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Stepwise interpretation of low density lipoprotein hypercholesterolemia and total lipid profile in clinical and subclinical hypothyroidism

Research article

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Abstract

The association between hypothyroidism and atherosclerosis is a most important clinical theme and as such hypothetized by the lipid alterations concurrent with the condition .This issue is being more relevant in the recent papers on the issue of coincidence or etiology. The methodology of this review is all based on major publications of the subject in distinguished journals. The results show that hypothyroidism occur from four to eleven percent in hyperlipidemic patients. The main mechanism of cholesterol elevation is the reduction of LDL-c clearance by interference of TH in the expression of LDL-c liver receptors. There is no higher production, but poor removal. The thyroid condition is treatable, be it primary, clinical or subclinical. Sites of action of thyroid hormones are described and linked to the lipid abnormalities their failure of function may lead to .Lipid profile alterations are described mechanistically to explain the elevation of apoB containing lipoproteins that constitute an increase in risk for cardiovascular events. Lipoprotein (a) is also mainly considered in the literature as higher in this condition. In the case of hyperlipidemia even after normalization of the thyroid a treatment for the lipids abnormality should be considered and put into practice. Statins are the first line hypolipidemic agents to be considered. In the case of introduction of combination therapy it is important to remember that the use of fibrates should be avoided due to a possible potentiation of myopathy induced by it. The use of Cholestyramine, in association with thyroid hormone, makes it difficult to absorb the latter.

Keywords

Cholesterol, Thyroid, Hypothyroidism, Heart risk, Atherosclerosis, Triglycerides, Dense LDL, Lipoproteins

Abbreviations

Apo-B - Apolipoprotein B

CAD - Coronary Artery Disease

GH - Growth Hormone

HDL-c - High Density Lipoprotein Cholesterol

IGF-1 -Insulin-Like Growth Factor Type 1

LDL - Low density lipoproteinas

LDL-c - Low Density Lipoprotein Cholesterol

LHTg - Hepatic Triglycerides Lipase

LP(a) – Lipoprotein(a)

LPL - Lipoprotein Lipase

TH - Thyroid Hormone

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TRH - Thyroid Releasing Hormone

TSH - Thyroid-Stimulating Hormone

VLDL-c – Very Low Density Lipoprotein Cholesterol

Introduction

Both dyslipidemias and thyroid diseases are common in the general population and, due to this fact, we could start by questioning: there is actually a change in lipid profile in thyroid diseases that would be contributory to the development of atherosclerosis or it is simply a mere overlap (Table 1).

Already in 1930, Mason et al. published a paper showing a correlation between cholesterol levels and states of hypo, euthyroidism and hyperthyroidism [1]. After this period, with the improvement of new techniques and the introduction of thyroid stimulating hormone (TSH) dosage by ultrasensitive method, several research studies have been carried out, enabling a better elucidation of the mechanism responsible for changes in lipid profile in hypo and hyperthyroidism.

Importance of the subject

It is well established that hypothyroidism, even in cases considered subclinical, is associated with a number of lipid metabolism changes that may predispose to the development of CAD [2,3] (Table 2).

We know that various aspects of intravascular lipid transport and lipoprotein metabolism suffer the influence of thyroid hormones [4].

According to O'Brien, hypothyroidism is associated with an increased risk of coronary disease, probably due to the impact of lipid changes he induced.

These changes are reversible with the introduction of thyroid hormones, as we will later see in the treatment approach.

Diekman et al [5] and Bruckert et al [6] found, respectively, 4.2% and 11% hypothyroidism in patients sent for dyslipidemia treatment. On the other hand, dyslipidemia was observed in 53% of patients with primary hypothyroidism[7].

Table 1: Dyslipidemia in hypothyroidism.

Coronary Artery Disease Association (CAD)
1. Mere coincidence
2. Increased risk factors

Table 2: Importance of the subject

Dyslipidemia - Hypothyroidism
a. Hypothyroidism is associated with factors for the development of CAD
b. Hypothyroidism dyslipidemia may be CURABLE
c. Hypothyroidism may be present in approximately 4.2% to 11% of patients with dyslipidemias

Table 3: Peripheral effects of thyroid hormones

1. Oxygen consumption and thermoregulation
2. Effects on bone growth and metabolism
3. Action on water metabolism and electrolytes
4. Action on lipid metabolism
5. Action on protein metabolism
6. Action on the metabolism of carbohydrates
7. Effects on the nervous system
8. Effects on the cardiovascular system

The suggestion given by these studies is that these patients, in the vast majority of cases, should have their thyroid function evaluated by determining free T_4 (Thyroid Hormone) and TSH tests by ultrasensitive method. With the use of this last test it would be possible to diagnose the presence of subclinical hypothyroidism, in which clinical manifestations are not evident, but may already be associated with high levels of low density lipoprotein (LDL-c).

Defining exactly what is considered subclinical hypothyroidism is a difficult task, since most researchers vary criteria for the diagnosis of this condition [8]. Speaking of Primary, Secondary and Subclinical hypothyroidism, it is important to comment briefly on the regulation of thyroid function and peripheral action of these hormones.

Thyroid gland function is effectively regulated by a feed-back mechanism involving hypothalamus (HRT), pituitary (TSH) and thyroid (T_4-T_3). HRT stimulates pituitary secretion of TSH, which stimulates the synthesis and secretion of thyroid hormones (TH). TH, in turn, at the level of the pituitary, inhibit the secretion of the TSH.

Periferly, TH exert multiple effects and it is possible to induce the expression of various genes (Table 3).

Let us limit ourselves to commenting on the specific points of lipoprotein biochemistry and physiology that are directly related to TH action, especially with regard to control, by these hormones, about the key enzymes of metabolism of lipoproteins. Intravascular lipoprotein metabolism involves exchange reactions between the

Table 4: Thyroid hormone action sites in lipid metabolism

In the adipitocytes: synthesis and activity of Lipoprotein Lipase (LPL)
In the oxytote: synthesis of Liver Lipase (LHTg), HDL-c and receptors for low density lipoproteins (LDL)
In peripheral somatic cells: increases the activity of LPL, synthesis and expression of LDL receptors

various classes of lipoproteins and the action of the three specific enzymes. All three enzymes suffer the influence of TH, which makes it important to know this control for a better clinical evaluation and treatment of dyslipidemias (Table 4).

TH perform an important action in the synthesis and activity of LPL, LHTg and Lecithin-cholesterol-acyl-transferase (LCAT). Transcellular transport synthesis and activity, particularly of LPL, is closely related to the plasma level of thyroid hormones [4,5].

Clinical-laboratory picture

We will not go into detail about the clinical picture of hypothyroidism. The difficulty is found in what is postulated subclinical hypothyroidism. There is still no consensus. For most authors [9], the picture would be defined by the presence of T_4 and T_3 levels within a "low normal" and moderately high TSH levels. The presence of antithyroid antibodies TPOab and TGab is of great value for diagnostic confirmation.

In some cases, it has been suggested to perform a stimulus test with TRH, where the encounter of a high response of TSH > 20 would be confirmatory.

Generally speaking, we will find an increase in cholesterol levels, but the degree of major dysfunction is related to the elevation of LDL-c and this elevation, in turn, is directly correlated with the degree of thyroid dysfunction i.e. free T_4 levels and TSH.

The most common type of dyslipidemia is type IIa and in these cases we can practically state that it is a primary hypothyroidism. In secondary hypothyroidism type IIb is more common. More recently, it has been demonstrated that, even though LDL-c is the most present alteration, with the introduction of new techniques, it has been found that the elevation of LDL-c is associated with an increase in apolipoprotein B (apo-B) and that TH can qualitatively alter the structure of the apo-B synthesized in the liver.

Regarding VLDL-c (lipoprotein of very low density), there is a small increase in its levels that consequently leads to a moderate increase in triglycerides, and this increase is more observed in obese hypothyroids. Changes in HDL-c levels are small and a slight elevation can be observed, which is determined mainly at the expense of the HDL_2 fraction. Other studies, however, have shown that in severe hypothyroidism, the HDL-c fraction may be slightly decreased or normal[3]. In secondary hypothyroidism HDL-c levels are lower when compared to primary hypothyroidism.

In the presence of hyperthyroidism we will find low LDL-c levels, even in elderly patients, when compared to normal control group [10].

Also in relation to lipid profile in hypothyroidism, it is important to comment on the researches performed relating lipoprotein levels(a) - Lp(a) with thyroid dysfunctions (Table 5).

What would be the main mechanism in the development of lipid profile changes in hypothyroidism (Table 6).

The main mechanism of cholesterol elevation is the reduction of LDL-c clearance by interference of TH in the expression of LDL-c liver receptors. There is no higher production, but poor removal.

We know that the concentration of lipids in plasma is determined by the balance between the entrance rate, that is, new synthesis and the rhythm of intravascular catabolism and cellular uptake. The clearance of lipoproteins from the same compartment is carried out through a receptor-mediated transport. Although the synthesis of these receptors is primarily governed by the content of intracellular cholesterol, TH is important for the synthesis and action of these receptors. There is a reduction in the synthesis and expression of LDL-c receptors with consequent decrease in LDL-VLDL-c clearance and elevation of their plasma levels.

Low TH levels lead to a decrease in the LPL and LHTg

Table 5: Lipid profile in hypothyroidism

Cholesterol	High
LDL-c	Very high
VLDL-c	Discreet elevation
HDL-c	Moderately high or normal
Triglycerides	Discreet elevation
apo-B	High
Lp(a)	High

Table 6: Hypercholesterolemia mechanisms in hypothyroidism

The major change is in the "clearance"
Reduction of expression of LDL-c receptors (LDL-c removal - VLDL-c)
Decrease in the activity of LPL and LHTg lipases (LDL-c/VLDL-c metabolism)
Cholesterol excretion reduction - via HDL-c system - in the liver
Indirect effect - growth hormone (GH) and growth factor "insulin like growth factor" (IGF-1).

activity, which leads, in addition to hypercholesterolemia, an increase in plasma triglyceride levels. There is also a decrease in lipolysis, with a lower mobilization of fatty acids from adipose tissue to the liver.

Regarding the activity of Lecithin-Cholesterol-Acyl-Transferase, which is of great importance in esterification of endogenous cholesterol, its activity is decreased in hypothyroidism. The removal of cholesterol via HDL system is therefore compromised. TH does not affect the rate of cholesterol conversion into bile acids and cholesterol absorption is normal.

How to explain variations in lipid profile in hypothyroidism. It is important, once again, to remember that cholesterol levels can be affected by diet - hormonal and genetic factors [11].

When we talk about hormonal factors, we want to refer in particular to the indirect effects of GH and IGF-1. It has been suggested that TH effects on LDL-c levels may indirectly suffer interference from GH and IGF levels [12]. This would explain the difference in clinical presentation between primary and secondary hypothyroidism.

Genetics interferes with the presentation of dyslipidemia. There are several loci, which are specific in the development of hyperlipoproteinemias. In the case of hypothyroidism, this manifestation may be associated with an alela variation of the LDL receptor.

Influence of thyroid hormones on Lp(a) levels

The greater interest in the determination of Lp(a) levels in thyroid diseases probably arose in the search for a factor of greater link between hypothyroidism dyslipidemias and the development of CAD. There is already compelling evidence linking high Lp(a) levels to the development of CAD. But the relationship between plasma levels of Lp and the states of: euthyroidism and hypothyroidism is not yet fully elucidated. The conclusion of several studies are divergent [13,14].

More recent studies point to the elevation of Lp(a) in hypothyroidism [15,16]. Due to the relevance of the problem, since Lp(a) has an atherogenic and procoagulant combination, associated with resistance to dietary and/or pharmacological treatments, there is a great need for further research in this field.

Regarding the association hypothyroidism and atherosclerosis, the findings of several studies show [17-20].

- Absence of conclusive relationship between myocardial infarction and hypothyroidism.
- Greater severity of coronary stenosis in patients with hypothyroidism.
- Strong association between myocardial infarction and hypothyroidism in elderly women.

Despite excellent documentation of the effects of TH on lipid metabolism, it is not yet possible to affirm that hypothyroidism is in itself a risk factor for atherosclerosis.

The interesting thing, in this respect, is that in the older works this association is placed in a well documented and categorical way. It is possible that the introduction of new diagnostic techniques, allowing the diagnosis of hypothyroidism, even in its subclinical presentation, has not allowed the development of severe hypothyroidism and consequently the lack of association direct with atherosclerosis. A greater association, however, has been reported in elderly women, where hypothyroidism is also more frequent.

Myocardial function is affected in hypothyroidism due to a lower supply of oxygen to the myocardium, a cause of possible ischemia. Thyroid dysfunction may have other risk factors for the development of CAD, in association with lipid changes.

Treatment

- Replacement thyroid hormone (L-Thyroxine).
- Repeat the lipid and hormonal profile evaluation after 4 to 5 weeks.
- Rule out the possibility of secondary hypothyroidism with GH deficiency.

Once the diagnosis of hypothyroidism is confirmed, we should start treatment with increasing doses of thyroid

hormone, preferably L-Thyroxine. Depending on age, start at 25 mcg and increase every two weeks, up to the sufficient dose for normalization of TSH and Free T_4 levels (usually between 100 and 200 mcg).

During this period, it is important to monitor the effects on heart rate, especially in the elderly, and not leave TSH levels below normal value (suppression).

If, after proper replacement with thyroid hormone, cholesterol and LDL-c levels still remain high, we should consider the use of hypolipidemics, especially statins.

In the case of introduction of combination therapy it is important to remember that the use of fibrates should be avoided due to a possible potentiation of myopathy induced by it. The use of Cholestyramine, in association with thyroid hormone, makes it difficult to absorb the latter.

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