Thyroid Disease as a Risk Factor for Cerebrovascular Disease

Meng-Han Yang, PhD,* Fu-Yi Yang, MD,† and Ding-Dar Lee, MD, PhD‡§

Background: Thyroid disease is the medical condition impairing function of the thyroid. Among this disorder category, hyperthyroidism is that the thyroid gland produces excessive amounts of thyroid hormones whereas hypothyroidism is that the thyroid gland does not produce enough thyroid hormone. Various studies have supported the comorbid association between thyroid disease and cardiovascular disorder. However, there is insufficient evidence to prove the relationship between cerebrovascular disease (CVD) and thyroid disease. *Methods:* In this study, we tried to verify that thyroid disease increases the risk of CVD development employing a population-based database, National Health Insurance Research Database of Taiwan. A total of 16,808 hyperthyroidism cases and 5793 hypothyroidism patients with corresponding control subjects were studied, respectively. Hazard ratio (HR) by the Cox regression was used to quantify risk of CVD in different groups of subjects, that is, case patients versus matched controls. Further stratification studies for risk factors of CVD were performed to evaluate the comorbid association between CVD and hyperthyroidism/hypothyroidism. *Results:* Evaluation results have shown that hyperthyroidism increased 38% of the hazard of developing follow-up CVD (adjusted HR, 1.38) whereas hypothyroidism increased even higher the risk (adjusted HR, 1.89). Further stratification studies for risk factors of CVD suggested that the comorbid association between hypothyroidism and CVD was comparable to those influences from cardiac risk factors, such as diabetes mellitus, hyperlipidemia, hypertension, or renal failure and so forth. *Conclusions:* Thyroid disease may predispose to onset of CVD. Advanced analysis is required to investigate the pathologic mechanism underlying the association between CVD and thyroid disease. **Key Words:** Hyperthyroidism—hypothyroidism—cerebrovascular disease—hazard ratio—NHIRD.

Thyroid disease is the medical condition impairing function of the thyroid. Among this disorder category, hyperthyroidism is a condition in which the thyroid gland produces and secretes excessive amounts of the free thyroid hormones: triiodothyronine (T3) and/or thyroxine (T4). Symptoms of hyperthyroidism may be nervousness, irritability, heart racing, hand tremors, anxiety, muscular weakness, and so forth. Thyroid hormone is also critical to normal function of cells, therefore in excess, it both overstimulates metabolism and exacerbates the effect of sympathetic nervous system. Graves' disease is the most common cause of hyperthyroidism,

From the *Department of Computer Science and Information Engineering, National Kaohsiung University of Applied Sciences, Kaohsiung, Taiwan; †Department of Neurology, Taipei Tzu Chi General Hospital, New Taipei, Taiwan; ‡Department of Dermatology, Taipei-Veterans General Hospital, Taipei City, Taiwan; and §Faculty of Medicine, Department of Dermatology, National Yang-Ming University, Taipei City, Taiwan, ROC.

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Address correspondence to Fu-Yi Yang, MD, The Department of Neurology, Taipei Tzu Chi General Hospital, No. 289, Jianguo Rd., Xindian District, New Taipei 23142, Taiwan, ROC. E-mail: menghanyang@cc.kuas.edu.tw; fuyi127@yahoo.com.tw.

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and the generally accepted treatment of hyperthyroidism involves temporary use of suppressive thyrostatic medication (antithyroid drugs).[1,2]

Contrarily, hypothyroidism is a common endocrine disorder in which the thyroid gland does not produce enough thyroid hormone. Numerous symptoms are associated with hypothyroidism, including fatigue, poor memory and concentration, swelling of the limbs, heavy periods, abnormal sensation, and so forth. In children, hypothyroidism leads to delays in growth and intelligence development.[3] Hypothyroidism can be well treated with manufactured levothyroxine, which is the hormone replacement management.[4]

Thyroid function has a profound effect on the heart, and cardiovascular mortality rates are increased in hyperthyroidism.[5] A recent nationwide study has shown that subjects had a higher risk of developing cardiovascular diseases (hazard ratio [HR], 1.34) after the diagnosis of hyperthyroidism.[6] On the other hand, it has been observed that adults with hypothyroidism had a high prevalence of coronary heart disease,[7] and long-lasting untreated hypothyroidism in children may be associated with proatherogenic abnormalities.[8] Therefore, it has been suggested that diagnosis and treatment of cardiac disease may benefit from including analysis of thyroid hormone status.[9]

However, although thyroid autoantibodies may be associated with the presence of intracranial artery stenosis in young stroke patients,[10] thyroid hormone cannot be used to estimate the functional stroke outcome.[11] There is insufficient evidence to prove that hyperthyroidism predisposes to cerebral ischemia.[12] Similarly, there is no evidence to suggest an association between hypothyroidism and ischemic stroke among healthy postmenopausal women.[13] A population-based cohort study also cannot validate the comorbid relationship between hypothyroidism and mild cognitive impairment.[14] On the other hand, a study reviewed records of patients admitted to the University of Louisville Stroke Center with a diagnosis of acute ischemic stroke or transient ischemic attack and found that 12% of patients with acute ischemic stroke or transient ischemic attack had hypothyroidism.[15] Moreover, a cohort study has found a slightly increased risk of stroke (adjusted HR, 1.10; 95% confidence interval [CI], 1.01-1.20) in patients with autoimmune thyroiditis.[16]

Because the association between cerebrovascular disease (CVD) and thyroid disease remains unclear, in this study, we tried to verify that thyroid disease increases the risk of CVD development using a nationwide population-based data source, National Health Insurance Research Database (NHIRD) of Taiwan. Validating the comorbid relationship between CVD and thyroid disease may benefit from good demographic diversity of this database because insufficient supports for this association concluded from previous studies might be because of selection bias.

Materials and Methods

National Health Insurance Research Database

The National Health Insurance (NHI) program in Taiwan was initiated in 1995 and currently covers over 99% of the Taiwanese population. Nearly all hospitals and clinics in Taiwan are contracted to support the program. In 2000, the National Health Research Institutes (NHRI) began being authorized by Bureau of NHI to construct the NHIRD to make release claims data available for academic research. Identities of subjects were encrypted by Bureau of NHI before sending claims data to NHRI, and the encrypted identities would be encrypted again by NHRI before the database being released for applications from academic institutes. This is now one of the largest nationwide medical data sets in the world and has been used in many epidemiologic studies. This study used the NHIRD through application from Bureau of NHI; the version was updated in 2010, which contains 1,000,000 random samples of insurants with no significant difference in age, sex, or insurance cost between the sample and the overall population. Insurance claim data of these samples over the period from 1996 to 2010, including diagnosis records and medication orders for outpatient and inpatient visits, were provided. In this database, disease diagnosis has been coded by The International Classification of Disease, ninth Revision, Clinical Modification (ICD-9 CM).

Case Definition and Control Selection

In this study, we would like to validate, respectively, the comorbid relationship between CVD and hyperthyroidism as well as hypothyroidism. The first group of cases in this study were adults (age ≥18 years) initially diagnosed with hyperthyroidism (ICD-9 CM codes: 242.xx and 775.3) and the second group with hypothyroidism (codes: 243 and 244.x), between 2002 and 2008, according to outpatient and/or inpatient records. For each case, the date when the diagnosis of hyperthyroidism or hypothyroidism was first made was defined as the index date.

In this case–control study, each case was matched against 3 insurants, selected randomly from the NHIRD without any diagnosis record for hyperthyroidism, hypothyroidism, and thyroid goiter between 1996 and 2010. As a control, he or she must have at least 1 outpatient/inpatient visit for any condition during that year and month of the index date for his/her corresponding matched case. The date of the first visit during that year and month was assigned as the control's index date. The control was also matched with the case in terms of age and sex. In our selection criteria, controls do not need to be healthy because exclusion of ill people as controls might distort the results.[17] Controls should have the same risk of CVD as the cases, whereas healthy