis initiated by thyrotoxicosis in young women with type 1 DM have been reported, all of which were diagnosed with Grave's disease (17). Hansen et al. performed a prospective study of thyroid function, morphology and autoimmunity in young patients with type 1 DM. They found thyroid ultrasonographic abnormalities with high thyroid auto-antibodies among these patients (18). Holl showed that there was an elevated thyroid antibodies expressed in type 1

DM patients. Thyroid autoimmunity was found in patients with HLA Types DR3 and DR4 (19).

Perros et al. in their study involving type 1 DM and type 2 DM patients found that the incidence of thyroid dysfunction was high in diabetic but highest in female type 1 DM patients and lowest in type 2 DM male patients (20). Also, a retrospective study by Demitrost and Ranabir concluded that type 2 DM is a major growing problem and that type 2 DM patients develop thyroid dysfunction later in life (21).

Papazinfropoulou et al. carried out a similar study to determine the prevalence of thyroid dysfunction among type 2 DM patients attending out-patient clinics. The prevalence was 12.3% with an excess of female patients taking the lead in comparison with normal groups ($p < 0.001$). Patients with thyroid dysfunction also had high body mass index (BMI) and high density lipoprotein (HDL) cholesterol, in comparison to patients without thyroid dysfunction (22). Also, Diezz et al. found that diabetic patient with thyroid dysfunction in their study had a prevalence of 9.7% (95% CI, 6.5-13.0%). The Wickman study, conducted in the late 1970s in England, reported a prevalence of 6.6% of thyroid dysfunction in adult general population (24, 25). The Colorado thyroid disease prevalence study found 9.5% of the studied population to have elevated thyroid stimulating hormone (TSH) while 2.2% had low TSH (25, 26).

The NHANESS study in the US population reported hyperthyroidism in 1.3% of subjects and further observed an increased frequency of thyroid dysfunction in diabetic subjects when compared to individuals without diabetes (25, 27).

Clinical Implication of Co-existence of Diabetes Mellitus and Thyroid Dysfunction Both diabetes mellitus and thyroid conditions involve a dysfunction of the endocrine system (1, 4,





s/N	AUTHOR/YEAR/LOCATION	TYPE OF DIABETES STUDIED	MAJOR THYROID PATHOLOGY	BASIC FINDINGS
1.	CARDOSO C. <i>et al.</i> (NIGERIA)	TYPE 1 DM TYPE 2 DM	SUBCLINICAL HYPOTHYROIDISM FOUND IN 21% TYPE 1 DM and 8.3% TYPE 2 DM patients	Females commonly affected while 46% had serum thyroid auto antibodies
2.	RADAIDEH AR <i>et al.</i> (2014) (JORDAN)	TYPE 2 DM	SUBCLINICAL HYPOTHYROIDISM (4.1%)	Thyroid peroxidase antibody (TPO ab) 8.3% thyroglobulin ab (Tg ab) – 2.5% prevalence of thyroid dysfunction was 12.5% 16% had thyroid dysfunction. GAD 65 ab were in 26% DM Thyroid autoimmunity was 10%
3.	AKBAR DH <i>et al.</i> (SAUDI ARABIA)	TYPE 2 DM		35% of type 1 DM had auto immune thyroid disease (AITD)
4.	RODRIGUES <i>et al.</i> (PORTUGAL)	TYPE 1 DM	AUTOIMMUNE THYROID DISEASE (AITD)	23.4% had positive TPO ab 7.8% had Tg ab 6.99. had both TPO and Tg abs 66.6% were females 57% had DM for at least 5years
5.	GHAWIL M <i>et al.</i> (LIBYA)	TYPE 1 DM	SUBCLINICAL HYPOTHYROIDISM (2.3%) OVER HYPERTHYROIDISM (0.9%) SUBCLINICAL HYPERTHYROIDISM (0.9%) OVER HYPERTHYROIDISM (0.9)	Thyroid ultrasonographic abnormalities thyroid autoantibodies 9.2% had thyroid auto antibodies 6.6% were TPO –ab positive 2.6% were Tab, TPo ab, AMA, and Tg ab positive
6.	HANSEN D <i>et al.</i> (2003) DENMARK	TYPE 1 DM	AUTO IMMUNE THYROID DISEASE	Increased frequency of thyroid dysfunction Elevated hyperthyroidism. Thyroid auto immunity higher in patients with HLA DR3/DR4
7.	RADAIDEH AR (2002) (JORDAN)	TYPE 1 DM	SUBCLINICAL HYPOTHYROIDISM OVERT HYPETHYROIDISM	Thyroid dysfunction is common in type 2 DM
8.	KADIYALA R. (UNITED KINGDOM)	TYPE 1 DM		
9.	HOLL RW. (GERMANY)	TYPE 1 DM		
10.	CHAOXUN WANG (2013) (CHINA)	TYPE 2 DM		





11.	PERROSS P <i>et al.</i> (SCOTLAND)	TYPE 1 DM AND TYPE 2 DM	SUBCLINICAL HYPOTHYROIDISM (4.8%) HYPOTHYROIDISM (0.9%) HYPERTHYROIDISM (0.5%) SUBCLINICAL HYPERTHYROIDISM (0.5%)	prevalence of thyroid disease 13.4%, highest in type 1 DM females with a rate of 31.4% and lowest in type 2 DM males, with a rate of 6.9%
12.	DEMITROST L AND RANABIR S (2012) (INDIA)	TYPE 2 DM	SUBCLINICAL HYPOTHYROIDISM	Presence of thyroid dysfunction is 31.2% in Females. DM patients are at higher risk. Most affected patients are > 45 years. Patient with BMI> 25 are at higher risk. Prevalence of thyroid dysfunction is 12.3%.
13.	PAPAZAFIROPOUPOU A <i>et al.</i> (2010) (GREECE)	TYPE 2 DM		
14.	DIEZ JJ <i>et al.</i> (2011) (SPAIN)	TYPE 2 DM	OVERT HYPERTHYROIDISM (3.5%). SUBCLINICAL HYPOTHYROIDISM (3.1%)	Thyroid dysfunction was in 32.4% and newly diagnosed thyroid dysfunction in 9.7% of the cases. High prevalence of thyroid auto antibodies. Thyroglobulin auto antibodies in 33% of type 1 DM patients. TPO ab in 38% of the patients
15.	LINBERG B <i>et al.</i> (SWEDEN)	TYPE 1 DM		

TABLE1: Table showing a summary of various findings linking thyroid dysfunction and diabetes mellitus from different parts of the world

25). DM and thyroid disorder mutually influence each other (25). Thyroid hormone affects the regulation of carbohydrate metabolism and pancreatic function and on the other hand, diabetes mellitus affects thyroid function tests to a large extent. Increased plasma glucose (Hyperglycemia) is enhanced by hyperthyroidism (29). Hypothyroidism is known to reduce the half life of circulating insulin (30). Hyperthyroidism also increases the glucose absorption by the gut through excess thyroid

hormones in circulation (31, 32) . In addition to these, hyperthyroidism enhances endogenous production of glucose through several mechanisms (25). Lipolysis is enhanced in patients with hyperthyroidism; with a resultant effect to cause hepatic gluconeogenesis.

On the other hand, hyperthyroidism causes a reduced rate of liver glucose production and this accounts for the decreased insulin demand in hyperthyroid diabetic patients (25, 33).

Effect of Diabetes Mellitus on Thyroid Dysfunction DM patients with hyperthyroidism





have increased levels of glycemic control difficulty and in a study; thyrotoxicosis was reported to cause diabetic ketoacidosis in DM patients (34). Altered thyroid hormone levels have been observed. For instance, reduced T3 levels have been observed in uncontrolled DM patients. Hypothyroidism enhances susceptibility to hypoglycemia, hence making DM management difficult in susceptible patients.

Generally, DM causes an increased risk of heart diseases. Since hyperthyroidism causes increased heart rate, combination of these will enhance cardiac failure in patients having these combined pathologies (35).

Genetic Basis of Thyroid Dysfunction/Diabetes Link Evidence suggests that there is a link between Type 1 DM and auto-immune thyroid diseases. Human Leucocyte Antigen (HLA) alleles encode within the major histo-compatibility complex (MHC). Chromosomes 6p21 have been recognized for several years being present in both Type 1 DM and AITD. HLA class 11 (HLA-DR) presents peptide antigens to T-cell, and HLA-DR3 allele is significantly associated with Type 1 DM and AITD 36. Also, a number of genes have recently been suggested to be associated with an increased rate of both conditions. The various loci have been identified: CTLA 4 (on chromosome 2q33), PTPN 22 (1p13), IFIH1 (2q24), CD25 (10q15), C12ORF30 (12q 24), ERBB3 (12q13), PTPN 2 (18p11), KIAA0350

(16p13), CD226 (18q22); INS (11p15), FCRL3 (1q23), and TSH receptor (14q 131) 37. Some studies have also identified various genes which are identified with gluconeogenesis, glycogen metabolism and insulin signaling. These genes are glucose-6-phosphate protein kinase (AKT2), beta-adrenergic receptors, inhibitory G protein (Gi), phosphoenol pyruvate kinase (PEPCK), pyruvate carboxylase (PC), GLUT (22, 39), malic enzyme (2, 39) and carbohydrate response element binding protein (39). Again, some other authors have linked at least four shared genes acknowledged to confer risk of development of both AITD and Type 1 DM. They are HLA 19, CTLA-440, PTPN2241, and FOXP3 genes (36).

Conclusion

The review of literature of many studies all over the world concludes that thyroid dysfunction and diabetes mellitus co-exist in some patients. This has a major negative effect on DM glycemic control and increases the potential for diabetic complications. Regular screening is, therefore, recommended to allow for earlier detection, preferably screened every 1 year for Type 1 DM and every 5 years for Type 2 DM. More research is needed to evaluate this association. Probably, patients with DM (Type 1 or Type 2) should be screened for thyroid dysfunction as frequently as possible.

Conflict of Interests: The author declares he has no conflict of interest to report.

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