Ischemic Stroke and Impact of Thyroid Profile at Presentation: A Systematic Review and Meta-analysis of Observational Studies

Rashmi Dhital, MD,* Dilli Ram Poudel, MD,* Niranjan Tachamo, MD,* Bishal Gyawali, MD,† Sijan Basnet, MD,* Pragya Shrestha, MD,* and Paras Karmacharya, MD‡

Background: Stroke is the fifth leading cause of mortality in the United States and a leading cause of disability. A complex relationship between thyroid hormone levels and severity of, and outcome after, stroke has been described. *Aim:* Our objective is to identify the association between baseline thyroid function profile and outcome after acute ischemic stroke. *Methods:* Studies looking at the association between thyroid function and functional stroke outcomes were identified from available electronic databases from inception to December 16, 2016. Study-specific risk ratios were extracted and combined with a random effects model meta-analysis. *Results:* In the analysis of 12 studies with 5218 patients, we found that subclinical hypothyroidism was associated with better modified Rankin scale scores at 1 and 3 months (odds ratio [OR] 2.58, 95% confidence interval [CI] 1.13-5.91, $P = .03$ and OR 2.28, 95% CI 1.13-3.91, $P = .003$, respectively) compared with the euthyroid cases. Likewise, patients with higher initial thyrotropin-releasing hormone (TSH) and fT3 or T3 levels had favorable outcomes at discharge (mean differences of TSH .12 [95% CI .03-.22, $P = .009$] and of fT3 .36 (CI .20-.53, $P < .0001$]) and at 3 months (mean differences of TSH .25 [95% CI .03-.47, $P = .03$] and of T3 8.60 [CI 4.58-12.61, $P < .0001$]). *Conclusions:* Elevated initial TSH (clinical or subclinical hypothyroidism) may correspond to better functional outcomes, whereas low initial T3/fT3 might correlate with worse outcomes in acute ischemic stroke among clinically euthyroid patients. This complex relation merits further well-designed investigations. Whether correcting thyroid profile with hormone supplementation or antagonism may lead to improved outcomes will require large, prospective, interventional studies. **Key Words:** Thyroid function tests—hypothyroidism—hyperthyroidism—ischemic stroke—stroke outcomes.

Introduction

Stroke is the fifth leading cause of mortality in the United States, with an incidence of approximately 795,000 (ischemic or hemorrhagic) per year and 1 out of 20 deaths attributed to it.[1] It is also a primary cause of long-term disability, with women experiencing greater disability than men.[2] The relationship of thyroid hormones with severity of, and functional outcomes after, ischemic stroke is a matter of increasing interest. Thyroid hormone levels are often altered in patients with stroke; with approximately 28% of ischemic stroke patients having

From the *Department of Internal Medicine, Reading Health System, Pennsylvania; †Department of Internal Medicine, State University of New York, New York, New York; and ‡Department of Internal Medicine, Rheumatology, Mayo Clinic, Rochester, Minnesota.

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Address correspondence to Rashmi Dhital, MD, 420 S Fifth Avenue, West Reading, PA 19611. E-mail: rashmi.dhital@outlook.com

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thyrotropin-releasing hormone (TSH) concentrations outside the reference range.[3] A complex relationship has been described between thyroid function and recovery from ischemic stroke, probably because thyroid hormone has both neurotoxic and neuroprotective effects.[4,5] Although critical to normal cell functioning, thyroid hormones can, in excess, overstimulate metabolism and exacerbate the sympathetic nervous system effect.[6]

Several prospective and retrospective studies have evaluated the correlation between thyroid hormone levels and the severity and functional outcome after acute ischemic stroke with conflicting results.[3,4,7-14] Although existing studies suggest that thyroid function tests (TFT) may predict poststroke outcome, it does not provide clear evidence of whether TFT measured at admission can be used as an independent prognostic factor. We therefore performed a systematic review and meta-analysis to look at the association between thyroid function profile and outcomes after acute ischemic stroke.

Material and Methods

We conducted an extensive literature search of major databases (PubMed, Embase, Cochrane, clinicaltrials.gov) using Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines to select studies reporting an association between TFTs and outcomes after acute ischemic stroke from inception to December 10, 2016.[15] We also hand-searched for relevant articles from the bibliographies of those articles (Fig 1). We used search terms under 2 broad search themes: "stroke" and "thyroid function," which were combined using a Boolean operator "AND" (Supplementary Appendix S1). Two investigators (RD and DRP) screened and reviewed reports and excluded irrelevant studies. Relevant data were extracted by 2 investigators (RD and DRP) and checked by another investigator (BG). Published full text articles in English were included in this study. We included studies looking at (1) patients diagnosed to have ischemic stroke (embolic, thrombotic, or stenosis) with a new focal neurological deficit, admitted within 7 days of symptom onset, with a corresponding lesion on magnetic resonance imaging (MRI) or computed tomography scan (CT); (2) measurement of thyroid function profile (abnormal or normal) at the time of admission or within 2 days of admission; and (3) one of the following outcomes: mortality or modified Rankin scale (mRs) score at discharge, 1 month after stroke, 3 months after stroke, or 1 year after stroke.

We excluded studies that included patients with overt thyroid disease or taking medications that could alter TFT (eg, levothyroxine, lithium, amiodarone) at the time of admission. We also excluded patients admitted after 7 days of stroke symptoms or those with hemorrhagic lesions on CT or MRI. Euthyroidism was defined as normal TSH and fT4; hypothyroidism as elevated TSH and decreased fT4; subclinical hypothyroidism as elevated TSH and normal fT4; and low-T3 syndrome as decreased T3 or fT3 with normal TSH. The normal value cutoffs were based on the study's definition, and we tried to convert the units as necessary for uniformity.

Study quality was assessed by 2 investigators (BG and RD) and discrepancies resolved by another (SB) using a modified Newcastle-Ottawa Quality Assessment scale for case control studies.[16] Outcomes from the included studies were calculated using the RevMan software version 5.3 for Windows (Cochrane Collaboration, Oxford, United Kingdom), and meta-analysis was performed by applying the Mantel-Haenszel method. Heterogeneity was

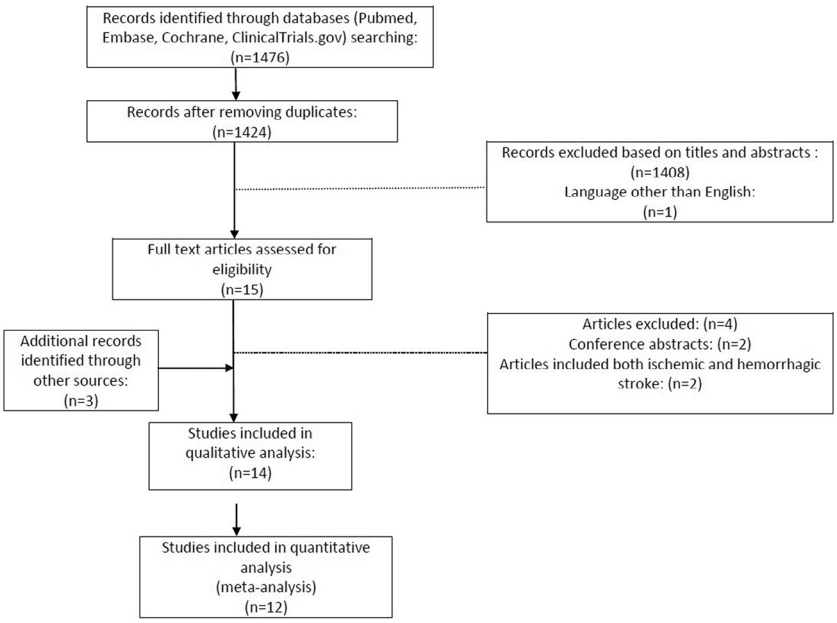

Figure 1. *Flow chart demonstrating systematic process of study selection (PRISMA diagram). PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses*