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7

Sex steroids and the thyroid

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Thyroid function is modulated by genetic and environmental causes as well as other illnesses and medications such as gonadal or sex steroids. The latter class of drugs (sex steroids) modulates thyroid function. Gonadal steroids exert their influence on thyroid function primarily by altering the clearance of thyroxine-binding globulin (TBG). While oestrogen administration causes an increase in serum TBG concentration, androgen therapy results in a decrease in this binding protein. These effects of gonadal steroids on TBG clearance and concentration are modulated by the chemical structure of the steroid being used, its dose and the route of administration. Despite the gonadal steroids-induced changes in serum TBG concentrations, subjects with normal thyroid glands maintain clinical and biochemical euthyroidism without changes in their serum free thyroxine (T4) or thyroid-stimulating hormone (TSH) levels. In contrast, the administration of gonadal steroids to patients with thyroid diseases causes significant biochemical and clinical alterations requiring changes in the doses of thyroid medications. Similarly, gonadal steroid therapy might unmask thyroid illness in previously undiagnosed subjects. It would be prudent to assess thyroid function in subjects with thyroid disease 6–8 weeks after gonadal steroid administration or withdrawal.

Introduction

Thyroid disease (clinical and subclinical) is estimated to affect 10% of the population. It is predominately a female disease and its incidence increases with age, so that as many as 20% of

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menopausal females may have hypothyroidism. The function of the thyroid is modulated by many factors including other illnesses and medications. Gonadal or sex steroids are an example of such modulation seen in subjects with normal thyroid function and, more importantly, in others who exhibit abnormalities in thyroid function. The term 'sex steroids' in this article encompasses a wide group of either endogenous or synthetic steroids that influence sexual function and differentiation and are used or abused clinically for various clinical purposes.[1]

This article reviews the known and potential effects of exposure to endogenous or exogenous sex steroids in humans. It discusses the impact of using such medications in subjects with presumed normal thyroid function and then addresses the known and potential effects in others with background thyroid disease.

Brief overview of normal thyroid physiology

In understanding the effects of sex steroids on thyroid function, one needs to have a clear understanding of thyroid hormone synthesis, metabolism, plasma transport and regulation by the hypothalamic–pituitary–thyroidal axis. The thyroid gland secretes thyroid hormone primarily as tetraiodothyronine (thyroxine or T4) and a lesser extent as triiodothyronine (T3). Over 80% of the T3 measured in the circulation is produced in the peripheral tissue by deiodination of T4.

Thyroxine-binding globulin

Thyroxine-binding globulin (TBG) is the main transport protein for thyroid hormones in the circulation. Approximately 75% of circulating T4 is bound to TBG and the rest is bound to transthyretin and/or albumin and a very small fraction (less than 0.01%) circulates unbound or free. Current thinking indicates that the free or unbound fraction of the hormone is responsible for its physiological function in all tissues. The affinity of TBG for binding T4 is 20-fold higher than its affinity for binding T3. There is one iodothyronine binding site per each molecule of TBG. The half-life of TBG is about 5 days and is cleared at a rate of 800 ml day^{-1}. TBG is a glycoprotein produced by the liver and carbohydrate makes up to 20% of its molecular weight.[2] TBG molecules can vary in the amount of sialic acid residues they carry. The clearance of TBG is affected by the degree of glycosylation such that when the number of sialic acid residues on TBG increases, its uptake and clearance by the liver will proportionately decrease.[2] Thus, as discussed in subsequent sections of this article, it is reasonable to predict a rise in serum TBG and, consequently, thyroxine levels during conditions associated with increased sialic acid content of TBG such as the case during oral oestrogen therapy.

Effect of medications on TBG

It becomes evident from the preceding discussion that alterations in TBG secretion and/or clearance will influence thyroid hormone metabolism. Many medications[3] and substances are known to effect TBG concentrations and/or its affinity to thyroxine. The most extensively studied drugs are oestrogens and androgens, which will be discussed later in detail. Other substances that are known to increase TBG concentrations are methadone and heroine. The long-term use of the latter drugs has been observed to increase TBG concentrations by 50%. It is also thought that mitotane and fluorouracil may increase TBG concentrations as an increase in total T4 (but not free T4) was observed with their administration. However, the clinical impact of these drugs on thyroid function is marginal. Glucocorticoids and niacin may cause a decrease in serum TBG concentrations. The latter influence of glucocorticoids is in addition to their ability to suppress thyrotropin secretion by the pituitary. High doses of intravenous furosemide have been shown to slightly and transiently increase free thyroxine levels and decrease total T4 levels by displacing thyroxine from its binding site on TBG.[3] However, the clinical impact of TBG alterations caused by niacin, glucocorticoids or furosamide is minimal.

TBG and gonadal steroids

Changes in TBG concentrations and peripheral deiodination of thyroxine play a central role in explaining the many effects of sex steroids on thyroid hormone physiology. Although the effects of