In Brief

Thyroid disease is commonly found in most types of diabetes. This article defines the prevalence of thyroid disease in diabetes and elucidates through case studies the assessment, diagnosis, and clinical management of thyroid disease in diabetes.

Diabetes Control in Thyroid Disease

Thyroid disease is a pathological state that can adversely affect diabetes control and has the potential to negatively affect patient outcomes. Thyroid disease is found commonly in most forms of diabetes and is associated with advanced age, particularly in type 2 diabetes and underlying autoimmune disease in type 1 diabetes. This article defines the prevalence of thyroid disease in diabetes, discusses normal physiology and screening recommendations for thyroid disease, and elucidates through case studies the assessment, diagnosis, and clinical management of thyroid disease and its impact on diabetes.

Thyroid Disease Prevalence

The prevalence of thyroid disease in the general population is estimated to be 6.6%, with hypothyroidism the most common malady. Participants attending a health fair in Colorado (n = 25,862) were screened for thyroid disease, using thyroid-stimulating hormone (TSH) and thyroxine (T4) measurements. Of the participants, 9.5% were found to have an elevated TSH level. Also, 6% of study participants were diagnosed with thyroid disease before the screening. However, 40% of those already diagnosed had elevated TSH levels, indicating inadequate treatment. In the undiagnosed population with TSH elevations, 9.9% were found to have an unrecognized thyroid abnormality. Several studies, including the Colorado study, have documented a higher prevalence of thyroid disease in women, with prevalence rates ranging from 4 to 21%, whereas the rate in men ranges from 2.8 to 16%. Thyroid disease increases with age. In the Colorado study, the 18-year-olds had a prevalence rate of 3.5% compared with a rate of 18.5% for those ≥65 years of age.

The prevalence of thyroid disease in diabetes has been estimated at 10.8%, with the majority of cases occurring as hypothyroidism (~30%) and subclinical hypothyroidism (~50%). Hyperthyroidism accounts for 12%, and postpartum thyroiditis accounts for 11%. Of the female patients with type 1 diabetes, 30% have thyroid disease, with a rate of postpartum thyroid disease three times that of the normal population. Ostensibly, this is because of the higher prevalence of thyroid disease in women, as well as the link to autoimmune disease. Once one autoimmune disease occurs, it is not uncommon for a different autoimmune disease to be present.

There are also reports that the prevalence of thyroid disease in type 2 diabetes is higher than in the general population. Whereas the Fremantle Diabetes Study found a 8.6% prevalence of subclinical hypothyroidism in women with type 2 diabetes in Australia, a study of the prevalence

Jennal L. Johnson, MS, RNC, FNP, BC-ADM, CDE
of autoimmune thyroid disease in type 2 diabetes in Jordan reported an overall prevalence rate of 12.5%, with subclinical hypothyroidism at 5%.5

Thyroid Anatomy and Physiology
A thorough understanding of the anatomy and physiology of the thyroid gland allows diabetes clinicians to understand the rationale for specific assessments and to rapidly identify thyroid abnormalities. The thyroid is the largest endocrine gland, weighing ~ 20 g. It is shaped like a butterfly or shield and is derived from the base of the tongue.6 The thyroid gland has significant blood flow; when compared by tissue weight, it has more blood flow than the kidney.7

Understanding the Role of the Thyroid
Thyroid physiology is based on a regulatory feedback system typically found in endocrine systems.7 The hypothalamus secretes thyrotropin-releasing hormone (TRH), which stimulates the anterior pituitary gland to secrete thyrotropin or TSH. TSH stimulates the anterior pituitary gland, releasing hormone (TRH), which in turn leads to increased TSH secretion and increased gland growth or goiter. Gland size, however, does not indicate thyroid function. Therefore, a goiter can be present in hypothyroidism, hyperthyroidism, or euthyroidism.

The thyroid gland is divided into lobules that have a distinct vascular supply. Each lobule has 20–40 follicles, and follicles are the basic functioning unit of the thyroid gland. The lumen of each follicle is filled with viscous colloid identified as the glycoprotein thyroglobulin. Thyroglobulin contains the molecular structure of thyroid hormones and is the precursor of all thyroid hormones.9 Thyroperoxidase (TPO) is a membrane-bound enzyme found on the surface of the follicular cell. It is necessary to catalyze iodide into an active intermediate, an important step in thyroid hormone synthesis.7 Thyroglobulin and TPO antibodies are useful thyroid laboratory test evaluations that can identify potential harm to the synthesis of thyroid hormone from an autoimmune process.

The follicle is surrounded by a single layer of epithelial cells and enclosed by a basement membrane. The basement membranes have parafollicular cells that have contact with follicle cells and produce calcitonin.7 Iodine is taken up as inorganic iodide via the “iodide trap” in the follicular cell. This aspect of thyroid physiology is important because the thyroid is the only gland that takes up iodine, which allows for scanning and treatment of the thyroid gland using radioiodine.

After thyroid hormones are synthesized and secreted into the serum, they are bound to serum carrier proteins TBG, thyroxine-binding prealbumin, and albumin. The affinity of the T3 receptor is much higher (~ 10 times) than that of T4.7 The majority of T4 (99.96%) and T3 (99.6%) are bound, and binding is affected by certain physiological or pathological states that increase or decrease TBG. Estrogen increases found in pregnancy, estrogen replacement, and birth control pills increase TBG, whereas androgens, glucocorticoids, and malnutrition decrease TBG.7

Free or unbound thyroid hormone enters cells and exerts a biological effect. The bound hormone serves as a reservoir that buffers short-term alterations in thyroid hormone secretion rates, facilitating a more steady state. Standard laboratory assays measure the total free and bound thyroid hormone levels of T4 and T3 unless free hormone levels are specifically requested. Free hormone levels are helpful in evaluating thyroid function in states of decreased or increased TBG.

Thyroid hormone exerts influences on numerous body systems, including growth and development, muscular function, sympathetic nervous system function, cardiovascular system, and carbohydrate metabolism. For example, thyroid hormone is necessary for maturation and differentiation during development. Children with hypothyroidism show bone maturation delays as well as delayed or absent puberty. Children with thyroid deficiency have stunted growth because inadequate thyroid hormone secretion lowers growth hormone. Thyroid hormone also plays an important role in lung maturation.7

Thyroid hormones are necessary for normal fetal and neonatal brain development by regulating neuronal proliferation and differentiation, myelogenesis, neuronal outgrowth, and synapse formation. The critical time for brain development starts in utero and continues to age 2. Deficiency of thyroid hormone during this important time can lead to structural and physiological impairment resulting in brain damage or severe neurological impairment.7 This process cannot be reversed once completed, which is the reasoning behind universal screening for congenital hypothyroidism.

Hypothyroidism in adults can lead to dullness, decreased reflexes, lethargy, delayed cognitive function, and excessive sleep, as well as psychological disturbances. Correcting the underlying thyroid abnormality can reverse impaired neurological functioning in adults. Hyperthyroidism in adults can also result in insomnia, decreased reflex time or hypereflexia, restlessness, excitability, and lack of focus and concentration.7

Thyroid hormones have metabolic functions that serve to control the basic hormone metabolic rate. Basic hormone metabolic rate is decreased in hypothyroidism and increased in hyperthyroidism. Thyroid hormones stimulate most metabolic pathways and are either anabolic and catabolic. In hypothyroidism, protein synthesis

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is decreased, as is protein degradation, which results in decreased percentage of protein body weight. Alternatively, hyperthyroidism increases protein synthesis and degradation, resulting in wasting.7 Thyroid hormones are lipolytic as well as lipogenic. However, there is usually more degradation compared to synthesis. In hypothyroidism, there is decreased fat synthesis and degradation, leading to increased body fat and elevated lipids. In hyperthyroidism there is increased fat synthesis and degradation, resulting in decreased lipids.

Thyroid hormones exert a direct effect on muscles. In hypothyroidism, this can lead to myopathies, muscle stiffness with associated discomfort and slowness of movements, increased muscle mass (mechanism unknown), and impaired muscle glycogenolysis, leading to glycogen accumulation.7 In hyperthyroidism, myalgias can also occur as well as muscle weakness, muscle wasting, and muscle fatigue, particularly in the proximal muscles in the legs, making it difficult to climb.

Within the cardiovascular system, thyroid hormones increase heart rate, myocardial contractility, and cardiac output by increased sinus node stimulation and direct effects on the myocardium.7 In hyperthyroidism, excess thyroid hormone produces myocardial hypertrophy. Thyroid hormones act as positive inotropes as well as positive chronotropes independent of circulating catecholamines. Resultant electrocardiogram changes show left ventricular hypertrophy. Stroke volume, heart rate, and mean systolic ejection velocity increase with decreased peripheral resistance because of increased production of vasodilators, with evidence of warm, moist skin and increased pulse pressure.

The opposite occurs in hypothyroidism. Peripheral resistance is normal or slightly increased by decreased secretion of vasodilators, resulting in cutaneous vasoconstriction evidenced by cold, dry skin. The ECG in hypothyroidism shows inverted T waves and low P, QRS, and T wave amplitudes. Excess thyroid hormone resembles increased sympathetic nervous system activity by increased beta-adrenergic stimulation, leading to increased heart rate, tremors, and excessive sweating.7 This stimulation could interfere with diabetic patients' ability to recognize hypoglycemia.

Thyroid Hormone Effects on Diabetes

The effect on carbohydrate metabolism can potentially lead to disruptions in diabetes control. Although the glucose level does not always change, there can be an abnormal response to glucose tolerance testing in hyperthyroidism because glucose rises faster than normal.7 Additionally, excessive thyroid hormones increase the rate of digestive tract absorption and thyroid hormone levels and therefore increase insulin resistance and insulin degradation.

In hyperthyroidism, glycogen synthesis and degradation increase, leading to decreased glycogen levels.3 Glucose absorption is increased, as well as utilization and production. Peripheral tissues have increased rates of glucose uptake that can lead to the aforementioned exaggerated glucose peak during a timed glucose test. Insulin requirements are increased, and, if not addressed adequately, control can decompensate, leading to diabetic ketoacidosis. Additionally, in patients with undetected diabetes, hyperthyroidism can unmask diabetes because glucose levels can be abnormally elevated because of increased insulin resistance.3 Increased dosages of diabetes medications may be necessary in those already treated, until thyroid function is stabilized and resultant glucose stabilization occurs.

In hypothyroidism, liver secretion of glycogen decreases, but so does degradation, leading to increased levels of glycogen. Absorption of glucose from the gastrointestinal tract is slowed, and glucose utilization is slowed in the peripheral tissues. The availability of gluconeogenic substrate is decreased. Additionally, the insulin half-life is prolonged, insulin levels are lower, and insulin secretion is reduced, which may lead to reduced insulin requirements. If exogenous insulin is not decreased, hypoglycemia may occur. It is likely that glucose levels will stabilize during hypothyroidism treatment. But when thyroid function is normalized, this may lead to higher blood glucose levels and adverse effects on glycemic control.

Screening Recommendations

The American Thyroid Association (ATA) recommends testing thyroid function in all adults beginning at age 35 and reassessing thyroid function every 5 years. More frequent testing is indicated in high-risk or symptomatic individuals. The American Association of Clinical Endocrinologists (AACE) recommends a screening TSH in women of childbearing age before pregnancy or during the first trimester.10

In 2005 AACE, ATA, and the Endocrine Society (TES) published a consensus statement regarding screening for subclinical thyroid dysfunction.11 The authors of the consensus statement recommended the measurement of anti-TPO antibodies in evaluating patients with subclinical hypothyroidism because those who are antibody positive have a higher risk of developing overt thyroid disease.11 For patients with type 1 diabetes, it is recommended to test for anti-TPO antibodies at diagnosis. If anti-TPO antibodies are present, it is recommended that clinicians perform annual TSH screening. In type 2 diabetes, it is recommended that clinicians measure TSH at diagnosis of diabetes and every 5 years thereafter.2

Case Studies

Case Presentation 1

M.J. is a 70-year-old woman with type 2 diabetes. She is evaluated in an outpatient endocrine clinic. She was diagnosed with diabetes recently and has not completed a comprehensive diabetes education program. Her fasting blood glucose levels are 110–115 mg/dl, and she does not check 2-hour postmeal blood glucose readings. She has no known macrovascular or microvascular complications.

She comes to clinic with complaints of fatigue and weight gain. She is taking glimperide, 4-mg tablet twice daily. It is interesting to note that the initial signs and symptoms presented and the routine screening results are consistent with the metabolic syndrome or diabetes. Unless the clinician screened for thyroid disease, the abnormalities could be attributed to the usual course of type 2 diabetes.

M.J.’s physical exam is normal except that she has a 45-g goiter. Her laboratory results are:

- TSH: 5.6 IU/ml (normal: 0.29–3.0)
- T4: 5.5 ug/dl (normal: 4.5–12.5)
- Positive for anti-TPO antibodies (normal: negative)
- Total cholesterol: 220 mg/dl (normal: 130–200)
- HDL cholesterol: 34 mg/dl (normal: 30–80)
- Triglycerides: 158 mg/dl (normal: 35–160)

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population data. The study found status of thyroid functioning, using 1994 and measured TSH and antithyroid antibodies, indicating subclinical hypothyroidism.

Treatment goals include initiating levothyroxine therapy, completing diabetes education, and improving glycemic control. The lipid levels will likely decrease with levothyroxine therapy. However, because diabetes is a risk equivalent for cardiovascular disease (CVD), a cholesterol-lowering agent such as a statin is also indicated. The statin can be initiated before determining the effect of thyroid hormone replacement on her lipid levels because the purpose of the statin is cardiovascular prevention.

Discussion
The Rotterdam Study (n = 1,149) showed that subclinical hypothyroidism may be a risk factor for CVD. Participants were female and > 55 years of age. Subclinical hypothyroidism was defined as a TSH > 4.0 mU/L with a normal free T4 level. Subclinical hypothyroidism was a strong risk factor for atherosclerosis and myocardial infarction (MI) in elderly women. Subclinical hypothyroidism was found to be a greater risk for MI in postmenopausal women than hyperlipidemia, diabetes, previous smoking, or hypertension. Additional studies have looked at the benefits of treating subclinical hypothyroidism, and the results showed that treatment to lower TSH resulted in lower total and LDL cholesterol levels. Alternatively, long-term data from the Whickham cohort published in 1996 found no higher rate of death from CVD in subjects with subclinical hypothyroidism compared with euthyroid subjects, contributing to the controversy surrounding treatment of subclinical hypothyroidism.

The National Health and Nutrition Examination Survey evaluated men, women, and children from 1988 to 1994 and measured TSH and antithyroid antibody levels to evaluate the status of thyroid functioning, using population data. The study found that the prevalence of antithyroid antibodies increases with age, is higher for female subjects, and is higher in whites and Mexican Americans than in African Americans. Anti-TPO antibodies may be positive before clinical disease occurs and therefore may be an indicator of early thyroid disease. Although still controversial, treatment of subclinical hypothyroidism is indicated in patients who are elderly, have elevated cholesterol, have TSH > 10 mU/L, and have other symptoms of hypothyroidism.

The goal of thyroid replacement therapy is to render the patient euthyroid without over- or underreplacement, with a TSH goal between 0.3 and 3.0 IU/ml unless thyroid cancer is present. Levothyroxine is a narrow therapeutic index drug, which means that there is a “narrow toxic to therapeuetic ratio with significant clinical consequences of excessive or inadequate treatment” that could impact bone, pregnancy, or heart. Within the past several years, several generic levothyroxine products have come to the market, and the U.S. Food and Drug Administration (FDA) has deemed them to be bioequivalent to some branded preparations. The major thyroid organizations (AACE, TES, and the ATA), have voiced concern about the methodology the FDA used to determine bioequivalence and recommended that levothyroxine not be substituted for other preparations.

The organizations’ joint position statement recommends that patients be maintained on the same brand of levothyroxine that they have been taking and, in the event they are switched to another brand or generic product, measure a serum TSH in 6 weeks and make adjustments as indicated. Patients should be educated about using the same brand of medication during treatment and, when picking up medications at the pharmacy, be told to indicate that the brand of thyroid medication should not be changed without first checking with their provider.

The initial dose of levothyroxine therapy is determined by the underlying cause of the disease, severity of dysfunction, and health and age of the person being treated. This is highly individualized; however, the adage in the elderly or those with underlying CVD is to start low (typically 25 µg daily) and go slow with drug titration.

The woman in this case study is likely to see improvement in her symptoms within 6–8 weeks after initiating levothyroxine therapy. It is important that she closely monitor her blood glucose levels because improved thyroid function may increase her glucose, leading to more hyperglycemia. She may need additional diabetes medication intervention.

Case Presentation 2
L.M. is a 38-year-old man with type 1 diabetes who uses an insulin pump. He presents with tachycardia, shortness of breath, decreased exercise tolerance, fatigue, muscle weakness, double vision, blisters on lower legs, weight loss, hyperglycemia, mood swings, anxiety/nervousness, heat intolerance, and increased frequency of bowel movements. Physical examination reveals:

- Skin: moist and warm, blisters with an orange peel appearance on both lower legs
- Head/eyes/ears/nose/throat: bilateral proptosis, stare, lid lag, scleral injection, double vision with eye motility, thyroid 60+ g and firm
- Heart: tachycardia, heart rate 106 bpm, regular rhythm without murmur
- Lungs: clear to auscultation and percussion
- Lower extremities: pretibial myxedema in lower legs
- Neurological exam: hyperreflexia

Laboratory results included:
- T4: 22.0 µg/dl (normal 4.5–12.5)
- TSH: < 0.01 IU/ml (normal 0.29–3.0)
- Thyroid-stimulating immunoglobulin: 300% (normal < 130%)
- Blood glucose: 345 mg/dl (normal < 100)
- A1C: 9.2% (normal 4.0–6.3)

Imaging revealed a 77% uptake in 4 weeks. The woman has Graves’ disease with type 1 diabetes and Graves’ disease. The prevalence of Graves’ disease with type 1 diabetes has been reported to be 0.3% in men and 2–19% in women. Patients
should be monitored closely to evaluate their response to thyroid therapy as well as their diabetes control. As Graves’ disease stabilizes, insulin requirements may decrease. It may be beneficial to place the patient in this case study on a glucose sensor because the glucose levels will be elevated initially, and higher doses of insulin will be needed. Once successful treatment is completed, close monitoring will also be necessary to avoid hypoglycemia when insulin requirements decrease.

Case Presentation 3

R.D. is an 18-year-old woman with type 2 diabetes diagnosed 5 years ago. Since her diagnosis, she has lost 50 lb through a diet and exercise program. She is normoglycemic. Coexisting health problems include polycystic ovarian disease and vitiligo. Family history is significant for thyroid disease. She was taking metformin until a recent positive pregnancy test.

The patient complains of fatigue, nausea, constipation, and feeling cold. Her weight loss plateaued several months ago, and now her weight is slowly increasing.

Physical examination is unremarkable except a 30-g thyroid. Laboratory results include:

- A1C: 6.2% (normal <4.0-6.3)
- Free T4: 0.6 ug/dl (normal 0.9–1.9)
- TSH: 13.4 IU/ml (normal 0.29–3.0)
- Positive for anti-TPO antibody (normal: negative)

A referral to a dietitian is recommended to evaluate adequate calorie intake for diabetes, pregnancy, and appropriate weight gain. Swift initiation of levothyroxine therapy is indicated because the patient is hypothyroid and pregnant. Initial symptoms should improve within 4–6 weeks unless they are secondary to the pregnancy rather than hypothyroidism.

The 1990 Haddow Pregnancy Study (n = 92) showed that euthyroid children of hypothyroid mothers had adverse results and hypothyroid children from hypothyroid mothers had fetal brain and IQ abnormalities.21 Euthyroid women with positive antithyroid antibodies had higher rates of miscarriage, women with higher TSH levels had a more than threefold increase in risk of very preterm delivery, and those with positive antithyroid antibodies had a twofold increase in preterm delivery. The rate of fetal death was 3.8% in women with TSH ≥ 6 mU/l and 8.1% in women with TSH ≥ 10 mU/l compared with 0.9% in women with TSH < 6 mU/l.21 In the first trimester, pregnant women are the sole source of thyroid hormones for their developing fetuses.

It is important to screen women of childbearing age and those in the first trimester of pregnancy for hypothyroidism to optimize thyroid function. History of another autoimmune disorder or a family history of thyroid disease increases the possibility of hypothyroidism, which underlines the need for screening. For patients newly diagnosed with thyroid disease, levothyroxine therapy should be initiated as soon as possible and at a dose as close as possible to the anticipated requirement. Dosage increases may be seen as high as 50% because of increases in thyroid hormone binding globulin in women already diagnosed with thyroid disease before pregnancy.22

Additional considerations include the effects of diabetes on pregnancy. In early pregnancy, patients with diabetes can be affected by pregnancy-related hormones that cause increased insulin secretion, decreased insulin requirements, and decreased glucose produced by the liver, which can lead to hypoglycemia.23 During the third trimester, the opposite occurs. Estrogen and cortisol can cause significant insulin resistance, therefore potentially causing hyperglycemia. Close monitoring of blood glucose during pregnancy allows for medication, diet, and exercise alterations to optimize diabetes control while normalizing thyroid function.

Summary

The prevalence of thyroid disease is higher in diabetes because of the increased age of diabetic patients as well as an autoimmune link. Untreated or inadequately treated thyroid disease can negatively impact diabetes control. Pregnancy is a challenging state associated with diabetes and can be complicated by the effects of untreated or undertreated thyroid disease.

References

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Jenal L. Johnson, MS, RNC, FNP, BC-ADM, CDE, is an endocrinology nurse practitioner at Endocrinology Associates in Phoenix, Ariz.

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