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Original article

Effects of levothyroxine treatment on insulin sensitivity, endothelial function and risk factors of atherosclerosis in hypothyroid women

Effets de la lévothyroxine sur la sensibilité à l'insuline, la fonction endothéliale et les facteurs de risque d'athérosclérose chez les femmes atteintes d'hypothyroïdie

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Abstract

Objectives. – Contradictory results are encountered in literature regarding the effects of hypothyroidism on the risk factors of atherosclerosis. We aimed to explore the changes in atherosclerotic risk factors and insulin sensitivity before and after levothyroxine replacement therapy in women with primary hypothyroidism and compare with that of healthy controls. *Patients and methods.* – Twelve patients (mean age of 34 ± 11.7 years) without an evident disease except for primary hypothyroidism (TSH ≥ 20 mIU/L) and eleven euthyroid, age-matched (33.8 ± 8.4 years) female volunteers as controls were included. Baseline thyroid hormones, lipid parameters, homocysteine, fibrinogen levels were measured in both groups. Flow-mediated endothelial-dependent vasodilatation (FMD) method was used to evaluate endothelial dysfunction. Insulin sensitivity was assessed by M values based on euglycemic hyperinsulinemic clamp technique. The same measurements were performed after 6 months of levothyroxine treatment and recovery of euthyroid state in hypothyroid patients. *Results.* – Treatment reduced total cholesterol ($P < 0.005$), LDL-cholesterol ($P < 0.005$), lipoprotein(a) ($P < 0.01$), fibrinogen ($P < 0.0001$) and homocysteine ($P < 0.0005$) levels. Treatment significantly improved M values of hypothyroid patients (3.68 ± 1.53 mg/kg.min vs 6.02 ± 1.21 mg/kg.min, $P < 0.0001$) and FMD (9.1 ± 3.7% vs 16.4 ± 4.4%, hypothyroid vs euthyroid, $P < 0.0001$). Significant correlations were found between M values and TSH ($r = -0.6$, $P < 0.005$), fibrinogen ($r = -0.53$, $P < 0.01$) measurements, free T3 ($r = 0.51$, $P < 0.02$) and free T4 ($r = 0.49$, $P < 0.02$) levels. FMD was significantly correlated with fibrinogen levels ($r = -0.49$, $P < 0.05$). *Conclusion.* – Insulin resistance, endothelial dysfunction, atherosclerotic risk markers improves with treatment of hypothyroidism.

Keywords: Hypothyroidism; Atherosclerosis; Insulin resistance; Endothelial function

Résumé

Objectifs. – La littérature rapporte des résultats contradictoires quant aux effets de l'hypothyroïdie sur les facteurs de risque d'athérosclérose. Nous avons voulu examiner les modifications de ces facteurs de risque d'athérosclérose comme de la sensibilité à l'insuline avant et après thérapie de remplacement par lévothyroxine chez les femmes souffrant d'hypothyroïdie primaire comparées avec des sujets sains. *Patientes et méthodes.* – Douze patientes (âge moyen de 34 ± 11,7) sans maladie déclarée si ce n'est une hypothyroïdie primaire (TSH ≥ 20 mUI/L) et onze témoins volontaires euthyroïdiennes, appariés pour l'âge (33,8 ± 8,4 années), ont été incluses. Les hormones thyroïdiennes de base, les paramètres lipidiques, l'homocystéine, les niveaux de fibrinogène ont été mesurés dans les deux groupes. La méthode de vasodilatation dépendante de l'endothélium, médiée par le flux, a été utilisée pour évaluer la dysfonction endothéliale. La sensibilité à l'insuline était évaluée par le calcul de médianes (M) sur la base de la technique de serrage hyperinsulinémique euglycémique. Les mêmes mesures ont été effectuées après 6 mois de traitement par lévothyroxine et récupération d'un état euthyroïdique. *Résultats.* – Le traitement a réduit les taux de cholestérol total ($p < 0{,}005$), LDL-cholestérol ($p < 0{,}005$), lipoprotéine(a) ($p < 0{,}01$), fibrinogène ($p < 0{,}0001$) et homocystéine ($p < 0{,}0005$). Le traitement a amélioré de manière significative les

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valeurs M des patientes hypothyroïdiennes (3,68 ± 1,53 mg/kg.min vs 6,02 ± 1,21 mg/kg.min, $p < 0{,}0001$) ainsi que la vasodilatation endothélium-dépendante (9,1 ± 3,7 % vs 16,4 ± 4,4 %, hypothyroïdie vs euthyroid, $p < 0{,}0001$). Des corrélations significatives ont été trouvées entre les valeurs M et les mesures de TSH ($r = -0{,}6$, $p < 0{,}005$), de fibrinogène ($r = -0{,}53$, $p < 0{,}01$), ainsi que les niveaux de T3 libre ($r = 0{,}51$, $p < 0{,}02$) et de T4 libre ($r = 0{,}49$, $p < 0{,}02$). La vasodilatation endothelium-dépendante était significativement corrélée avec les taux de fibrinogène ($r = -0{,}49$, $p < 0{,}05$). *Conclusion.* – L'insulinorésistance, la dysfonction endothéliale, les marqueurs de risque d'athérosclérose augmentent avec le traitement de l'hypothyroïdie.

Mots clés : Hypothyroïdie ; Athérosclérose ; Insulinorésistance ; Fonction endothéliale

1. Introduction

Hypothyroidism is a condition caused by insufficient release of thyroid hormones from thyroid glands and affects a considerable part of the population, with a worldwide prevalence estimated to be 0.2–2%. Overt hypothyroidism in adult women and despite some controversial results, subclinical hypothyroidism in elderly women has been associated with increased atherosclerotic risk [1–4].

A substantial amount of evidence confirms that hypothyroidism might present with a variety of metabolic changes including hypertension, hypercholesterolemia, decreased lipolysis, increased LDL oxidation and no change or reduction in glucose synthesis [3–6]. The changes in these metabolic parameters which are also defined as traditional risk factors for atherosclerosis designate the prognosis of hypothyroidism and set the bases for premature atherosclerosis or cardiovascular disease; both conditions being encountered with an increased prevalence in cases of hypothyroidism [7]. As well as the above mentioned parameters, increased levels of Lp(a) in hypothyroid patients compared to euthyroid patients has been reported and several studies have shown decrease in Lp(a) levels after appropriate T4 replacement therapy [8–10].

In recent years, novel risk factors for atherosclerosis have been identified [11] and studies that are focused on relating these factors to thyroid status have been published. Homocysteine is one of these novel risk factors and elevated levels were found in overt hypothyroidism [12,13]. However, contradictory results of homocysteine levels in subclinical hypothyroidism have been reported [14,15]. A very recent study performed in women with newly diagnosed and non-treated hypothyroidism showed a significant decrease in the level of total homocysteine following L-thyroxine treatment [16].

Endothelial dysfunction is one of the earliest signs of atherosclerosis development [17]. Lekakis et al. showed endothelial-dependent vasodilatation to be negatively correlated with TSH levels and a significant reduction in brachial artery diameter in hypothyroid subjects was observed compared to healthy controls [18]. In a more recent study, Fernandez-Real et al. have concluded endothelial vasodilatation to be intrinsically related with thyroid functions and suggested that the alterations in thyroid and endothelial function tests are not directly linked to thyroid status but denote the changes in more common cellular functions shared by these two systems [19].

The link between insulin sensitivity and atherosclerotic cardiovascular disease progression has been assessed by prospective studies. IRAS study, and more recently the study of Henley et al. have revealed the positive association between insulin sensitivity and atherosclerosis development [20,21]. Although the first reports claimed that hypothyroidism does not directly cause insulin resistance [22], Roos et al. demonstrated that low normal FT4 levels are significantly associated with insulin resistance and thus increased cardiovascular risk [23].

In the present study, we aimed to evaluate insulin sensitivity, endothelial function and atherosclerotic risk markers in newly diagnosed untreated female patients with primary hypothyroidism and explore the changes after levothyroxine replacement therapy and compare with that of healthy controls.

2. Materials and methods

2.1. Population and study design

The study was performed in Endocrinology Clinic of Marmara University Hospital. Twelve non-smoking women between 18–50 years of age and without an evident disease except for newly diagnosed primary hypothyroidism (TSH ≥ 20 mIU/L, T3 and T4 normal or low) whose BMI values lower than 27 kg/m^2 were included in the study. Eleven euthyroid, non-smoking, age-matched women volunteers without an evident disease and a family history of coronary artery disease or diabetes were included as the control group. The study was approved by the institutional ethics committee and all subjects gave written informed consent.

The patients who met the inclusion criteria and gave signed informed consent underwent a protocol that lasted for three days. In the first day, the medical histories of all patients were obtained and physical examinations were performed. Based on the patients' complaints and physical examination results, the scoring system that was developed by Zulewski et al. and that shows a significant correlation with thyroid hormone levels was applied [24]. Endothelial functions were also evaluated on the same day by flow-mediated endothelial-dependent vasodilatation method. On the second day, patients were asked to collect 24 hour urine samples for evaluation of renal functions and measurement of albumin excretion rate. On the final day, body