A POPULATION-BASED COHORT STUDY ON THE ASSOCIATION OF HYPERTHYROIDISM AND ANTI-THYROID DRUGS (ATDS) WITH THE RISK OF HYPERLIPIDEMIA AND THE EFFECTS OF ATDS ON HEPATIC GENE EXPRESSION

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Abstract - Thyroid dysfunction has a significant impact on several cardiovascular risk factors, such as blood lipid levels, which lead to hyperlipidemia. Hypothyroidism is relatively common and is associated with an unfavorable effect on lipids. Conversely, hyperthyroidism can be associated with a favorable lipid profile. There are three drugs available to treat hyperthyroidism, namely 6-n-propyl-2-thiouracil (PTU), methimazole (MMI), and carbimazole (CBM, a prodrug for MMI). Several reports have shown that although these drugs play a major role in maintaining the endocrine function of the thyroid hormones, they might be hepatotoxic. Until now, there have been no reports on the association of hyperthyroidism with hyperlipidemia in patients undergoing PTU and MMI/CBM treatment and the possible underlying mechanisms. Therefore, we conducted a large, nationwide cohort study using data from the Longitudinal Health Insurance Database (LHID) to assess the risk of hyperlipidemia associated with using ATDs among Taiwanese patients. We also evaluated the possible roles of PTU and MMI in the hepatic expression of several genes that may affect the blood lipid levels. The cohort study involved 13,667 patients with hyperthyroidism and the corresponding comparison cohort had four times as many patients. Kaplan-Meier analysis of hyperlipidemia incidence showed that it was significantly higher in the hyperthyroidism cohort than in the comparison cohort. Compared to patients without hyperthyroidism, 3,917 patients with hyperthyroidism developed hyperlipidemia with an incidence of 18.7, 11.8 cases per 10,000 persons-years, and adjusted hazard ratio of 1.5 (95% CI, 1.41, 1.59). With only PTU or MMI/CBM treatment, patients with hyperthyroidism developed higher risk of hyperlipidemia than those without hyperthyroidism: 1.78-fold (95% CI, 1.51-2.11) and 1.43-fold (95% CI, 1.27-1.60), respectively. Further, we found that although the expression of hepatic genes that code for the circulating remnant lipoproteins were decreased by PTU and MMI treatment, these drugs increased the hepatic lipogenic gene expression. Taken together, we conclude that treatment of hyperthyroid patients with PTU and MMI reduces their thyroid hormone status and the expression of genes involved in lipoproteins clearance; conversely, it increases the lipogenic gene expression, resulting in abnormal blood lipid profiles.