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Lipid profile and levels of homocysteine and total antioxidant capacity in plasma of rats with experimental thyroid disorders

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Abstract This study focuses on the relationship between serum levels of cholesterol and homocysteine with that of total antioxidant capacity in rats with thyroid dysfunction.

Adult male Wistar rats were divided into three groups, a control (euthyroid), hypothyroidism and hyperthyroidism, each of them containing ten rats. Hypothyroidism was induced by administration of 0.1% aminotriazole in drinking water for 3 weeks. Hyperthyroidism was induced by chronic subcutaneous injection of L-thyroxine (100 μg/day, dissolved in 200 μL saline solution/100 g body weight) for 3 weeks. The control and hypothyroid groups were injected subcutaneously with the same volume of saline solution.

Results showed that hyperthyroidism is characterized by reduced serum thyroid stimulating hormone (TSH) levels despite increased free thyroxine (FT_4) and free triiodothyronine (FT_3) levels.

Significant ($p < 0.05$) elevation in serum levels of total homocysteine (t-Hcy) is reflected by a decrease in serum total antioxidant capacity (TAC) production in hypothyroidism comparing to control.

There was a significant ($p < 0.05$) elevation in serum levels of lipid profile (cholesterol, triglyceride and LDL) in hypothyroidism. Significant ($p < 0.05$) reduction occurred in the levels of cholesterol and triglyceride in hyperthyroidism. The association of hyperhomocysteinemia and lipid abnormalities occurring in hypothyroidism may represent a dynamic atherogenic state.

Introduction

Thyroid disease, namely hypothyroidism and hyperthyroidism, constitutes the most common endocrine abnormality in recent years, diagnosed either in subclinical or clinical form. Thyroid disease is associated with various metabolic abnormalities, due to the effects of thyroid hormones on nearly all major metabolic pathways.

Thyroid hormones, thyroxine (T_4), and triiodothyronine (T_3) play an important role in all major metabolic pathways. They regulate the basal energy expenditure through their effect

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on protein, carbohydrate, and lipid metabolism. This might be a direct effect or an indirect effect by modification of other regulatory hormones such as insulin or catecholamines (Kim, 2008). Many studies reported that thyroid hormones stimulate cholesterol synthesis by inducing 3-hydroxy-3-methyl-glutaryl coenzyme A reductase in the liver (Cachefo et al., 2001; Beylot, 2001). In addition thyroid hormones influence all aspects of lipid metabolism including synthesis, mobilization, and degradation. Furthermore, thyroid hormones affect lipoprotein lipase activity and thus, the hydrolysis of triglycerides into very-low density lipoprotein (VLDL) and chylomicrons into fatty acids and glycerol (Cachefo et al., 2001). Finally, thyroid hormones modulate lipid metabolism by upregulation of the low density lipoprotein (LDL) receptors, which results in enhanced catabolism of the LDL particles.

In hypothyroidism, lipoprotein lipase activity in the adipose tissue has been found normal or decreased, in addition to decreased hepatic lipase activity resulting in normal or high levels of triglycerides (Abrams et al., 1981). In hyperthyroidism, although lipoprotein lipase activity is usually normal (Tan et al., 1998), an increased liver fatty acid synthesis and oxidation are observed due to enhanced acetyl-CoA carboxylase 1 and carnitine palmitoyltransferase Ia expression leading to increased VLDL biosynthesis (Liu and Brent, 2010). Moreover, hyperthyroidism is characterized by reduced serum TSH levels despite increased free thyroxine (FT4) and free triiodothyronine (FT3) levels.

Dyslipidemia is a common metabolic abnormality in patients with thyroid disease, either in the overt or subclinical forms of the disease, and constitutes the end result of the effect of thyroid hormones in all aspects of lipid metabolism leading to various quantitative and/or qualitative changes of triglycerides, phospholipids, cholesterol, and other lipoproteins. Dyslipidemia also occurs due to the coexisting metabolic abnormalities in thyroid disease including oxidative stress and insulin resistance, which induce further or aggravate the existing dyslipidemia, via a vice–vicious cycle (Santi et al., 2010; Tagami et al., 2010).

Moreover, homocysteine is a marker for low thyroid and low B vitamins (should be less than 9) so the higher total homocysteine concentrations seen in the elderly may be caused by many factors including malabsorption of B12 or a suboptimal intake of B-vitamins (especially vitamin B_{12}), reduced kidney function, medications that reduce the absorption of vitamins (as in the case of H2 receptor antagonists or proton-pump inhibitors reducing B12 absorption) (Ruscin et al., 2002) or increase in the catabolism of the vitamins (as in the case of metformin reducing blood levels of B12 and folic acid). Certain diseases are associated with higher homocysteine levels, as can such lifestyle factors as smoking (Targher et al., 2000), coffee consumption (Temple et al., 2000), and excessive alcohol intake (Sakuta and Suzuki, 2005). Lack of exercise, obesity (Yun et al., 2013) and stress are also associated with hyperhomocysteinemia.

Thus, the present study was carried out to investigate the changes in lipid profile associated with disturbances in serum levels of cholesterol and homocysteine with that of total antioxidant capacity in rats as a result of experimentally-induced hypo- and hyperthyroidism.

Material and methods

Thirty adult male Wistar rats (200–250 g) were used for the current study after being procured from the Animal House of El-Nile Company for Pharmaceutical Products, Cairo, Egypt. The animals were acclimatized for 2 weeks in the Animal House of Zoology Department, Women's College, Ain Shams University before induction of hypothyroidism or hyperthyroidism in them. Five rats were housed per wire floored cage in an air-conditioned room (22 ± 2 °C) with 12 h light/dark cycle and had free access to standard laboratory chow diet (El Nasr Co., Cairo, Egypt) according to National Research Council (NRC, 1977) and water *ad libitum*. The protocol of this study was approved by the Department of Zoology Council, Women's College, Ain Shams University, Egypt, which has an ethical authority.

Animals were divided into three groups, control animal (euthyroid) group, hypothyroidism rat group and hyperthyroidism rat group, each of them containing ten rats. Hypothyroidism was induced by administration of 0.1% aminotriazole (Sigma Chem. Co., St. Louis, MO, USA) in drinking water for 3 weeks as previously described by Lopez et al. (2001). Whereas, hyperthyroidism was induced by chronic subcutaneous injection of L-thyroxine (100 μg/day, dissolved in 200 μL saline solution/100 g body weight) (Sigma Chem. Co., St. Louis, MO, USA) for 3 weeks according to Lopez et al. (2002). The control animal (euthyroid) group and hypothyroid animals were injected subcutaneously with the same volume of saline solution (0.9% NaCl). At the end of each treatment, animals were dissected under slight anesthesia by ether, blood samples were collected by heart puncture, centrifuged and the sera were separated and stored at −20 °C until assayed.

Estimation of serum thyroid stimulating hormone (TSH)

Thyroid stimulating hormone (TSH) was assayed by radioimmunoassay (RIA) kit using the solid phase component system (Phoenix Pharmaceuticals, Inc., USA) as described by Patrono and Peskar (1987).

Estimation of serum hormonal profile

Serum total triiodothyronine (T_3) and total thyroxine (T_4) levels were estimated by a radioimmunoassay method kit using solid phase component system according to Ekins (1978) and Chopra et al. (1972). The kits were purchased from Diagnostic Product corporation (DPC), USA. Serum free triiodothyronine (FT_3) and free thyroxine (FT_4) levels were estimated by a radioimmunoassay method kit using solid phase component system according to Ekins (1978) and Siegel et al. (1978). The kits were purchased from Phoenix Pharmaceuticals, Inc., USA.

Estimation of serum T_3-uptake

T_3-uptake was assayed using ELISA techniques. The kits were purchased from Immuno-Biological Laboratories, Inc. (IBL-America), Minneapolis, USA according to Witherspoon et al. (1981).