REVIEW ARTICLE

Undetected hypothyroidism and its anesthetic implications

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SUMMARY

Hypothyroidism is a common disorder affecting the cardiovascular, respiratory, hematopoietic, and renal organ systems. Each of these systems is particularly relevant in the management of the surgical patient. Most reported complications have occurred in patients with unrecognized hypothyroidism. In general, treatment of recognized hypothyroidism is recommended before any surgical procedure whenever possible and normal levels of thyroid hormone should be documented as part of the preoperative evaluation. Such a strategy is likely to result in better surgical outcomes with improved morbidity and mortality.

Key words: Hypothyroidism; Thyroid hormone; Morbidity; Mortality

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INTRODUCTION

Thyroid hormones have profound effects on metabolism and hence a wide variety of actions in every organ system of human body. They play a crucial role in regulating myocardial function, pulmonary ventilation, energy homoeostasis, vascular tone, water and electrolyte balance, and normal function of the central nervous system.[1] Hypothyroidism is a condition in which synthesis of the thyroid hormone is insufficient to meet bodily needs. In hypothyroidism thyroid gland fails to function adequately, resulting in reduced levels of thyroid hormone in the body. There are many causes of hypothyroidism. This deficiency may originate in the thyroid gland or may be the result of a disease process outside of the thyroid gland. The endogenous reason is autoimmunity developed against the thyroid gland termed as chronic autoimmune thyroiditis. Its variant Hashimoto's thyroiditis is a condition in which there is destruction of the gland. The most common cause of primary hypothyroidism in iodine rich countries like United States and Japan is Hashimoto's thyroiditis.[2] The exogenous reason for hypothyroidism is the low intake of iodine. Hypothyroidism is also caused by surgical removal of the thyroid gland, thyroid ablation with radioactive iodine, and external irradiation. It is also associated with diabetes[3], infertility[4], obesity[5] and certain drugs (such as lithium and interferon); being more common in females than males[2] and may manifest in severe or subclinical form.

Subclinical hypothyroidism is characterized by elevated serum level of thyroid stimulating hormone (TSH) in an apparently healthy individual. The prevalence of overt hypothyroidism in iodine-replete communities is in the range of 1–2%[2]. The prevalence of subclinical hypothyroidism in the United States is 4-8·5%[6,7]; it increases with age and may differ among ethnic groups.[7]

Hypothyroidism produces major derangements of human physiology. The incidence of perioperative morbidity associated with undiagnosed or untreated hypothyroidism is unknown. However, major complications have been reported in intraoperative recognition of hypothyroidism. These included depression of myocardial function, decreased hypoxic and hypercapnic ventilator responses, abnormal baroreceptor function, and reductions in plasma volume.[8] In unrecognized hypothyroid patient presence of anemia, hypoglycemia, hyponatremia, decreased free water excretion, and impaired hepatic drug metabolism may all adversely influence responses to anesthesia.

Thus preoperative recognition of hypothyroidism is essential for the safe anesthetic management of patients. It is now widely accepted that euthyroid state marked by adequate levels of thyroid hormones is necessary to obtain the best possible results from any kind of surgical intervention.[2] A thorough knowledge of the epidemiology, pathophysiology and pharmacological issues related to anesthesia case management for hypothyroidism is essential to provide high-quality care.

Effects on Cardiovascular System

The most important adverse effects of hypothyroidism that may predict a bad surgical outcome are those affecting cardiovascular function. The cardiovascular manifestations of hypothyroidism are the result of decreased action of thyroid hormone on both the heart and the peripheral circulation.[9,10] Hypothyroid patients have impaired cardiac contractility with decreased cardiac output, increased peripheral vascular resistance, decreased blood volume and peripheral oxygen consumption. Cardiac parameters indicate depressed myocardial function in hypothyroid patients. As compared to normal subjects, cardiac output decreases by as much as 30% to 50%[11], heart rate decreases slightly, and cardiac contractility is adversely affected with subnormal systolic and diastolic function. Cardiac cycle is also affected by hypothyroidism. The degree of pre-ejection period prolongation and the reduction of left ventricular ejection time correlate directly with the severity of clinical hypothyroidism. A decrease of 60% in the left ventricular ejection time and a prolongation of the pre-ejection period by 40% is reported in cases of severe hypothyroidism.[1] These changes may be particularly important for the surgical patient with some degree of preexisting heart failure.

The molecular changes underlying these abnormalities are multifactorial. Deposition of glycosaminoglycans in the myocardial tissues has been documented. Thyroid hormones influence cardiac function by exerting their effect on several genes in the cardiac myocytes either in a positive or negative fashion. The activities of several enzymes involved in regulation of calcium fluxes in the heart are also controlled by thyroid hormone. Alterations in calcium handling seen in the cytoplasmic reticulum and a depression of the myosin ATPase activity contribute to the observed decrease in myocardial contractility.[12] A decrease in the rate of calcium uptake and calcium-dependent ATP hydrolysis has been demonstrated in myocardial sarcoplasmic reticulum of hypothyroid animals.[13] These effects suggest an effect of thyroid hormone on myocytes independent of classic nuclear gene transcription action.

An increased peripheral vascular resistance is routinely seen in hypothyroid patients. This is believed to be due directly to the deficiency in thyroid hormone, specifically triiodothyronine (T_3). T_3 seems to exert a vasodilatory effect by a direct action on the smooth muscle of the blood vessels and an effect on endothelial function.[14,15] The decrease in oxygen demand of peripheral tissues associated with hypothyroidism may also play a role in the increase of systemic vascular resistance, which in turn causes an increase in the cardiac afterload. A lowering of the cardiac output follows, because of a decrease of the left ventricular ejection fraction and a small drop of the heart rate. An effect on blood pressure is also seen with an increase in diastolic pressure and a decrease in the systolic pressure. However, mean blood pressure remains largely unaltered even in the presence of increase in systematic vascular resistance and in cardiac output in hypothyroidism. Occasionally hypertension is not an uncommon finding, and the classic finding of a reduced pulse pressure is also seen.[1] Loss of the cardiovascular responses to acute increases in intrathoracic pressures is often seen in the setting of hypothyroidism. As such, there is an absence of the usual reflex slowing of heart rate and loss of the compensatory increase in diastolic arterial pressure following a Valsalva maneuver, implying a hypothyroidism-induced baroreceptor defect.[1,16] This condition may explain in part the tendency of hypothyroid patients to become hypotensive when exposed to anesthetic agents.

Many of the hemodynamic changes due to hypothyroidism suggest a decrease in adrenergic tone but this is not caused by decreased levels of catecholamines. A complex interaction between thyroid hormones and catecholamines seems to exist. Catecholamine levels are paradoxically increased during hypothyroidism. To this effect, various hypotheses have been put forward including a decrease in □-adrenergic receptor number, an increase in the adenylate cyclase inhibitory G-protein, adenylyl, or change in other cellular signaling pathways that can diminish □-adrenergic sensitivity.[17,18]

A variety of electrocardiographic abnormalities have been reported in hypothyroid patients, particularly in the perioperative period. Hypothyroidism is classically associated with bradycardia but its degree is often modest in most patients.[19,20] Other more severe abnormalities have also been documented with some frequency, including syndrome of torsade de pointes with a long QT interval and ventricular tachycardia.[21,22] Electrocardiograms may demonstrate low voltage and other nonspecific ST changes.[19,23] Patients with

longstanding hypothyroidism typically have elevated cholesterol levels and abnormal coagulation parameters that may predispose them to cardiovascular events such as myocardial infarction or cerebrovascular accidents in the perioperative period. Several studies have looked at cholesterol levels of hypothyroid patients as compared with euthyroid controls and document a worsening lipid profile with worsening thyroid function.[24,25] A correlation between even mild or subclinical hypothyroidism and increased risk for coronary events was documented in the Rotterdam study.[26]

Effects on Respiratory System

In hypothyroid patients several abnormalities in the respiratory functions have been described,[27] such as low maximal breathing capacity and a diminished diffusing capacity for carbon monoxide. In severe hypothyroidism, hypoxic ventilatory drive can be greatly depressed, showing almost no increase in minute ventilation even at low alveolar oxygen tension. Hypercapneic ventilatory drive is also often severely impaired. Respiratory muscle weakness is one of the many factors implicated in the etiology of impaired respiratory function induced by altered gene expression of key gene products in the muscle cells[28] and dysfunction of the phrenic nerve that innervates them.[29] However, most of the available evidence for these abnormalities in humans comes from studies conducted in small numbers of patients. The presence of hypothyroidism with muscular dysfunction together with increased size of the muscles has been called Hoffmann's syndrome[30]. Hypothyroidism is associated with sleep apnea and all its complications, which can adversely influence surgical outcome[27] or make postoperative extubation problematic. Direct obstruction to the upper airway may occur due to increased tongue size and obesity seen in hypothyroidism. However, improvement in symptoms with levothyroxine replacement is possible even in the absence of weight loss. Reduced ventilatory drive related to muscle weakness and obesity may result in atelectasis, reduced lung volumes and reduced exercise capacity. Although a rare occurrence of central sleep apnea is reported in a hypothyroid patient,[31] providing another mechanism for hypothyroidism induced sleep apnea but little is known about the mechanisms underlying the interaction of thyroid hormones with the respiratory centers of the brain.

Thyroid hormone accelerates surfactant production and its synthesis is decreased in hypothyroidism. In animal models, improvement of surfactant synthesis and improved clinical outcomes has been documented with T_3 therapy.[32] This is relevant in the perioperative period when severe stress, such as sepsis causes decreased surfactant synthesis and worsening of the respiratory function. The effect of thyroid hormones on surfactant synthesis in humans has been studied in neonates at risk for respiratory distress syndrome but molecular mechanisms by which thyroid hormone influences surfactant synthesis or function is not yet elucidated. Hypothyroid patients have slowed drug metabolism and the addition of pharmaceutical agents that suppress respiratory function (like sedatives or commonly used anesthetics) can precipitate respiratory failure. There are some reports in the literature indicating that hypothyroid patients tend to be more susceptible to anesthetic agents.[33] The use of tranquilizers, narcotics, and hypnotics should be avoided or reduced to a minimum. There is some experimental data from animal studies indicating that thiobarbiturates may have antithyroid properties, a factor that needs to be taken into account if these agents are used in these patients.

Effects on Renal Function, Electrolyte Metabolism & Plasma Volume

Hypothyroidism has multiple negative effects on renal functions like increased systemic vascular resistance, decreased renal perfusion, increased antidiuretic hormone (ADH), decreased atrial natriuretic factor (ANF), and decreased activity of the rennin-angiotensin-aldosterone system. A number of studies has documented these effects after follow up and therapy with thyroid hormone in hypothyroid patients.[34,35] Other renal alterations observed in hypothyroidism are; inability to produce maximally concentrated or diluted urine, reduced corticopapillary tissue concentration gradients for urea, impaired urinary acidification and decreased glomerular filtration rate.[36-38] The abnormalities in glomerular hemodynamics at the single nephron level are characterized by hypoperfusion and decreased permeability of the glomerular capillaries, resulting in a reduction of whole glomerular filtration rate.[39] These hemodynamic changes suggest the presence of vasoconstrictor compounds influencing renal function; among them participation of angiotensin II has been suggested.[40] Recent findings suggest that association of hypothyroidism with changes in ATP metabolism play a greater role in the pathophysiological mechanisms involved in the abnormalities of renal function in hypothyroidism.[41] Worsening renal function is not a rare event in the early postoperative period, often associated with intra-operative hypotension, and this is likely to be a more common phenomenon in the presence of hypothyroidism.[42] There have been some reports in the literature of hypothyroidism presenting as chronic renal failure, resolving completely with restoration of euthyroidism.[43] The hyponatremia

that is commonly associated with hypothyroidism must be considered in surgical patients who develop worsening renal function in the perioperative period, and its correction is easy and safe. The basis for the decreased plasma volume in hypothyroid patients is multifactorial. The capillary permeability increases and induces a shift of water and albumin into the interstitial space. Another factor is the deposition of glycosaminoglycans in the interstitial tissues which induces nonpitting edema in severe and prolonged hypothyroidism. These large molecules may have an osmotic effect inducing further shifts of fluids from the intravascular to the extravascular space, resulting in decreased effective plasma volume. Elimination of various drugs through the kidneys can be severely diminished by hypothyroidism. A classic example would be the elimination of digoxin, which is impaired in patients with hypothyroidism. This could induce severe or even life-threatening cardiac arrhythmias. This is also true for many of the anesthetic agents used for surgery[1].

Effects on Hemopoietic and Coagulation Systems

Hypothyroidism is frequently associated with anemia but few changes in other blood cellular elements occur. Erythropoiesis is reduced owing to low metabolic rate, decreased oxygen consumption and drop in erythropoietin levels during hypothyroidism. Anemia is reported in about 25% to 50% of hypothyroid patients,[44] and more often encountered in children.[45] Such anemia is usually normochromic and normocytic and these patients have normal iron stores, with a hypocellular bone marrow and normal red cell differentiation.[46] Iron deficiency may be responsible for this anemia in some but not all cases. Hypothyroid patients may be at greater risk for iron deficiency because of reduced iron absorption or increased blood loss. Hypothyroidism is often associated with menorrhagia, that provide another potential for reduced iron stores in women. As hypothyroidism is often an autoimmune disease, it is occasionally associated with pernicious anemia, another autoimmune illness.[47] The most common red cell morphological abnormality is macrocytosis that is associated with vitamin B12 or folic acid deficiency besides anemia. No significant effect has been documented on any of the white blood cell populations. There are reports in the literature of patients with a bleeding diathesis associated with hypothyroidism. It is mostly a mild form although severe cases have been described.[48] Hypothyroidism also effects coagulation cascade most often unmasked during a surgical or dental procedure. A decrease in plasma factor VIII concentration along with prolonged partial thromboplastin time is reported in hypothyroid patients.[49] Acquired von Willebrand's disease is also seen in association with hypothyroidism.[50] Possible etiologies include a decrease in plasma factor VIII coagulant activity and von Willebrand antigen activity. Levothyroxine is required to adequately treat these abnormalities. On the other hand, patients with hypothyroidism have been noted to have a prolonged half life of several other coagulation factors, such as factor II, VII, and X.[51] Hypothyroidism has little impact on platelet counts but a mild defect in platelet function may occur.[52] This may be related to increased immunoglobulin deposited on the platelet membrane. Hemorrhagic tendency in some patients has been attributed to a qualitative defect in platelet function that might be corrected by levothyroxine supplementation.

Diagnosis of Hypothyroidism

The symptoms of hypothyroidism are varied and depend on the severity and duration of thyroid hormone deficit. Accordingly, assessment of these patients should include an evaluation of their thyroid status. The sensitive TSH study is the most valuable laboratory study in the diagnosis of hypothyroidism. To help uncover the possibility of an underlying hypothyroid state, a detailed history should be obtained from the patient or the family about prior thyroid diseases, thyroid surgery, radiation therapies (radioactive iodine or neck irradiation), treatment with any thyroid medicines, or family history of thyroid disease. A detailed physical examination is of equal importance. Classic signs of hypothyroidism, such as the dry skin, a slowed deep tendon reflex relaxation phase, bradycardia, hypothermia or the presence of a goiter must be sought.

Although the prevalence of unsuspected overt hypothyroidism is low, community screening for hypothyroidism in healthy adults has revealed evidence of significant thyroid disease. In the Whickham survey, 8% of women and 3% of men were found to have subclinical disease.[53] In the Colorado screening survey, where 9% of the population had an elevated thyrotropin (TSH), 74% had TSH values between 5.1 and 10 mU/L.[6] Although no such survey has so far been conducted in Pakistan but a few small studies reported overt hypothyroidism in 4.0%, and subclinical hypothyroidism in 7.2% of patients referred for thyroid testing.[54-56] Pakistan is an iodine deficient country and typical Pakistani diet contains low iodine content (40 μg/day) which is 3.8 times lower than recommended (150 μg/day) for adult subject.[57] In regions with iodine deficiency a relatively low prevalence of hypothyroidism

is expected. It is because iodine deficiency has been reported to facilitate the development of toxic nodular goitre, whereas a high iodine intake may increase the prevalence of autoimmune hypothyroidism.[58,59] In iodine sufficient areas like Japan thyroid autoimmunity is the main cause of hypothyroidism.[60] Currently, Government of Pakistan is patronizing the ongoing iodine supplementation program that has relevance to enhance in incidence of hypothyroidism in future after achieving iodine sufficiency at population level.

CONCLUSION

Hypothyroidism produces profound changes in normal physiology of virtually every organ system. It diminishes oxygen consumption and promotes low metabolism leading to disturbances in hemodynamic, cardiac, respiration and renal functions. Depression of myocardial function, decreased hypoxic and hypercapnic ventilatory responses, abnormal baroreceptor function, and reductions in plasma volume, may all be present. In addition, the presence of anemia, hypoglycemia, hyponatremia, decreased free water excretion, and impaired hepatic drug metabolism may all adversely influence responses to anesthesia. Preoperative recognition of hypothyroidism is essential for the safe anesthetic management of these patients.

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