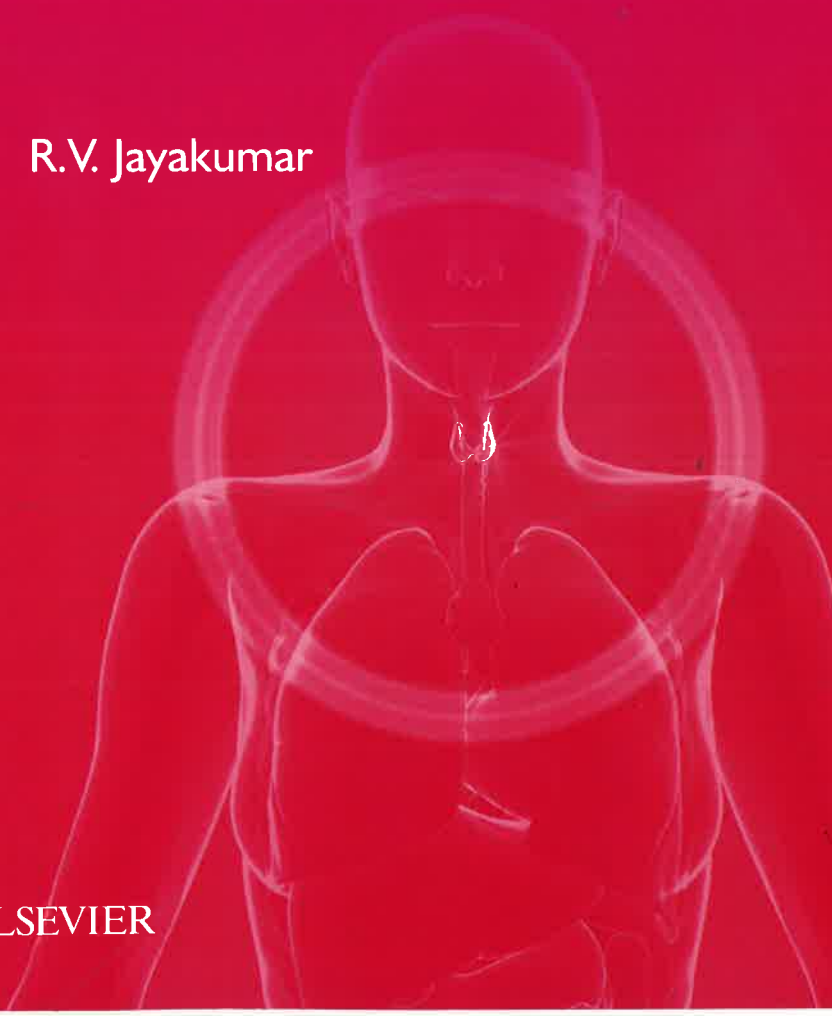
Hypothyroidism & Diabetes

Indian Consensus Statement

R.V. Jayakumar



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Preface

Diabetes mellitus and hypothyroidism are two common endocrine problems in clinical practice. When these occur in a patient, the clinical picture of each of them may worsen as derangements tend to occur in almost all the metabolic functions of the body. The diagnosis can be difficult at times, owing to similar symptomatology and masking of clinical scenario by each other.

Also these two conditions—when occur together—aggravate the complications of both the illnesses. For instance, there is a negative impact on thyroid profile, the insulin requirements keep fluctuating with change in thyroid status and levothyroxine supplementation. There is an increased preponderance to develop recurrent hypoglycemic attacks, difficulties in achieving a good control over glycemic status. There is worsening clinical picture, affecting a range of musculoskeletal and cardiovascular problems, alterations in lipid profile and enhancement of atherosclerotic changes in blood vessels.

There is also an early development and rapid progression of microvascular complications such as retinopathy and nephropathy leading to an impairment of visual and renal functions, and severe respiratory morbidities. It also results in greater derangements in the PFT (pulmonary function tests), poor outcomes of pregnancy to both mother and the fetus, infertility and altered mentation being few amongst the many. Also, the drug therapy of the two conditions is seen to affect each other.

Hence, a knowledge of the synergistic picture of diabetes mellitus as well as hypothyroidism is crucial in diagnosis and management of these illnesses.

In this manuscript, we have taken the opinion of leading Endocrinologists and looked into a large number of publications relevant to the topic and came to this consensus statement. I am sure that this document will be a stimulus for all, to look into this combination of endocrine problems.

R.V. Jayakumar
Founder President, Indian Thyroid Society

An Insight into Hypothyroidism and Diabetes Mellitus

R.V. Jayakumar

Hypothyroidism and diabetes mellitus are two of the most common endocrinal disorders encountered in clinical practice and affecting the people of all age groups in varying proportions.[1–4,10] However, the prevalence of hypothyroidism shows a rising trend as the age advances and is common in females. Type 1 diabetes mellitus is frequently observed in younger age group and type 2 diabetes mellitus is often seen in adults. Many times, both hypothyroidism and diabetes mellitus are seen in co-existence.[1–10]

The knowledge of the association is essential as it imposes diagnostic and therapeutic challenges. They are found to aggravate the complications of each other such as increasing cardiovascular morbidity and mortality, worsening of lipid profile, difficulty in achieving euglycemia, impairment of visual, cognitive, and renal functions, severe respiratory morbidities, poor outcomes in pregnancy.[1–34]

The synergism of the two conditions makes the diagnosis difficult at times. This is due to their similar clinical picture which mimic each other on several occassions.[4,5]

The possible reasons postulated for this association could be of genetic, biochemical or hormonal origin. Impaired P13k/Akt signaling is a hallmark feature of insulin resistance and thyroid hormones clearly promote beneficiary changes in this signaling cascade.[4]

Difficulties in achieving glycemic control should prompt a physician to think about this association.[1–10,13,14,17] In a hypothyroid state, hypoglycemia may be a common finding which may have a subtle presentation due to its neuro-cognitive effects.[1–10,13,14,17] Similarly euthyroid state following levothyroxine treatment may unmask the hyperglycemic status of the person with diabetes mellitus.[1–10,13,14,17]

The awareness of this synergism also helps while considering the treatment of the two in many clinical scenarios. Hence, a definitive understanding of the pathophysiology of the association and management issues need to be comprehended.

PATHOGENESIS OF DIABETES MELLITUS

Diabetes mellitus is characterized by hyperglycemia with or without glycosuria occurring as a result of decreased insulin secretion, increased glucose production, impaired action of insulin and reduced glucose utilization.[4,10,12,13] Environmental factors coupled with genetic susceptibility are responsible for the distinct pathological types of diabetes mellitus in any individual.[4,10,12,13]

Diabetes Mellitus Type 1

- A defect in the glucose-insulin signaling pathway owing to a glucokinase deficiency may lead to a permanent neonatal diabetes mellitus.[10,12]
- Other autoimmune diseases are extremely common in the background of type 1 diabetes mellitus.[10,12]
- The chief antibodies involved in pathophysiology are Islet Cell Cytoplasmic Antibodies (ICCA – present in 90% of patients with type 1 diabetes mellitus), antibodies against Glutamic Acid Decarboxylase (GAD – in almost 80% of such patients), Islet Cell Surface Antibodies (ICSA – found in 80% of these patients) and anti-Insulin Antibodies (IAAs- shows a relative risk of developing diabetes mellitus type 1).[10,12]

Diabetes Mellitus Type 2

- There is an impairment of insulin secretion as well as a decrease in insulin sensitivity to peripheral tissues.[10,12]
- Genetic factors coupled with improper lifestyle habits plays an important role in the pathogenesis of type 2 diabetes mellitus.[10,12]
- HLA-DR 3 and 4 haplotypes are the crucial markers for beta cell destruction in the patients with type 2 diabetes mellitus.[10,12]
- The insulin resistance in these patients is probably a result of the hyalinization of the islet cells of the pancreas due to deposition of amylin (an amyloid polypeptide).[10,12]

- Two types of insulin resistance have been observed: Type A insulin resistance which is hereditary and type B insulin resistance which has an autoimmune origin.[10,12]
- Insulin resistance could occur as a consequence of downregulation of insulin receptor.[10,12]

PATHOGENESIS OF HYPOTHYROIDISM

Hypothyroidism is regarded as the most common thyroid disorder worldwide characterized by either a symptomatic clinical state affecting multiple organ systems, subclinical hypothyroidism with few minor symptoms or an asymptomatic hypothyroidism.[4,7–10,13–15] The commonest cause attributed is iodine deficiency; however, in iodine-sufficient areas, autoimmune and drug induced reasons account for commonest causes. Several types have been postulated.[1,4,10,13–15]

- ***Congenital Hypothyroidism:*** It is the most important preventable cause of hypothyroidism.[4,7–10] Untreated congenital hypothyroidism can cause severe neurological adverse consequences if left untreated; hence the need for neonatal screening. Early treatment with thyroxine results in improved IQ levels.
- ***Autoimmune Hypothyroidism:*** It is not very common in children. Environmental factors coupled with factors like polymorphism in some immunomodulatory genes contribute to autoimmune hypothyroidism. Owing to its gradual progression, the patients may sometimes have a normal T_3 (Triiodo thyronine) and T_4 (Tetra – iodo thyronine) levels. these normal T3 and T4 levels are possibly because of compensatory rise in thyroid stimulating hormone (TSH) levels with/without minor symptoms resulting in subclinical hypothyroidism. However, when the circulating thyroid hormone levels fall (unbound T_4 first) coupled with clinical symptoms, then the result is an overt or clinical hypothyroidism. Measurement of thyroid peroxidase antibodies (TPO antibodies) can help in diagnosis.[1–10,13]
- ***Iatrogenic hypothyroidism*** is also not uncommon and can be often diagnosed prior to the onset of symptoms. Transient hypothyroidism usually occurs 3–4 months post radioiodine treatment and is reversible with a low dose of thyroxine treatment supplemented till the recovery. Mild hypothyroidism is also seen post subtotal thyroidectomy due to stimulation of TSH by remnant of gland which may also be reversible after a period of few months following the surgery.[10]
- ***Iodine deficiency*** leads to endemic goiter in adults and cretinism in children.[8,10]
- Goiter and hypothyroidism can also be induced sometimes by *a chronic iodine excess.*[8,10]

- **Secondary Hypothyroidism** usually never occurs in isolation as solely the rise in TSH but it is almost always accompanied by deficiency of other anterior pituitary hormones as well.[8–10]

Mechanism Involved in Hypothyroidism

- The follicular cells of the thyroid gland secrete T4 (the major form) and T3 (the predominant active form) are present in the circulation.[1–6,10–15]
- Actions of these thyroid hormones are regulated by a family of intracellular deiodinases (DIOs) at the tissue level.[1–6,10–15] Major actions of thyroid hormones are mediated by binding to thyroid hormone receptors (TRs) in the nucleus of target cells.[1–6,10–15]
- Hepatic type 1 DIO mediates peripheral T4 to T3 conversion.[1–6,10–15]
- In the hypothalamus and pituitary, DIO2 converts T4 to T3 which is concerned with the negative feedback regulation of the hypothalamic-pituitary-thyroid axis.[1–6,10–15]
- DIO3 converts T4 to reverse T3 and T3 to T2, thereby restricting or limiting TH action.[1–6,10–15]
- These receptor genes (TRα, TRβ) are present on chromosomes 3 and 17.[1–6,10–15]
- TRα1 is predominantly expressed in the colon, myocardium, central nervous system, and skeletal muscle.[1–6,10–15]
- TRβ1 is mostly expressed in the kidney and liver.[1–6,10–15]
- TRβ2 plays a major role in negative feedback regulation at the level of the hypothalamus pituitary axis.[1–6,10–15]
- In healthy individuals, 100% T4 thyroidal, 20% T3 thyroidal, 80% extrathyroidal from the conversion of T4 to T3 mediated by DIO 1 & 2.[1–6,10–15]
- Amount of intracellular T3 available for binding nuclear TR (thyroid receptor) is modulated by:
  a) DIO3 mediated conversion of T3 to T2
  b) Transporters like MCT 8.[1–6,10–15]
  Free T4 might be high and free T3 may be low when the patient is supplemented by levothyroxine and it indicates limited peripheral T3 conversion.[1–6,10–15]

A timely diagnosis of both these clinical conditions in their initial stages receiving appropriate early corrective measures prevents the development of co-morbid states.

THE CO-EXISTENCE OF DIABETES MELLITUS AND HYPOTHYROIDISM

It is an extremely common scenario in clinical practice to encounter both thyroid disease and diabetes mellitus together and their associations have

been cited in a number of studies.[1,4,5,7–9,13–15] Prevalence of co-existence is estimated to be around 10.8%.[1,4,7–9] Majority of cases occurring as hypothyroidism (36% approximately) and subclinical hypothyroidism (51% approximately).[1,4,8,9]

Malfunctions in genetic, biochemical and hormonal systems could be the basis for such an association.[4,8–10] Thyroid dysfunction is also encountered more in patients with diabetes mellitus than the normal population and this has important clinical implications.[10] Type 1 diabetes mellitus has a higher incidence of thyroid disorders in comparison type 2 diabetes mellitus.[1–5,10,12] Autoimmunity could be the link to thyroid dysfunction associated with diabetes mellitus.[1–5,10,12]

Once an autoimmune disease occurs, it is not uncommon for a different autoimmune disease to be present.[1–5,10,12] Autoimmune thyroid disease and type 1 diabetes mellitus are caused by dysregulation of immune surveillance and tolerance.[1–5,10,12] Treatment of thyroid dysfunction in a patient with diabetes will reduce the rate and extent of complications and will also ensure better glycemic control.[1–5,10,12]

All these aspects will be discussed in this Consensus Document.

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Epidemiology of Diabetes Mellitus and Hypothyroidism

Krishna Sheshadri

A.G. Unnikrishnan

Diabetes mellitus and hypothyroidism are the two most common endocrine disorders encountered in day-to-day clinical practice.[1–5] The evidence to prove the association of their co-existence and the problems related to their synergism has been gaining momentum in the past few years.

As estimated by the International Diabetes Federation, globally, over 415.0 million population had diabetes mellitus in the year 2015 and this figure is expected to increase to 642.0 million by the year 2040.[1] Similar estimates were made amongst the male vs female and urban vs rural population which have been summarized in Table 1.[1]

Table 1.
Global Data on Prevalence of Diabetes Mellitus

	Prevalence of diabetes mellitus in 2015 (in millions)	Expected prevalence of diabetes mellitus in 2040 (in millions)
Worldwide	415.0	642.0
Men	215.2	328.4
Women	199.5	313.3
Urban	269.7	477.9
Rural	145.1	163.9

Worldwide, every 1 out of 11 adults has diabetes mellitus.[1] One in 2 adults with diabetes mellitus remain undiagnosed[1] and 1 out of 7 births is affected by GDM (gestational diabetes mellitus).[1] 542000 children are affected with type 1 diabetes mellitus.[1] About 12% of the global health expenditure is spent on diabetes mellitus.[1]

India is on the *second* position in the world for the number of adults with diabetes mellitus and the first being China. In India, 69.2 million adults were affected with diabetes mellitus as estimated in 2015, however, this figure is expected to rise to 123.5 million by 2040.[1] Also, India is ranked *second* globally with respect to the number of children in the age group of 0–14 years which are suffering from type 1 diabetes mellitus, estimated at around 70,200 children.[1]

Considering the SEAR (South-East Asian Regions) which comprises of 7 countries namely, India, Nepal, Bangladesh, Mauritius, Sri Lanka, Bhutan, and Maldives, it has been found that 86% of the population from this region resides in India.[1] India has been found to home the largest number of children with type 1 diabetes mellitus from SEAR.[1] About 36.5 million Indians were estimated to have an impaired glucose tolerance in the year 2015.[1] However, this prevalence is expected to rise to 63.5 million by the year 2040.[1] Hyperglycemia has been observed in about 24.2% of the pregnant women belonging to the SEAR countries in the age group of 20–49 years.[1] Nearly half of the diabetic population here remain undiagnosed for several years posing to severe health issues.[1] The prevalence of diabetes mellitus in Indian urban areas has been estimated to range between 5.6% to 12.4% whereas it ranges from 2.4% to 2.7% in the rural areas of the nation.[6] India contributes maximum to the mortality rate from SEAR out of which around 1 million deaths are due to diabetes mellitus alone.[1]

Hypothyroidism is also a common health problem affecting 1 in 10 people in India.[2] As per an Indian publication, 3.9% of the study population suffer from overt hypothyroidism whereas 9.4% have a subclinical hypothyroidism.[3] Half of the subclinical hypothyroidism cases test positive for anti-TPO antibodies.[3] The prevalence is higher in females with 11.4% as compared to males with 6.2%.[3] A very high prevalence of congenital hypothyroidism is also found in India accounting for 1 out of 2640 neonates as compared to the global estimate of 1 in 3800 newborns.[3] After the Salt Iodization Programme supported by GOI (Government of India), the prevalence of hypothyroidism in selected regions of UP has been found to decrease from 100/1000 to 18/1000.[2] However, significant data is not available from other states to conclude such results.[2] A higher prevalence of hypothyroidism has observed in the inland

cities like Kolkata, Delhi, Ahmadabad, Bangalore and Hyderabad amounting to 12% approximately as compared to 9% seen in coastal cities like Mumbai, Goa, and Chennai.[2]

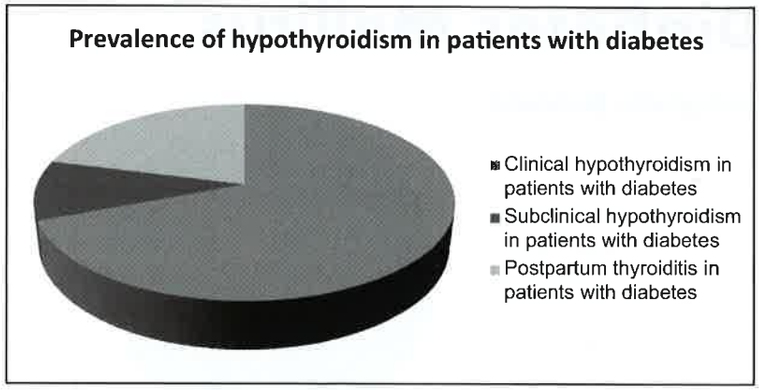
The co-existence of diabetes mellitus and hypothyroidism is not uncommon. In fact, patients with diabetes mellitus are more commonly affected with thyroid dysfunction compared to the general population.[4] The knowledge of this synergism is equally important as there are serious clinical implications of the two on each other. Whenever these occur together, the details have been discussed in the literature. Various studies have been found to demonstrate this synergism, few of which have been mentioned in Table 2.

Table 2.
Clinical Studies Evaluating the Co-existence of Hypothyroidism and Diabetes Mellitus[4]

Study	Population	Type of diabetes mellitus	Thyroid dysfunction (%)
Celeni et al	Hospitalized patients	Type 1 diabetes mellitus	31.4
Perros et al	Hospital, clinic	Type 1 and type 2 diabetes mellitus	13.4
Radaideh et al	Hospital, clinic	Type 1 diabetes mellitus	12.5
Gray et al	Hospital, clinic	Type 1 diabetes mellitus	12
Smithson et al	Community practice	Type 1 and type 2 diabetes mellitus	10.8
Chubb et al	Community study	Type 1 diabetes mellitus	10.4
Kordonouri et al	Multi-center study	Type 1 diabetes mellitus	9.5
Hansen et al	Community study	Type 1 diabetes mellitus	4.8

Overall, the prevalence of thyroid disease in general population is estimated to be 6.6%, however, 10.8314% of these patients also have diabetes mellitus simultaneously.[5] Out of these, 36% people with diabetes have an overt clinical hypothyroidism, 5.13% have a subclinical hypothyroidism and 11% women suffer from postpartum thyroiditis.[5] This data has been depicted in the diagram given below.

Prevalence Rates for Thyroid Disease with Diabetes Mellitus[5]



Thyroid disorders are found to be more common amongst type 1 diabetes mellitus patients probably owing to an underlying, common autoimmune mechanism.[4] High prevalence of thyroid dysfunction is observed in women with type 1 diabetes mellitus amounting to 31.4%, and a low prevalence is seen in men with type 2 diabetes mellitus estimated to be 6.9%.[4]

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The Interplay of Hypothyroidism and Diabetes Mellitus

Ganapathi Bantwal

Thyroid disorders are very frequently encountered in the patients with Diabetes Mellitus.[1–3] The prevalence of thyroid disorders along with diabetes mellitus rises with age and is also higher in women as compared to men.[4] Diabetes being more common than hypothyroidism[4] and is usually picked up first in the clinical practice.

REASONS FOR THE ASSOCIATION[1–6]

There is an underlying autoimmune pathological mechanism involved in hypothyroidism. For example, Hashimoto's hypothyroidism (as autoimmune thyroiditis, which most frequently induces hypothyroidism). Diabetes mellitus especially the type 1 is majorly caused due to an autoimmune mechanism.[1–6]

1. Signalling pathways are common.[1–6]
2. Genetic susceptibility is linked in both of the disorders and a similar set of genes are involved: PTPN-22 (a T – cell regulatory gene), CD - 25, CTLA – 4, TSH – R, HLA – DR.[1–6]
3. Deletion of MHC Chromosome 6p21.[1–6]
4. Feedback loops of thyroid hormone and insulin sensitivity are very closely related to appetite and the expenditure of body's energy.[1–6]

CROSS-TALK BETWEEN HYPOTHYROIDISM AND DIABETES MELLITUS

Type 1 diabetes mellitus occurs as a result of a complex interaction of genetic, biochemical and hormonal factors leading to an abnormal expression of

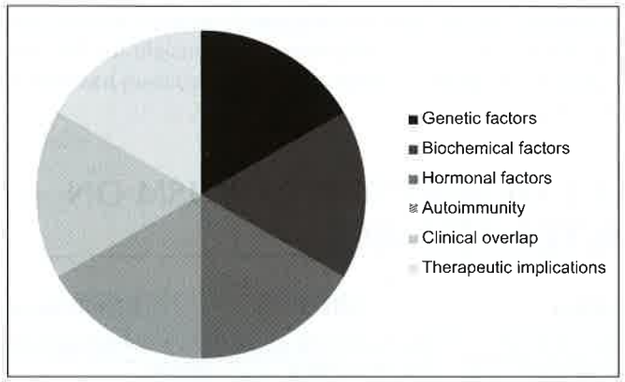

Figure 1. Key factors responsible for interplay between type 1 diabetes mellitus and hypothyroidism.

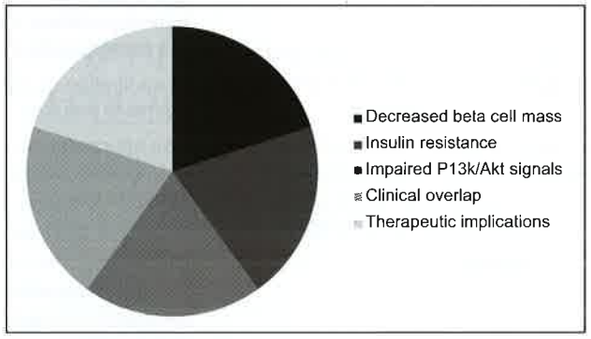

Figure 2. Key factors responsible for interplay between type 2 diabetes mellitus and hypothyroidism.

SUMMARY OF FIGURES 1 AND 2:

- Clinical overlap—Obesity, dyslipidemia, depression.[4–9]
- Autoimmunity—Type 1 diabetes mellitus and autoimmune thyroid disorders (Hashimotos, Pernicious anemia along with celiac disease)[1,4–7]
- Therapeutic implications:
  - A. Poor glycemic control and hypoglycemia in undiagnosed thyroid disorders.[4–10]
  - B. Metformin affecting TSH levels.[5,10]
  - C. Altered absorption of thyroxine due to other drugs.[4–6,9,10]

5'adenosine monophosphate-activated protein kinase (5'AMPK). 5'AMPK is responsible for modulating insulin sensitivity and the feedback mechanism of thyroid hormones.[6,7] However, in patients with type 2 diabetes mellitus, the key mechanism is a reduction in insulin secretion due to an inappropriate beta cell mass and function and this problem is complicated by the low levels of thyroid hormones.[6,7] Impaired P13k/Akt signals is the hallmark feature of insulin resistance. The thyroid hormones clearly promote beneficiary changes in this signalling cascade.[5] The key factors responsible for the interplay in type 1 and type 2 diabetes mellitus with hypothyroidism has been depicted in Figures 1 and 2.

EFFECT OF HYPOTHYROIDISM ON DIABETES MELLITUS

Observation	Effect	Significance
Impairment of renal insulin clearance[6,7,10,11]	Decreases the insulin requirements in people with diabetes mellitus	Frequent hypoglycemic attacks **Lower doses of insulin are needed** **Correction of hypothyroidism improves the renal function**
Decrease appetite[4–10]	Decrease insulin release	Dose titration of antidiabetic agents is required
Decreased fat synthesis and degradation[4,6,8,10]	Increased triglycerides and LDL (low density lipoproteins)	Can aggravate pre-existing dyslipidemia and predispose to atherosclerosis Increases cardiovascular morbidity Thyroxine replacement reverses these lipid abnormalities
Treatment of hypothyroidism is levothyroxine supplementation[1,5–7,9,10]	Increases myocardial contractility and heart rate	Can precipitate angina attacks if levothyroxine started in full doses Hence lower doses of thyroxine should be started and gradually up titrated in patients with heart disease
Low RBC turnover leading to altered erythrocyte life span[4,5,12]	False elevation of HbA_{1c}	Challenge to diabetes diagnosis and monitoring of glycemic control

Observation	Effect	Significance
Increase peripheral vascular resistance and decrease cardiac output[1,4–10]	Increased risk of nephropathy in patients with diabetes mellitus	Treating hypothyroidism improves renal function
Endothelial dysfunctions[13]	Impaired blood flow-mediated vasodilatation and peripheral vascular resistance	Increased risk of cardiovascular diseases
Increase insulin resistance[1,4–12] and also increased insulin sensitivity	Dose of anti-diabetic medications required in higher amounts Dose may decrease if insulin sensitivity is increased	Once the thyroxine replacement is instituted, the demand for anti-diabetic drugs reduces in proportion to the patients as per the improvement in the thyroid functions Hence, there is a need for regular blood sugar monitoring while treating hypothyroidism in patients with diabetes mellitus

EFFECT OF DIABETES MELLITUS ON HYPOTHYROIDISM

Observation	Effect	Significance
Severe diabetic nephropathy has clinical features like fatigue, edema, weight gain and pallor[4,5,7,9–11]	Clinical presentation is similar to hypothyroidism	Diagnosis of diabetic nephropathy may be masked by hypothyroidism and vice-versa. Hence there is a need for proper screening
Poor control of diabetes may cause reduced peripheral conversion of T4 to T3 and decreased protein binding of T4[5–7,11]	Low T3, T4 and disproportionately low TSH in serum	Overdiagnosis of central hypothyroidism In such cases T3 and T4 not reliable for diagnosis Free T3 and T4 levels need to be measured for an accurate diagnosis

Observation	Effect	Significance
In euthyroid individuals, elevated levels of insulin in blood circulation along with insulin resistance occurring due to diabetes[4,5]	Excess stimulation of thyroid follicles leading to proliferation of thyroid tissue	Large goiter-like size of thyroid gland with nodularity
Metformin, the most commonly used drug in treatment of type 2 diabetes mellitus, suppresses TSH without changing free T3 and T4 levels[4,10,30]	During metformin therapy, serum TSH is low After 3 months of metformin withdrawal, there is rebound increase of TSH secretion Also, metformin has shown to decrease the size and nodularity of goitrous thyroid	Ultra-sensitive TSH needs to be measured for accurately monitoring thyroid state in the diabetic patient The goitrous thyroid benefits by metformin treatment because of thyroid size reduction and decrease nodularity

The double trouble when hypothyroidism co-exists with diabetes mellitus has been discussed in abovementioned table.

CLINICAL EFFECT OF SYNERGISM BETWEEN HYPOTHYRODISM AND DIABETES MELLITUS

Carbohydrate Metabolism

In a patient with hypothyroidism, there is a decrease in absorption of glucose from the gastrointestinal tract, a relative loss of appetite, reduction in peripheral utilization of glucose, a fall in hepatic glucose output and a decline in the availability of gluconeogenic substrates.[4,5,7,9] There is an abnormal expression and translocation of GLUT-2 resulting in a state of insulin resistance. Also, glycogen metabolism is decreased and a reduced ratio of insulin synthesis is observed.[4,5,7,9] The half-life of insulin is prolonged owing to a decreased renal clearance of insulin.[4,5,7,9]

Effect: There is an increased predisposition to frequent hypoglycemic episodes.[4,5,7,9]

Lipid Metabolism

Thyroid hormones have both the lipolytic and the lipogenic activity. But the lipolytic activity is greater as compared to the lipogenic activity.[4–9,11,12] Therefore, in hypothyroidism, owing to decreased fat synthesis and degradation, there is an overall increase in body fat along with elevation of lipid levels.[4–9,11,12] Low concentration of intracellular fatty acid have a protective role in regulating insulin sensitivity of hepatocytes.[4,5,8,9,11] Thyroid hormones either by lipid oxidation or by preventing the cellular uptake of fatty acids help in maintaining insulin sensitivity of the hepatocytes.[4–9,11,12] Triglycerides and cholesterol levels are decreased because of enhanced LDL clearance.[4–9,11,12] Even in the Subclinical hypothyroidism there is an elevation of the total cholesterol(TC), LDL-C along with a small rise in levels of TG and the insulin resistance.[4–9,11,12]

In patients of type 2 diabetes mellitus, there is an increase in intracellular triglycerides (TG) in liver, muscle and pancreas thereby impairing insulin signalling and its secretion causes impairment in glucose response. Central obesity often seen in people with type 2 diabetes mellitus causes a TG overload in abdominal adipocytes.[4–9,11,12] These adipocytes exhibit poor response to the insulin restraining lipolysis thereby contributing to insulin resistance.[4,5,9,11] These enlarged visceral adipocytes flood the portal circulation with free fatty acids (FFA) at metabolically inappropriate time, when FFA should be oxidized, thus exposing non adipose tissues to fat excess.[11] This leads to ectopic TG accumulation in muscles, liver and pancreatic beta-cells, resulting in insulin resistance and beta-cell dysfunction.[11] The central adipose tissues tend to upset this balance by releasing large amounts of FFA.[4–6,9,11]

Effect: Co-existence of diabetes mellitus and hypothyroidism results in a severely deranged lipid profile thereby, increasing the cardiovascular morbidities in these patients.[4–9,11,12]

Protein Metabolism

Both the protein synthesis as well as its degradation are reduced in hypothyroid individuals.[6,11] The net result obtained is a reduced percentage of the proteins contributing to body weight.[6,11] Insulin facilitates intracellular short-side-chain amino acids uptake, enhances genetic expression of proteins, stimulates RNA transcription along with translation and inhibits hepatic proteolytic enzymes. Hence, insulin deficiency results in protein catabolism.[6,11]

In patients of type 1 diabetes mellitus, there is an increased protein degradation and amino-acid oxidation owing to insulin deficiency. Treatment with insulin reverses these effects.[6,11]

Effect: Muscle wasting and weakness is aggrevated.[6,11]

Immune Dysfunction

Thyroid hormones have a role as modulators of the immune activities.[4,14,15] Cytokine synthesis, generation of Reactive Oxygen Species (ROS), chemotaxis, phagocytosis, and immune functions of the mononuclear cells are all altered in a hypothyroid state.[4,14,15] In hypothyroidism, the levels of ROS and pro-inflammatory molecules like Interleukin-1β, macrophage inflammatory protein 1-α are known to increase. Thyroid hormones also affect cell mediated immune responses and NK-cell activity.[4,14,15]

Effect: Hypothyroid state adds on to the immunosuppressive effect of a diabetic individual.[4,14,15]

Fertility

Hypothyroidism can affect fertility due to sex hormone imbalance, luteal phase defects, hyperprolactinemia, interference with libido, spermatogenesis, ovulation and can also cause anovulatory cycles. It can also contribute to the risk of recurrent miscarriages.[16] Reproduction and fertility is very much dependent on thyroid hormones.[16] Hypothyroidism is associated with hyperprolactinemia because of increase production of TRH (thyrotropin releasing hormone) which has an adverse effect on the ovarian function.[16] Sex hormone binding globulin, LH, FSH and testosterone are all decreased in hypothyroidism.[16] Menstrual irregularities and infertility are common both in patients of type 1 and type 2 diabetes mellitus as well as in the patients with hypothyroidism.[16] Delayed menarche, early menopause coupled with menstrual irregularities like secondary amenorrhea and oligomenorrhea are all found to be contributory in the fertility issues.[16] The presence of an autoimmune thyroid disease complicates the menstrual and fertility problems further.[16]

Diabetes affects the erectile and ejaculatory functions adversely. Spermatogenesis, sperm motility and sperm volume are also altered negatively.[17,18]

Effect: In these patients, treatment of hypothyroidism and achieving a good glycemic control can help in conception.[16–18] Also, the sexual functions seem to be affected adversely in these patients.[16–18]

Pregnancy-related Complications

Thyroid dysfunctions and gestational diabetes mellitus both can have a negative impact on the pregnancy outcomes for both the mother and the fetus.[1,4,5,16–18] Hypothyroid pregnant women have a higher incidence of abortions in the first trimester, intra-uterine fetal deaths and neurological problems in fetus.[1,4,5,16–18] Increased risk of gestational hypertension, shoulder

dystocia, need for cesarean sections in mother and macrosomic fetuses, fetal death, neonatal hypoglycemia, prolonged neonatal jaundice, polycythemia and hypocalcemia in newborns are few of the common complications. These babies are also at high risk of developing type 2 diabetes mellitus and obesity in future.[1,4,5,16–18]

There is an increased risk for diabetes in women later who had hypothyroid state during pregnancy or had gestational diabetes mellitus, especially those having a positive family history of both DM and hypothyroid disorders. They also show a higher prevalence of antithyroid autoantibodies positivity.[1,4,5,16–18] Thyroid profile reflects a high level of TSH and low levels of free T4 in overt hypothyroidism coupled with symptoms at times. A subclinical hypothyroidism is reflected as a high TSH and a normal free T4.[1,4,5,16–18]

Effect: Dreadful pregnancy outcomes to mother and the fetus necessitates the need for every pregnant lady's routine thyroid and diabetes screening during pregnancy.[1,4,5,16–18]

Hair Disorders

Thyroid hormones facilitate the amino acid incorporation into the proteins. Hair loss in hypothyroidism is usually telogen effluvium.[1,19] However, alopecia areata, which is an immunological disorder having an autoimmune pathology, is also not uncommon.[1,19] Treatment with thyroxine in the patients induces hair regrowth.[1,19]

Hair loss in diabetes is due to poor blood circulation which affects the ability of hair follicles to open normally.[1,20] In these patients, hair follicles do not produce new strand or filament and the old filament dies and falls off.[1,20] As there is no replacement of the hair filament, gradual thinning of hair is experienced.[1,20] Drugs used for the treatment of diabetes may also interfere with normal hair growth.[1,20] Diabetes causes both physiological and psychological stress and anxiety which is found to adversely affect hair growth.[1,20]

Effect: Hair loss is aggravated in the patients of diabetes mellitus with a concomitant hypothyroidism.[1,19,20]

Anemia

In hypothyroidism, most common variety of anemia seen is normochromic normocytic type. It is due to inadequate stimulation by impaired erythroid colony developed by thyroid hormones deficiency, low erythropoietin levels and diminished oxygen distribution to the tissues.[1,21] Thyroxine replacement improves this anemia.[1,21] Also, an iron deficiency anaemia may be seen in hypothyroid females owing to menorrhagia and it is the second most common type of anaemia in these patients.[1,16,21] However, pernicious anemia due to

vitamin B_{12} deficiency is also not uncommon.[1,28]

Anemia in diabetes is normocytic normochromic.[1,22] In diabetics with CKD, deficiency and hyporesponsiveness to erythropoietin is observed and these nephropathic patients exhibit a greater degree of anemia.[1,22] Anemia in diabetic patients is a potential risk to renal replacement therapy.[1,22] If anemia is corrected early in patients with diabetes, the rate of decline of renal functions can be reduced.[1,22] Vitamin B_{12} deficiency is also extremely common in patients of diabetes mellitus which could be as a result of an autoimmune etiology in type 1 diabetes or a metformin-induced deficiency or a poor lifestyle and dietary deficiencies.[29]

Usual causes of worsening anemia in patients with diabetes generally presents as symptomatic severe autonomic neuropathy, resulting in efferent sympathetic denervation of kidney and impairment of production of erythropoietin in appropriate levels, damage to the renal interstitium, systemic inflammation and decreased levels of erythropoietin release. Erythropoietin deficiency predisposes the patients of type 1 diabetes mellitus more than type 2 for anemia.[1,22]

In female patients with diabetes, anemia is seen more comment than males. The iron stores are not related to this usually but erythropoietin deficiency is often seen.[1,22]

Effect: 1. Worsening of anemic picture may result in confusing clinical scenario to diagnose the exact cause of anemia. This may be refractory to corrective measures if underlying pathology is not being taken care of.[1,21,22]

2. Excess iron has a role in diabetes development, hence there is a need for evaluating cause and appropriate adequate correction.[1,21,22]

Respiratory Problems

In hypothyroidism, anything from mild dyspnea to complete respiratory failure may be encountered.[1,24,25] A few among the number of reasons postulated include affection of central ventilatory control, depression of hypoxic ventilatory drive, myopathy of respiratory muscles (inspiratory and expiratory) strength of respiratory muscle being directly proportional to thyroid control, decrease metabolic activity and increase deposition of glycosaminoglycans in interstitial tissues. Hence, the decrease in PFT which is reversible with treatment.[1,24,25]

In patients of diabetes, microangiopathy of pulmonary capillaries, autonomic neuropathy, myopathy of respiratory muscles, changes in collagen are few of the reasons for diminished vital capacity of lungs, reduced pulmonary volumes, low diffusion capacity of lungs (DLCO), increase sleep apnea, lower basal bronchial tone, decrease sensitivity to cough reflex and increase risk of infections.[1,23]

Effect: A synergism of diabetes with hypothyroidism worsens the pulmonary functions.[1,23–25]

Fatigue and Exercise Intolerance

Owing a limited respiratory reserve, restricted cardiac reserves, reduced muscle strength and ease of muscle fatigue, hypothyroid patients are prone to fatigue and develop exercise intolerance easily.[1,24,25]

Individuals with diabetes mellitus have an autonomic neuropathy when it is long standing.[1,23] Reason for exercise intolerance in these patients includes neuronal fatigue leading to decreased transmission of neurotransmitters, low levels of cellular storage of ATP and creatinine phosphate especially in patients with type 2 diabetes mellitus, thereby reducing the capacity to synthesize, store and use glycogen leading to exercise intolerance eventually. These factors are further complicated by increase production of serum and muscle lactic acid which is the major mediator of process of fatigue. Also, there is a failure of the resting heart rate to return to baseline early in diabetics. Hence, the need to give enough rest period to diabetics during exercise.

Patients of type 1 diabetes mellitus show a greater resistance to fatigue to anaerobic exercises while type 2 show for aerobic exercises.

Effect: Combination of the two aggravates the physical debility of these patients making their activities difficult.

Cardiovascular Effects

Both the hypothyroidism and diabetes mellitus have shown to cause significant dyslipidemias, creating an atherogenic profile which can predispose to hypertension and heart diseases.[1,4–9,11,12] They also increase obesity directly or indirectly which in turn affects the heart once again.[1,4–9,11,12]

Effect: The co-existence of hypothyroidism and diabetes mellitus warrants the need to monitor these patients closely to be able to reduce co-morbidities.[1,4–9,11]

Effects on Insulin Secretion

Thyroid hormones have a direct action in controlling the insulin secretion. In hypothyroidism, there is a remarkable effect on the expression of glucose transporter protein with a downregulation of the GLUT 5.[1,2,4–9,11,12] Also, there is impairment of GLUT 4 translocation across the cell's plasma membrane. Negative regulation occurs in the enzymatic degradation of the intracellular glucose.[1,2,4–9,11,12]

The glucose-induced secretion of insulin by β cells is also decreased.[1,2,4–9,11,12] Hypothyroidism affects glucose uptake adversely.[1,2,4–9,11,12] Also, there is fall in

the rates of glycogen synthesis and glucose oxidation.[1,2,4–9,11,12]

The insulin secretion decreases, insulin levels are reduced and half-life of insulin is prolonged which may lead to reduced insulin requirements in patients of diabetes mellitus with a co-existing hypothyroidism.[1,2,4–9,11,12]

Insulin sensitivity is found to improve with increase in concentrations of thyroid hormones. Insulin sensitivity depends on generation of intracellular T3.[1,2,4–9,11,12] Polymorphisms of the DIO2 along with reduced T3 generation is found to be associated with insulin resistance.[1,2,4–9,11,12]

Effect: 1. Owing to decreased insulin requirements, frequent hypoglycaemic attacks are observed. These hypoglycaemic incidences are more frequently seen in patients on exogenous insulin therapy.[1,2,4–9,11,12]

2. Insulin sensitivity improves with euthyroid state.[1,2,4–9,11,12]

Thermogenesis

Thyroid helps in thermoregulation via mitochondrial respiration adinotriphosphate and the brown adipocytes resulting in an increase thermogenesis in hyperthyroidism and decreased in hypothyroidism.[1,26,27] This thermogenesis is altered in the presence of insulin resistance or insufficiency. Diabetes mellitus impairs thermoregulatory functions.[1,26,27] Insulin can increase body temperature by a sympathetically mediated mechanism through its central action.[1,26,27] But hypoglycemia inhibits thermogenesis.[1,26,27] Hypoglycemia, diabetic neuropathy and vasculopathy, ketoacidosis are also associated with hypothermia.[1,26,27] Autonomic neuropathy is a known cause for impairment in heat conservation.[1,26,27]

Effect: 1. In the background of the insulin resistance or insulin insufficiency, there is reduced postprandial thermogenesis following glucose ingestion especially in obese individuals. In diabetes, the thermogenic effect of glucose and the glucose tolerance are reduced.[1,26,27]

2. Patients of diabetes mellitus having hypothyroidism are more intolerant to cold.[1,26,27]

Catecholamine Response

Insulin resistant individuals show a blunting of sympathetic nervous system responses to falling glucose whereas, in hypothyroid individuals, there is dissemination of adrenoreceptors even though they have a higher sympathetic activity and hence even a significantly stronger activity of adrenergic system most of the times does not suffice to compensate "Catecholamine Specific Resistance".[1,4,6,11,12]

Effect: 1. Insulin and counter-regulatory hormonal imbalance is responsible for hypoglycemia in diabetic patients.[1,4,6,11,12]

2. Delayed recovery from hypoglycemic attacks because of blunting or suboptimal response to counter-regulatory hormones.[1,4,6,11,12]

Other Organ Systems and Their Complications

Both diabetes mellitus and hypothyroidism can influence many organ systems in varying degrees.[1,2,4,12] For instance, retinopathy and nephropathy may occur early in these patients, obesity is increased by both, osteoporosis is worsened, depression and altered mental functions, lowered immunity, predisposition to metabolic syndrome and sleep disturbances to name a few.[1,2,4,12]

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Challenges in the Management of Co-Morbid Diabetes Mellitus and Hypothyroidism

Mala Dharmalingam

Diabetes mellitus and hypothyroidism, are common endocrine problems in clinical practice.[1–4] Hence it is important to understand the diagnostic and therapeutic challenges arising out of this association[1,2,3] because of considerable overlap between their clinical presentations.[1–4] Asymptomatic hypothyroidism is very common in patients with diabetes mellitus.[1–3] Underlying pathophysiology of both these conditions usually have an autoimmune origin.[1–4] Undiagnosed and untreated hypothyroidism, may result in difficulty in achieving euglycemic state. Similarly an undiagnosed and untreated diabetes can adversely affect normal thyroid hormone levels.[1–4]

The challenges and complications of this synergism have been briefly discussed in this chapter.

DIAGNOSIS

Subclinical and overt clinical hypothyroidism are frequently associated conditions found in patients with diabetes mellitus.[1–4] Few clinical trials have shown a decreased rate of glucose disposal and its metabolic clearance along with a very low rate of renal insulin clearance in the patients of hypothyroidism.[4] Unidentified thyroid problems can adversely affect the control of diabetes mellitus and also aggravate its complications.[1–4] Clinical picture may be confusing at times, for example: Severe form of diabetic

nephropathy may mimic hypothyroidism clinically (fatigue, edema, weight gain and pallor).[1–5]

Changes in the results of the thyroid function tests seen are in non-thyroidal illnesses may be found in patients with a poorly controlled diabetes mellitus.[1,4,6]

Any one autoimmune condition warrants the screening of other autoimmune pathologies.[5,6] Those with an autoimmune hypothyroidism have increased risk of either autoimmune hypothyroidism itself or even Grave's disease.[5] Hence, it is advisable to always screen for other autoimmune conditions like Diabetes Mellitus Type 1, Vitiligo, Pernicious Anaemia, Addison's Disease, Alopecia Areata, Dermatitis herpetiformis, Rheumatoid arthritis, SLE, Chronic Hepatitis (in the active phase), Celiac Disease, Sjögren's Syndrome, and Myasthenia Gravis, etc.[5] *Women with diabetes mellitus are three times more prone to developing postpartum thyroiditis.*[2,5]

ALTERATION OF THYROID PROFILE DUE TO DIABETES MELLITUS

Glycemic status of an individual plays a pivotal role in altering the thyroid profile by its influence on the serum T3 (triiodothyronine) levels, peripheral conversion of T4 to T3, baseline serum TSH (thyroid stimulating hormone) levels and the response of TSH to the TRH (thyrotropin releasing hormone).[6,7] Thyroid hormones and insulin have an antagonistic action on each other.[6] In the background of hyperglycemia, there is a reversible inhibition of the hepatic concentration and activity of T4-5-iodinase, thereby leading to a decline in serum T3, elevation of reverse T3 and variable levels of T4.[6] Also, the nocturnal peak of TSH is low in these patients.[6,7] All these events collectively result in a poor thyroid profile in the patients with diabetes mellitus.

FLUCTUATING INSULIN REQUIREMENTS

Thyroid hormones exert effects on almost every metabolic process of the body.[6] In patients with hypothyroidism, there is an overall reduction in the secretion of insulin from beta-cells of the pancreas and a development of relative peripheral resistance to the action of insulin.[4,6,7,9] Also, the patients of diabetes mellitus having hypothyroidism exhibit an abnormal glucose metabolism in the form of an impaired glucose absorption from the gut, decreased hepatic glucose output, reduced gluconeogenesis and a poor peripheral glucose uptake coupled with a decreased ratio of insulin synthesis.[4,6,7] In patients with subclinical hypothyroidism, there is a decline in the insulin-stimulated transport of glucose owing to abnormal expression and

translocation of GLUT-2 leading to insulin resistance.[6,9] Thus, the net result is a reduced insulin requirement and increased frequency of hypoglycemic episodes.[4,6,7]

PRESENCE OF HYPOGLYCEMIA

In patients of type 1 diabetes mellitus, there is a complex interaction of genetic, biochemical and hormonal factors leading to a perturbed expression of 5'adenosine monophosphate-activated protein kinase (5'AMPK) which is responsible for modulating insulin sensitivity and feedback mechanism of thyroid hormones.[8,9] However, in patients with type 2 diabetes mellitus, the key mechanism is a reduction in insulin secretion due to an inappropriate beta cell mass and function and the problem is further complicated by the low levels of thyroid hormones.[8,9]

An inappropriate secretion of insulin leads to activation of the body's physiological processes.[4,6,7] These include glucagon, cortisol, adrenaline and growth hormone actions.[4,6,7] Hypothyroid patients exhibit a relative insufficiency of adrenal gland and show impairment of hypothalamo-pituitary-adrenal response to hypoglycemia.[4,6,7] The diminished cortisol activity coupled with altered glycogenolysis worsens the hypoglycemia and delays recovery.[4,6,7] All this, in conjunction with decreased glucagon, diminished effects of glucagon on the liver, slowing of gastric emptying, reduced renal insulin clearance, slow absorption of glucose in the intestine and reduced portal venous flow resulting in a state of refractory hypoglycemia.[4,6,7]

In cases of spontaneous hypoglycemia refractory to treatment, the possibility of panhypopituitarism is usually considered. However, in diabetes mellitus, when the frequency and the rate of hypoglycemic events increases and is not explained by any other factor like diet, drug and lifestyle, the ruling out hypothyroidism is a must.

EFFECT OF DIABETES MELLITUS ON THYROID FUNCTION

Higher levels of insulin in the blood coupled with insulin resistance is observed in patients with diabetes mellitus with concomitant hypothyroidism.[4,7,8] Insulin acts as a growth-promoting factor[4] and its action on the thyroid gland results in proliferation of thyroid follicles leading to the formation of nodules and an enlarged thyroid.[4,7,8] This, in turn, leads to a gradual worsening of thyroid function.[4,7,8]

ALTERATIONS IN LIVER PHYSIOLOGY

Patients with hypothyroidism and co-existing diabetes mellitus exhibit an impaired glucose metabolism.[4,6–9] There is an impairment of absorption of glucose from gut, delayed peripheral glucose assimilation, inappropriate gluconeogenesis, a low to normal hepatic glucose output, reduced glucose disposal in peripheral tissues and an altered expression of GLUT2.[4,6–9] Thus, leading to an increased susceptibility to hypoglycemic episodes and a worsening of glycemic control.[4,6–9]

SKELETAL MUSCLE ASSOCIATION

An important factor in overt hypothyroidism is Insulin resistance and its inability to sustain the glucose utilization adequately by the muscles.[4,8] Thyroid hormones directly affect the muscles by causing an impairment of glycogenolysis in muscles leading to glycogen accumulation. Hence, myopathies, stiffness, discomfort, slowing of movements, increase in muscle mass are all common in hypothyroid diabetics.[4,6,8]

EFFECT ON CARDIOVASCULAR SYSTEM

Thyroid hormones lead to an increased stimulation of sinus node of the heart.[2,4,6,8] They also exert a direct impact on the myocardium.[2,4,6,7,8] Thus, there is an increase in the heart rate, enhanced myocardial contractility and cardiac output. Peripheral resistance is usually normal but there may be a slight increase due to a decrease secretion of vasodilators (hence cutaneous vasoconstriction leading to the dry and cold skin). Also, there is an increase predisposition to anginal attacks and hypertension.[2,4,5,7,8] *ECG may show an Inversion of T-waves, low voltage amplitudes of P, QRS complex and T wave.*[4,5,7,10] Diabetes mellitus increases the cardiovascular morbidities and worsens the clinical scenario.[2–8]

MICROVASCULAR DISEASES

Higher frequency of microvascular complications like nephropathy and retinopathy in subclinical hypothyroid patients has also been noted.[2,4–7] The severity of retinopathy in hypothyroid patients is also greater as compared with the diabetics alone.[2,4–7] Hence, this causes diagnostic and therapeutic challenges in co-existence of diabetes mellitus and hypothyroidism.

DYSLIPIDEMIA

Thyroid-stimulating hormone (TSH) receptors are present on the surface of both thyroid follicular cells and adipocytes.[4,5] Therefore, TSH stimulates lipolysis.[4,5] Subclinical hypothyroidism can cause rise in LDL and cholesterol levels in serum which may worsen pre-existing dyslipidemia, if any, and predispose to atherosclerosis.[4–8]

The altered lipid status appears to be mediated via an imbalance between MAPKK and Pi 3 – KINASE expression.

DRUG-INDUCED COMPLICATIONS

Antidiabetic preparations and drugs used for thyroid hormone supplementation are shown to affect the patients having hypothyroidism and diabetes mellitus simultaneously.

Example: Metformin is usually the first line of treatment in any diabetic individual.[4,5] It has shown to suppress TSH secretion from pituitary gland via inhibition of the hypothalamic enzyme AMPK.[4,5,7,8,10] This effect is perhaps independent of thyroxine treatment and does not affect T3 and T4 profile.[4,8–10] Metformin has also shown to decrease the size of thyroid nodule in the patients with the insulin resistance.[4,10]

In addition, thyroid hormones can precipitate angina in patients of diabetes mellitus due to increased heart rate and myocardial contractility.[4,5] Hence, a careful titration of the dose of thyroxine supplementation is required in these patients.[4,5]

To conclude, a knowledge of the synergistic picture of diabetes mellitus and hypothyroidism is crucial in diagnosis and management of these illnesses.

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Management of Diabetes Mellitus and Hypothyroidism in Co-Existence

K.M. Prasanna Kumar

Diabetes mellitus is one of the commonest endocrinal pathology observed in clinical practice.[1–7] The prevalence of hypothyroidism is also increasing rapidly worldwide.[1–7] Both these diseases, when occur in a patient simultaneously, can impose difficulties in their management.

The goals of the management are:

- Symptomatic management.
- Improvement in the quality of life.
- Early diagnosis and management of the immediate as well as the long-term complications. Example: cardiovascular, renal, ophthalmic, etc.
- Monitoring of the therapy.

Important considerations while investigating a known case or a patient suspected to have diabetes mellitus and hypothyroidism in co-existence has been summarized in Table 1.

Table 1.
Investigations—Important Considerations

- Achieve glycemic control and then assess serum TSH levels in patients of type 1 diabetes mellitus.[4,5,7]
- Poor glycemic control, dyslipidemia, altered liver enzymes, hypoglycemic attacks and bradycardia in type 2 diabetes mellitus, warrants a TSH evaluation.[1,4–7]
- Free T3/T4 evaluation should be considered in acutely ill patients.
- Use of a third generation ultra-sensitive serum TSH is recommended in all patients with diabetes mellitus with hypothyroidism for dose-adjustments especially when the patient is on insulin therapy.[12]
- A_{1c} used as an adjunct in monitoring glycemic control of diabetes mellitus, it may be falsely elevated in hypothyroid patients owing to the alteration in RBC life span.[1,4,7]

Table 2 describes the various guidelines for the thyroid screening in patients with diabetes mellitus.

Table 2.
Thyroid Screening in a Patient with Diabetes Mellitus

Guidelines	Type 2 diabetes mellitus	Comments
Thyroid function in type 2 diabetes mellitus and in diabetic nephropathy. Indian study. *Journal of Clinical and Diagnostic Research*[8]	If the thyroid dysfunction is left unrecognized and uncorrected, it can result in a poor glycemic control in patients with type 2 diabetes mellitus. Uncorrected hypothyroidism worsens the renal functions, accelerates the progression of hypothyroidism and increases the morbidity of such patients	Regular screening of thyroid function can result in improved clinical outcomes in patients with diabetes mellitus
American Thyroid Association. Guidelines for Detecting Thyroid Dysfunction[7]	Patients with diabetes mellitus require more frequent screening for thyroid	Recommends TSH estimation from 35 years of age, thereafter once in every 5 years in adults. High-risk patients may require more frequent testing

Guidelines	Type 2 diabetes mellitus	Comments
American Association of Clinical Endocrinologists. Diabetes Guidelines, 2007[7]	Not mentioned specifically	Frequent screening for diabetes is recommended
American Association of Clinical Endocrinologists. Thyroid disease clinical practice guidelines[7]	Thyroid palpation and TSH at the time of diagnosis and at regular intervals especially if goiters or other autoimmune conditions are present	Recommends screening of pregnant women for type 2 diabetes
British Thyroid Association and Association of Clinical Biochemistry. Guidelines, 2006[7]	TFT (thyroid function test) recommended to determine the baseline. Routine screening not recommended	TSH and antibodies measurement recommended during pregnancy and in the postpartum period
American Diabetes Association. Standards of Medical Care in Diabetes, 2009[7]	Does not mention specifically	Thyroid palpation in all elderly patients (50 years) with diabetes and in those with existing dyslipidemias recommended

TREATMENT IN VAROUS CLINICAL SCENARIOS

Clinical Hypothyroidism

In a patient with euglycemic state, Levothyroxine (LT4) is administered at a dose of 1.6 µg/kg body weight daily. However, in many patients, even lower doses are sufficient. In cases of post–Grave's disease hypothyroidism, low-dose LT4 replacement is given (75–125 µg/day). However, in adults with a cardiovascular problem, 50–100 µg/day of LT4 is required.[1,4–11]

In a patient with prediabetic state, treatment of hypothyroidism is done similar to that in euglycemic state, with regular monitoring of glycemic status and lipid profile to check for co-existing dyslipidemias. Lifestyle and dietary modifications should also be considered for a better glycemic control and prevention of progression to frank diabetes mellitus.[1,4-11]

In patients with type 1 diabetes mellitus, Levothyroxine is used to treat hypothyroidism. It also benefits by enhancing the insulin sensitivity.[1,4-11] Frequent monitoring of blood glucose is advisable in these patients. Insulin therapy may be started if needed under strict glucose monitoring due to tendency of recurrent hypoglycemic episodes. Hence, frequent dose alterations may be required. Agents like α-glucosidase inhibitors may be used.[1,4-11]

In patients with type 2 diabetes mellitus, levothyroxine is used to treat hypothyroidism. Oral antidiabetic agents (single or multiple drug regimens based on degree of hyperglycemia and co-morbid states) are administered. Insulin is considered only in specific situations such as pregnancy, acute infections, uncontrolled diabetes mellitus and surgeries.[1,4-11] Special attention should be on drugs that benefit the metabolic state in hypothyroidism: Example, metformin. Metformin is the most commonly used drug in diabetes mellitus. Metformin suppresses TSH emphasizing the need for a regular monitoring of TSH during the metformin therapy.[4,5,7] α-glucosidase inhibitors and statins (also improves dyslipidemia without altering thyroid profile) may be prescribed.[1,4-11]

Drugs aggravating this double-trouble situation must be remembered. Bile acid sequestrants used in the treatment of diabetes elevate plasma triglycerides and may worsen pre-existing dyslipidemias in patients with hypothyroidism.[5]

Subclinical Hypothyroidism

Routinely, treatment of subclinical hypothyroidism is not required till TSH < 10 mU/L in a euglycemic state.[1,4-11] Treatment of subclinical hypothyroidism should be considered if the patient is symptomatic or serum anti-TPO antibodies are positive or there is worsening of dyslipidemia.[1,4-11]

Summary of few of the important treatment options for managing diabetes mellitus and hypothyroidism occurring simultaneously in a patient has been depicted in Table 3.

Table 3.
Important Treatment Options for Hypothyroidism in Co-morbid Diabetes Mellitus[1,4-11]

Diabetic status	Thyroid State		
	Clinical hypothyroidism	Subclinical hypothyroidism	Euthyroid
Euglycemia	Levothyroxine (LT4) daily dosing	Routinely treatment not required till TSH <10 mU/L	–
Prediabetes	Treat hypothyroidism with levothyroxine Lifestyle and dietary modifications for a good glycemic control	Usually, no medications given	Screen for hypothyroidism Regular monitoring of blood glucose (fasting and postprandial) and A_{1c}. (obesity is not always hypothyroidism) Lifestyle and dietary modifications alone can help Usually no medications given
Type 1 diabetes mellitus	Levothyroxine is used to treat hypothyroidism. Insulin therapy under strict glucose monitoring. α-glucosidase inhibitors and Pramlintide may also be used	Usually no treatment for hypothyroidism Insulin therapy under strict glucose monitoring. α-glucosidase inhibitors and Pramlintide may also be used	Screen for hypothyroidism Insulin therapy with/without oral antidiabetic agents. (Individualized patient approach is a must). α-glucosidase inhibitors and Pramlintide may also be used

Diabetic status	Thyroid State		
	Clinical hypothyroidism	Subclinical hypothyroidism	Euthyroid
Type 2 diabetes mellitus	Levothyroxine is used to treat hypothyroidism Oral antidiabetic agents (single or multiple drug regimens based on degree or hyperglycemia and co-morbid states. Insulin only in specific situations. Special attention should be on drugs that benefit metabolic state in hypothyroidism: E.g. Metformin, α-glucosidase inhibitors, and statins	Usually no treatment for hypothyroidism. Oral antidiabetic agents (single or multiple drug regimens based on degree or hyperglycemia and co-morbid states. Insulin only in specific situations. Special attention should be on drugs that benefit metabolic state in hypothyroidism. E.g. Metformin, α-glucosidase inhibitors, and statins	Screen for hypothyroidism. Oral antidiabetic agents (Individualized patient approach is a must). Insulin therapy required in selected situations, e.g.: • Uncontrolled diabetes • Acute infections • Pregnancy • Surgery Oral antidiabetic agents (single or multiple drug regimens based on degree or hyperglycemia and co-morbid states. α-glucosidase inhibitors may be considered Type 2 DM patient ↓ Nutrition + ↑ physical activity + weight loss + metformin ↓ Re-assess A_{1c} ↓ Combination therapy: Metformin + second agent ↓ Re-assess A_{1c} ↓ Combination therapy: Metformin + two other agents. AND/OR Insulin + Metformin

OTHER CONSIDERATIONS IN MANAGEMENT OF HYPOTHYROIDISM AND DIABETES

Patients with suppressed TSH of any form including overtreatment with levothyroxine are at a higher risk of atrial fibrillation.[1,4–11]

In the patients on a high dose of levothyroxine (>200 µg/day), an elevated TSH could indicate poor compliance. In such patients, normal T4 may be found.[1,4–11]

If a patient misses one dose, he can be advised to take 2 doses of levothyroxine at once.[10]

Rarely, LT4 may cause pseudotumor cerebri.[1,4–11]

Liothyronine (LT3) is also available but owing to a short half-life 3–4 doses per day are required. Also, it is associated with fluctuating T3 levels. Hence, it is not useful clinically. Combination therapy of LT3 and LT4 does not provide any clinical benefits.[1,4–11]

Thyroid analogues (still under clinical trials) also called as thyromimetics have been introduced to the market owing to their lower side-effect profile and promising results on dyslipidemias.[1,4–11] They are synthetic thyroid hormone agonist and effectively lowers LDL, triglycerides, Apolipoprotein B and Lipoprotein A levels by altering the process of atherogenesis having a mechanism distinct from statin drugs with a possible synergism with statins.[1,4–11] E.g. Carbohydrate response-element binding protein (Ch-REBP), Tiratricol, D-thyroxine, Eprotiromone (KB 2115), Diodothyropropionic acid.[10]

In patients of diabetes mellitus having a coronary artery disease, levothyroxine can exacerbate angina by increasing heart rate and increasing myocardial contractility. Hence, in patients with cardiovascular complications, it is advisable to start with a lower dose of thyroxine.[4,10]

Thyroid hormones increase insulin sensitivity, thereby benefit of reduced frequency of hypoglycemic attacks can be obtained in these patients.[4,10]

Patients with an elevated TSH in spite of adequate dosing of LT4 may benefit from metformin. LT4 may regularize TSH, but may not regularize neurocognitive functions due to polymorphisms in the receptor and transporter in the brain. In such a situation, there is a theoretical advantage of using LT3[1,4–11]

To conclude, a holistic treatment of this double-trouble situation includes a lifestyle improvement, de-addiction, exercise and yoga coupled with an individually titrated drug therapy and timely screening for end-organ damage.[1,4–11]

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Key Points

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1. Hypothyroidism and Diabetes mellitus both are common endocrine disorders.
2. Autoimmune thyroid disease and Type 1 Diabetes Mellitus are caused by dysregulation of immune surveillance and tolerance.
3. The possible reasons postulated for an association between type 2 diabetes mellitus and hypothyroidism could be of genetic, biochemical or hormonal origin. Impaired P13k/Akt signals is a hallmark feature of insulin resistance and thyroid hormones clearly promote beneficiary changes in this signalling cascade.
4. TIDM (Type 1 Diabetes Mellitus) and (AITD) Auto-Immune Thyroid Disorders are both included in the Poly-Glandular Syndrome (Type 2 and 3).
5. Postpartum autoimmune thyroiditis, a transient condition at times, is almost 3 times more commonly found in Type 1 Diabetes Mellitus patients than the rest of the normal population.
6. If one autoimmune condition is present, it is beneficial to screen for the other.
7. In congenital syndromes e.g., Down's syndrome and Turner's syndrome; routine screening of hypothyroidism and diabetes is a must.

8. Women with type 1 diabetes should be screened for serum TSH, FT4 and thyroid peroxidase antibody status during preconception, at ANC registration when pregnant and at 3 months postpartum.
9. There is a high frequency of asymptomatic thyroid dysfunction in patients with type 1 diabetes.
10. Patients with type 1 diabetes should have a check of thyroid function included in their annual *review.*
11. Patients with type 2 diabetes should have their thyroid function checked at diagnosis but routine annual thyroid function testing is not recommended.
12. Patients with diabetes require more frequent screening for thyroid disorders as compared to general population.
13. There are increased triglycerides and LDL (low density lipoproteins) in hypothyroid subjects with diabetes which thereby aggravate the pre-existing dyslipidemia and which ultimately predisposes to atherosclerosis and increases cardiovascular morbidity.
14. Thyroxine supplementation in an elderly patient with heart disease can precipitate angina attack in individuals with compromised cardiovascular status.
15. Metformin, a first-line antidiabetic medication, suppresses TSH. It also shrinks the thyroid nodules in goiter.
16. Thyroxine replacement therapy enhances insulin sensitivity, reverses dyslipidemias and improves diabetes control.
17. Patients with suppressed TSH of any form, including overtreatment with T4 can precipitate atrial fibrillation.
18. Hypothyroidism and diabetes when occur together, increase the risk of diseases like nephropathy, cardiovascular complications, infertility, and menstrual disturbances.
19. Poor glycemic control, dyslipidemia, altered liver enzymes, bradycardia and hypoglycemic attacks warrant TSH evaluation in a subject with diabetes.
20. In acutely ill diabetic patients, free T3 and T4 should be evaluated along with TSH to avoid spurious results. If TSH is elevated along with deranged T3 and T4, it may be of a diagnostic significance.
21. Obesity is a hallmark of metabolic syndrome seen in patients with diabetes. But hypothyroidism may often be associated with weight gain and a higher BMI. Hence, there is a need to evaluate these patients for both diabetes and hypothyroidism.

22. Fluctuating insulin requirements should sound the physician to investigate the patient for thyroid functions by the ultrasensitive immunoassay for serum TSH, to assess drug compliance and diet, and also consider other elements in the hypothalamo-pituitary axis.
23. Impairment of renal insulin clearance decreases the insulin requirements and results in frequent hypoglycemic episodes in these patients. Hence, the need for lower doses of anti-diabetic preparations.
24. Both diabetes mellitus and hypothyroidism are found to aggravate the complications of each other on the many organ systems like increasing cardiovascular morbidity and mortality, worsening of lipid profile and anemic status, and difficulty in achieving euglycemia.

Clinical Case Scenarios Illustrating the Management of Diabetes Mellitus with Hypothyroidism

A.G. Unnikrishnan

Ganapathi Bantwal

CASE 1: THYROID AND DIABETES – AN ILLUSTRATIVE CASE

A.G. Unnikrishnan

INTRODUCTION

Mr. X, a 25-year-old gentleman had type 1 diabetes for 8 years. He is on basal bolus insulin therapy and his last HbA_{1c} reading is 6.9%. Six months ago, a screening test for diabetes-related complications showed no evidence of neuropathy, nephropathy or retinopathy.

Recently, over the last 6 months, he has been gaining weight. His current weight is 82 kg and his height is 171 cm. He has gained 6 kg in the last 6 months. He also has constipation.

CLINICAL EXAMINATION

Clinical examination is unremarkable. He does not have a goiter.

LABORATORY INVESTIGATIONS

Thyroid function tests carried out show the following reports:

Serum T4—3.5 ug/ dl (normal 5–12)

Serum TSH—87 uIU/ ml (normal 0.4–4.2)

Serum anti-thyroid peroxidase antibody—111 IU/l (normal <60)

TREATMENT

In view of hypothyroidism, he was started on levothyroxine 125 µg/day. After 6 weeks, TSH was 3.9 uIU/ml. His weight had reduced to 79 kg, and he reported no constipation and remarkable improvement in general well-being.

DISCUSSION

Autoimmune thyroid disease is one of the most common causes of hypothyroidism. Importantly it can affect specifically people with other autoimmune diseases.

Studies have reported that about one-fourth to one-third of subjects with type 1 diabetes have autoimmune thyroid disease and hypothyroidism.[1]

A significant proportion of subjects with type 1 diabetes have thyroid autoantibodies positive (thyroid peroxidase, and much less common, anti-TSH receptor antibody positivity). About 18% of subjects with type 1 diabetes may have positivity to thyroid antibodies.[1] About 19–41% of subjects with type 1 diabetes may have hypothyroidism.[2] The influence of thyroid antibody positivity on the natural history of type 1 diabetes or development of polyglandular autoimmunity has not been established.

As type 1 diabetes affects younger population, the influence of hypothyroidism on growth, maturation, and intellectual ability may be important to consider. Hence, all subjects with type 1a diabetes (autoimmune subtype of type 1 diabetes) require annual testing of thyroid function using simple tests such as serum TSH. Thyroid antibodies could help predict hypothyroidism- but their exact role as a clinical test in predicting hypothyroidism among subjects with type 1 diabetes remains to be studied and established. Treating co-existent hypothyroidism will help improve the health and overall quality of life of subjects with type 1a diabetes.

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CASE 2: HYPOTHYROIDISM IN DIABETES

Ganapathi Bantwal

Mrs. X is a 42-year-old woman with type 2 diabetes for the past 8 years. She was initially diagnosed to have diabetes when she presented with osmotic symptoms; she was initiated on oral hypoglycemic agents (OHA) (glimepiride and metformin) and advised to make appropriate lifestyle and dietary modifications.

Though she was compliant with her medications and diet, she would not visit the doctor frequently. For the past 2 years, she has been taking insulin (premixed 30/70 twice daily doses) in addition to the OHA as her glycemic control was told to be poor. She has never had a complete comprehensive evaluation for diabetes complications in the past.

For the past 6 months, she has been experiencing severe fatigue and somnolence, and is unable to walk long distances due to shortness of breath. She also complains of heavy monthly menstrual bleeding that started around 6 months ago, but has been amenorrhic for the past 2 months. She has gained 4 kg of weight, has dry itchy skin, has lost her appetite and feels extremely tired through the whole day. She has stopped her usual insulin doses for the past 2 weeks in view of severe lethargy.

CLINICAL EXAMINATION

Clinical examination reveals features of gross hypothyroidism with pallor and hepatomegaly (2 cm below the right costal margin). The fundus examination reveals no retinopathy.

LABORATORY INVESTIGATIONS

Blood Investigations

Hb: 6 g/dl

PS: Microcytic hypochromic blood picture

Creatinine: 1.8 mg/dl

Electrolytes: Na126 mEq/L, K—3.8 mEq/L, Cl—103 mEq/L

Liver panel: Albumin—3.1 g/dl, AST—65 IU/L, ALT—200 IU/L, ALP—245 IU/L

Lipid panel: Total cholesterol: 280 mg/dl, HDL cholesterol: 34 mg/dl, LDL cholesterol: 180 mg/dl,

Triglycerides: 358 mg/dl

Abdominal USG

Fatty hepatomegaly

Thyroid Profile

TSH: 550.6 IU/ml (normal 0.29–3.0)

T4: 1.5 µg/dl (normal: 4.5–12.5)

Positive for anti-TPO antibodies (titers >1300)

Glycemic Assessment

Hemoglobin A_{1c} (A_{1c}): 6.9%

6-point glucose profile:

Fasting—78 mg/dl

2 hours post breakfast—106 mg/dl

Pre-lunch—72 mg/dl

2 hours post lunch—64 mg/dl

Pre-dinner—71 mg/dl

2 hours post dinner—92 mg/dl

DISCUSSION

This case illustrates that the metabolic changes occurring as a part of hypothyroidism may alter many aspects of diabetes control and its associated complications.

The effect of thyroid hormones on carbohydrate metabolism may potentially cause variations in glycemic control of patients with diabetes. In presence of overt hypothyroidism, glycogen synthesis and secretion from the liver reduces along with a concomitant reduction in degradation of glycogen.

Similarly, absorption of glucose from the gut and rate of gluconeogenesis is reduced, and so is the utilization of glucose by the peripheral tissues. The net result is usually low normal glucose values with absence of severe hypoglycemic episodes. However, insulin levels are decreased even though the half-life is prolonged because of a reduction in insulin secretion. Hence, a patient using exogenous insulin may develop hypoglycemia if the dose is

not reduced, which is demonstrated in this case study. There is a discrepancy between the monitored plasma glucose values (7-point profile) and the glycated hemoglobin, which appears to be higher than expected. The patient described above has probably developed iron deficiency anemia secondary to the menorrhagia associated with hypothyroidism. Iron deficiency anemia may lead to falsely elevated glycated hemoglobin in the presence of low normal glucose readings.

Hypothyroidism is known to cause a reversible elevation in serum creatinine; this has been attributed to the reduction in GFR (GFR falls by about 40%) and to the associated myopathy and rhabdomyolysis. There is also evidence of increased glomerular capillary permeability to proteins leading to proteinuria. Both these findings may be wrongly interpreted as presence of diabetic kidney disease, when in fact, they are reversible with levothyroxine therapy. Hypothyroidism is now emerging as a possible modifiable risk factor for developing NAFLD or NASH. As NAFLD is usually associated with diabetes, the presence of abnormal liver enzymes and fatty liver in a patient with diabetes and hypothyroidism warrants re-evaluation following therapy with levothyroxine. The thyroid hormones control circulating lipid levels by upregulating the LDL receptors in the liver via the SREBP2 protein. Hypothyroidism typically worsens the dyslipidemia associated with diabetes; increase in total cholesterol, LDL cholesterol and triglycerides are seen. The increase in LDL levels attributable to hypothyroidism is usually around 30%; hence, additional statin therapy would be required in this patient to get the cholesterol levels down to the target range. However, it would be prudent to avoid initiating statins before correction of hypothyroidism as the risk of myopathy and rhabdomyolysis are higher.

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