The rule of two-thirds in thyroid epidemiology

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Rule of Halves

The rule of halves is accepted as a reality in chronic disease epidemiology, including diabetes, hypertension, and depression.¹⁻³ Broadly speaking, the rule states that only one-half of persons living with a particular chronic condition are diagnosed or known to have it; one-half of those who are diagnosed seek treatment, and one-half of those who seek treatment achieve desired therapeutic goals.

An extension of the rule of halves can also be made. We propose that “if properly defined, half of all persons with a predisease state convert to clinical disease”⁴ For example, 50% of persons with prediabetes, progress to diabetes.⁴

Indian Thyroid Epidemiology

In this editorial, we assess Indian epidemiological studies on thyroid disorders through the “rule of halves” mirror. There are three large-scale epidemiological studies on thyroid disorders which have been published from India.⁵⁻⁷ These landmark efforts have served to highlight the heavy burden of thyroid dysfunction and disease in the country. Results from the two studies which assessed adult populations have shown a high prevalence of thyroid autoimmunity and subclinical hypothyroidism (SCH).⁵,⁶ Overt hypothyroidism (OH) is less frequent, though the eight-city study may have over-reported its prevalence due to bias resulting from following a camp-based strategy to recruit participants.⁵

Known Diagnosis

Unnikrishnan et al. enrolled 5376 participants across eight cities in India and reported overall OH prevalence of 10.95% (n = 587). Of these 587 participants, 186 had previously undetected hypothyroidism while 401 were self-reported cases. Thus, one-third (31.7%) of all hypothyroid subjects did not know they had the condition. An equally accurate statement would be that two-thirds of all hypothyroid persons are aware of their diagnosis.

Optimal Therapeutic Outcome

Of the 401 self-reported cases, accurate dosing details of thyroxine therapy were available with 379 patients. Relative to diabetes and depression, thyroid disorders are relatively easy to treat. Keeping this in mind, the rule of halves is not expected to apply to treatment outcomes in thyroidology. Rather, a law of two-thirds could operate. The mean thyroid-stimulating hormone (TSH) values reported by Unnikrishnan et al. suggest the same. Among these 379 participants, 272 had a TSH <5.5 μIU/mL, while the remaining one-third (n = 107, 28.23%) had a TSH >5.5 μIU/mL, in spite of being on a similar dose of thyroxine.

As a hypothesis, it could be proposed that another rule of two-thirds is operational in clinical thyroidology practice. The law states “of all persons who receive appropriate medical therapy for thyroid disorders, only two-thirds adhere to, or persist with treatment as advised by the physician.” However, this law needs to be corroborated by further research.

Conversion from Subclinical to Clinical Hypothyroidism

SCH was observed in 430 (8.02%) participants in the eight-city study. The SCH: OH ratio thus becomes 430:587 or 0.73, which is quite close to two-thirds. However, when the same ratio is assessed for SCH and newly diagnosed OH (excluding persons with a known history of hypothyroidism), it becomes 186: 430 or 0.43, which is slightly more than one-third.

Conversion from Antibody Positivity to Hypothyroidism

A total of 1171 subjects tested positive for anti-thyroid peroxidase antibody. Antibody positivity is known to be a predisease state. The prevalence of (OH + SCH) as...
compared to all antibody-positive persons was (587 + 430): 1171 or 1017:1171 or nearly one. When we assess all SCH as a function of all antibody-positive participants, however, the ratio turns out to be 430:1171 or 0.37. Thus, the ratio of the number of antibody positive persons to individuals with SCH is approximately 2:1.

**HYPERTHYROIDISM**

A total of 36 (0.67%) participants were diagnosed with hyperthyroidism, while subclinical hyperthyroidism was seen in 68 (1.27%) subjects. Here, too a rule of two-thirds seems to be in operation: subclinical hyperthyroidism contributes to two-thirds (65.8%) of the total number of all hyperthyroid disorders.

**SUMMARY**

We, therefore, propose that a rule of thirds, rather than the rule of halves, operates in the Indian thyroid epidemiology. One-third of all antibody-positive persons convert to SCH; two-thirds of those convert to OH (one-third if only newly diagnosed OH is assessed); two-thirds of all OH are diagnosed, and two-thirds of all OH who receive thyroxine are well controlled.

The general health camp-based methodology of Unnikrishnan et al., with its inherent selection bias, is a limitation which must be noted while making such claims. The results of this study are therefore not to be used to make epidemiological presumptions in the Indian setting. At the same time, it is possible that large-scale availability of direct access testing for thyroid function[8], and concerted efforts in social marketing of timely thyroid care[9] have led to a greater prevalence of known thyroid dysfunction, rather than the unknown disease. Larger epidemiological research with robust study design, therefore, is required to confirm this rule.

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| Access this article online |
|---------------------------|
| Quick Response Code:      |
| Website: www.ijem.in      |
| DOI: 10.4103/2230-8210.192919 |

Cite this article as: Kalra S. Unnikrishnan AG, Talwar V. The rule of two-thirds in thyroid epidemiology. Indian J Endocrinol Metab 2016;20:744-5.