**Brief Communication**

**Indices of thyroid epidemiology**

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**ABSTRACT**

This brief communication proposes various indices of epidemicity and endemicity which may be used to predict the future prevalence of hypothyroidism. Taking advantage of knowledge related to the natural progression of autoimmune thyroid disease, it uses data from two recent Indian epidemiological studies to assess the epidemicity or endemicity of thyroid disease in the country. The hypothesis generated in this communication will be of help to clinicians as well as policy makers.

**Key words:** Autoimmune thyroid disease, endemicity of thyroid dysfunction, epidemicity, epidemicity of thyroid dysfunction, index, overt hypothyroidism, prevalence, subclinical hypothyroidism, thyroid epidemiology, thyroid peroxidase

**HISTORICAL PERSPECTIVE**

As the term “endemic goiter” testifies, the prevalence of goiter has been used to assess endemicity of thyroid disorders in a particular area or population. Along with urinary iodine concentration and serum thyroglobulin, goiter prevalence has been recommended as a marker of iodine deficiency disorders (IDD).

Defined clinically or on ultrasonography, a prevalence of 10% or more has been widely used to define endemic goiter. With changing trends in the etiopathogenesis of thyroid disorders, fuelled by concerted efforts to eradicate IDD, however, the clinical presentation of thyroid disorders has changed. Goiter is relatively less prevalent now, as autoimmune thyroid disease (AITD) replaces IDD as the major cause of thyroid dysfunction, and as persons present relatively early for treatment.

**MODERN DATA**

Two large studies have recently (2012) reported upon the epidemiology of thyroid disease in India. Unnikrishnan et al., evaluated 5360 adult subjects recruited from eight cities across India while Marwaha et al., evaluated 4302 adults from New Delhi. While Unnikrishnan et al., documented “history of goiter” in 2.25% subjects, Marwaha et al., found “clinical goiter” in 9.6% of their cohort.

Assessing goiter prevalence as the only criterion of endemicity of a thyroid disease, however, ignores the significant burden of agoitrous AITD that India faces.

**ENDEMICITY OF THYROID DYSFUNCTION**

The term “endemic” refers to the usual prevalence of a given disease within a given geographic area or population group. Conventionally, a disease is considered to be existing in a population when it is a public health problem...
while the severity of the public health problem may be measured by its prevalence in case of chronic disease. The notion of “usual prevalence” and calling a disease as “endemic” implies the persistence of the disease for some time with minimal change or variation in its prevalence. To be more precise, epidemiologists often utilize a variation cut-off of “within two standard deviations (SD)” of the prevalence in previous years/decades, depending on the chronicity of the problem, to label a condition as “usual” or “endemic.”

In the light of changing epidemiology and etiology of thyroid disorders, new indicators and indices need be developed to assess both their magnitude and endemicity or epidemicity. In addition, new prevalence cut-offs for defining thyroid disorders as public health problems, and indices for predicting the future endemicity/epidemicity of emerging thyroid disorders will be required. In the current scenario, assessing endemicity of AITD and hypothyroidism by measurements of immunologic (thyroid antibodies) or biochemical (serum thyroid stimulating hormone [TSH]) abnormalities seems both rational and feasible.

Unnikrishnan et al., report prevalence rates of 21.8%, 3.5% and 8.02% for anti-thyroid peroxidase (anti-TPO) positivity, overt hypothyroidism (OH) and subclinical hypothyroidism (SCH). Marwaha et al. corresponding figures are 13.3%, 4.2% and 19.3%. Using the 10%, cut off, anti-thyroid autoimmunity and (OH + SCH) are endemic in India according to both authors. OH is endemic as per the national data reported by Unnikrishnan et al. A detailed analysis of the data reveals that though inter-city differences are observed, prevalence rates for anti-TPO positivity and OH are higher than 10% in all eight cities surveyed.

In the study by Marwaha et al., TPO antibody (Ab) were analyzed by electrochemiluminescence assay (Cobas-Roche Elecys 1010 analyser) with an analytical sensitivity of 5 IU/ml and values above 34 IU/ml were arbitrarily considered as TPO Ab positive. In the study by Unnikrishnan et al., anti-TPO antibodies were measured by the enzyme-linked immunosorbent assay using Immulite 2000 (Siemens Diagnostics Llanberis, Gwynedd, UK) with an analytical sensitivity of 5 IU/ml and a positivity cut-off of 35 IU/ml.

**Epidemiology of Thyroid Dysfunction**

The word “epidemic,” on the other hand, is a noun or adjective which describes the occurrence in a community or region of cases of an illness, specific health-related behavior, or other health-related events clearly in excess of normal expectancy. Similar to that described above for endemicity of a disease, the criterion of “more than 2 SD” may be considered to know whether cases are clearly in excess of normal expectancy or not. Its use will be apt only if one is able to demonstrate a risk in the prevalence of hypothyroidism, over a given time frame, preferably measured in decades or blocks of years. Significant changes in the etiopathogenesis, and diagnosis of thyroid disease, coupled with the lack of nationally representative data on the prevalence of thyroid dysfunction from earlier years, however, do not allow such analysis.

**Proposed Indices of Thyroid Epidemiology**

The astute epidemiologist may use the natural history of the progression of AITD to assess and predict future trends in prevalence rates of thyroid dysfunction. Persons with anti-TPO positivity are classified as having AITD, irrespective of thyroid function. All persons with AITD are at risk of developing SCH, which may progress to OH. The prevalence of AITD in a given population, therefore, may provide an indication toward rise or fall or, if analyzed in depth, even an approximate estimate or prediction of the future prevalence trends of SCH and OH. According to the landmark Whickham study, the odds ratios for the occurrence of hypothyroidism in persons having positive thyroid antibodies and normal TSH were 8 for women and 25 for men. With the added presence of SCH, the values increased to 38 and 173, respectively. For instance, using a modeling of the Whickham data, it has been calculated that for a 50-year-old woman with TSH = 6 mU/L and positive anti-thyroid antibodies, the probability that the authors reported for developing hypothyroidism 20 years later was about 57–99%, especially if age is factored in. Such modeling is complex and even controversial. For example if age is factored in, as TSH rises from 4 to 8 mU/L in the presence of thyroid antibodies, with an age of 35 years, the chances of becoming hypothyroid are 29% and 61% respectively. However, if the age were to be 50 years, the probabilities based on such modeling are 38% and 70% respectively. Save variability in time period required for the transitions from one clinical state to the other, this trend in clinical situation looks more or less comparable to that seen in prediabetes, where a proportion of individuals progress to frank diabetes. The possible differences in progression of euthyroid AITD when compared to the Wichkam study could be due to ethnic differences, etc. Such trend has been utilized by various researchers, who have proposed the use of simple mathematical indices designed to assess the epidemiology of diabetes. These include the diabetes prevalence in previous years/decades, depending on the chronicity of the problem, to label a condition as “usual” or “endemic.”
epidemiology index (EpI), and the diabetes endemicity index (EnI).[8,13]

We hypothesize and propose similar indices to predict the trends in epidemiology/endemicity of hypothyroidism, using available data for the prevalence of anti-TPO positivity, SCH, and OH. In general, a statistically higher prevalence of anti-TPO positivity and/or SCH implies a higher future burden of OH, thus predicting a possible future “epidemic” while a prevalence of anti-TPO positivity and/or SCH more or less equal to that of OH suggests a future stable, persistent or “endemic” state [Table 1].

Relationships between the prevalence of AITD, SCH and OH in populations at different stages of transition might be complex. However, hypothetically in a fashion similar to that observed for TGI and IGT,[6,14] the proportions of prevalence of SCH plus OH, OH, and SCH plus OH made up by prevalence of SCH, SCH, and anti-TPO positivity respectively seem to have a negative correlation with the prevalence of OH in general population. It thus suggests that the indices, as proposed in Table 1, may have some predictive significance for endemicity and epidemicity or the potential for increase in OH prevalence in the circumstance of increased premorbid conditions like AITD or SCH.

Applying these indices to the data reported by Unnikrishnan [et al. and Marwaha et al.], a varying picture emerges. The higher prevalence of thyroid antibodies in the study by Unnikrishnan et al., as compared with Marwaha et al., could be because of differences in the assay methods used. However, the prevalence of overt, undetected hypothyroidism in both studies remains similar, that is 3.5% in the study by Unnikrishnan et al., versus an OH prevalence of about 4% by Marwaha et al., Using data from the study by Unnikrishnan et al., the hypothyroid EnI (HeNI) suggests that hypothyroidism is endemic to India (index > 2). The overt HeNI also suggests endemicity if the eight-city data are used (index > 1), while the AITD EnI supports endemicity only if Marwaha et al. result are used in computing.

Future epidemiology that is prediction of an increase in the prevalence of hypothyroidism can be measured using the similar EpI, which are reciprocal equations of their sister EnI. The hypothyroid EpI (HePI) calculates as < 0.5 with data from the multi-city study, thus refuting the notion that the prevalence of OH will rise in the near future. New Delhi’s results predict an overt HePI > 1 and the HePI > 0.5, while national data suggest an AITD EpI > 1. Thus, there is inconsistent support for the epidemiology of hypothyroidism in India.

**Limitations**

We do not intend to convey that by simply constructing such indices, one may predict the future prevalence of OH or SCH accurately. In general terms, assuming that people with AITD or SCH progress to OH at a greater rate, than people with AITD or SCH die, it seems reasonable to suggest that if the prevalence of AITD or SCH is high relative to that of OH, future OH prevalence will be higher. Ideally speaking, while crafting these indices, we must account for deaths due to the disease, a background death rate, and estimated conversion rates from anti-TPO positivity to SCH or OH in various populations. While proposing these indices for AITD/SCH/OH prevalence trends, we assumed a scenario similar to that of IGT and diabetes as regards to, but not limited to, these issues.

Theoretically, if all independent variables which influence the prevalence of ATD, SCH and OH are known, it might be feasible to develop more predictive models. The development of such models will be facilitated by the documentation of prevalence and incidence trends of AITD, SCH and OH in well-defined populations. These hypothesized proposed indices are likely to predict only the rise or fall in the future trends in prevalence and may be of use as an illustrative indicator, for public health purposes. However, further analysis, research and supplementary evidence are required to substantiate the cut-off values, robustness, validity and reliability and full utilization of these proposed indices.

| Table 1: Proposed thyroid epidemiology indices |
|-----------------------------------------------|
| **Index** | **Definition** | **Index value hypothesized to be predictive** | **Unnikrishnan et al.** | **Marwaha et al.** |
|-----------------------------------------------|-----------------------------------------------|------------------------|---------------------|
| HEnI  | Prev OH + Prev SCH/prev SCH | >2 | 18.97/8.02=2.36 | 23.5/19.3=1.22 |
| OH EnI | Prev OH/prev SCH | >1 | 10.95/8.02=1.36 | 4.2/19.3=0.22 |
| AITD EnI | Prev SCH + Prev OH/prev anti-TPO positivity | >1 | 18.9/21.85=0.87 | 23.5/13.3=1.77 |
| HePI  | Prev SCH/prev SCH + Prev OH | >0.5 | 8.02/18.97=0.42 | 19.3/23.5=0.82 |
| OH Epl  | Prev SCH/prev OH | >1 | 8.02/10.95=0.73 | 19.3/4.60=4.60 |
| AITD Epl | Prev anti-TPO positivity/prev SCH + Prev OH | >1 | 21.85/18.97=1.15 | 13.3/23.5=0.57 |

SCH: Subclinical hypothyroidism, TPO: Thyroid peroxidase, Prev: Prevalence rate, HePI: Hypothyroid endemicity index, OH EnI: Overt hypothyroid endemicity index, OH Epl: Overt hypothyroid epidemiology index, AITD EnI: Auto immune thyroid disease endemicity index, HePI: Hypothyroid epidemicity index
Summary

The world faces a major burden of noncommunicable disease, of which hypothyroidism is one. Though somewhat neglected, hypothyroidism is a major public health challenge. The aim of this communication is to appreciate the epidemiological work being done in thyroidology and to stimulate construction of predictive models for the prevalence of thyroid disease. The hypothesized indices proposed in this editorial offer a simple mean of objective analysis of current prevalence, and prediction of the future prevalence, of hypothyroidism. The concept offers help to policy makers, epidemiologists, and thyroidologists, who work in tandem to quantify the burden of thyroid dysfunction and hence that appropriate steps can be taken to limit the disability caused by this condition.

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Conflicts of interest
There are no conflicts of interest.

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