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Data mining: Seasonal and temperature fluctuations in thyroid-stimulating hormone

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ABSTRACT

Background: Thyroid-stimulating hormone (TSH) plays a key role in maintaining normal thyroid function. Here, we used "big data" to analyze the effects of seasonality and temperature on TSH concentrations to understand factors affecting the reference interval.

Methods: Information from 339,985 patients at Peking Union Medical College Hospital was collected from September 1st, 2013, to August 31st, 2016, and retrospectively analyzed. A statistical method was used to exclude outliers, with data from 206,486 patients included in the final analysis. The research period was divided into four seasons according to the National Weather Service. Correlations between TSH concentrations and season and temperature were determined.

Results: Median TSH levels during spring, summer, autumn, and winter were 1.88, 1.86, 1.87, and 1.96 μIU/L, respectively. TSH fluctuation was larger in winter (± 0.128) than in summer (± 0.125). After normalizing the data from each year to the lowest TSH median value (summer), TSH appeared to peak in winter and trough in summer, showing a negative correlation with temperature. Pearson correlation analysis indicated that the monthly median TSH values were negatively correlated with temperature ($r = -0.663$, $p < .001$).

Conclusions: This study showed significant seasonal- and temperature-dependent variation in TSH concentrations. Thus, these might be important factors to consider when diagnosing thyroid function disorders.

1. Introduction

Thyroid-stimulating hormone (TSH) is the major regulatory hormone of the hypothalamus-pituitary-thyroid system, responsible for the regulation of numerous processes, including thyroid cell proliferation, thyroid hormone synthesis, and secretion [1]. Thus, TSH plays an important regulatory role in maintaining normal thyroid function. Furthermore, serum TSH is the most sensitive indicator of thyroid function, a key diagnostic indicator of subclinical thyroid disease, and a therapeutic target during thyroid hormone replacement [1–3], thus making TSH a valuable tool for monitoring patient health and disease [4].

To date, several TSH tests have been developed for clinical use worldwide [4–6]. However, recently, many laboratories have turned to "big data" to analyze the factors affecting TSH values and to establish a TSH reference interval [8–11]. The EP28-A3 [11], jointly issued by the Clinical Laboratory and Standard Institution (CLSI) and International Federation of Clinical Chemistry (IFCC), is the authoritative guideline for establishing the TSH reference interval. These guidelines were created using multiple large-scale clinical studies [8,9]. One of the main updates in the new edition [11] was the recommendation to use indirect sampling of existing clinical data from a relatively healthy population to establish general reference intervals. This analysis

Abbreviations: TSH, thyroid-stimulating hormone; CLSI, Clinical Laboratory and Standard Institution; IFCC, International Federation of Clinical Chemistry; PUMCH, Peking Union Medical College Hospital; SOP, Standard operating procedure; IQC, Internal quality control; EQAs, External quality assessments; SD, Standard deviations; K-S, Kolmogorov-Smirnov; IQR, Interquartile range

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compensates for the limitations of direct sampling (e.g., season, quantity).

Notably, in the 1990s, various studies showed that TSH concentrations, and thus the TSH reference interval, were affected by season, age, sex, and other factors [4,11,12]. TSH concentrations have been found to peak in winter and trough in summer, with an absolute difference of 10% to 15% [4,13]. Therefore, we speculated that using big data from extensive clinical studies that are cross-year and cross-seasonal to explore seasonal- and temperature-related fluctuations in TSH could provide useful information to establish an adequate reference interval. However, previous studies used data primarily from only one year or during a particular time period.

In this study, we used big data collected over three consecutive years to conduct a retrospective analysis of serum TSH. This allowed us to evaluate seasonal and temperature trends that previously have been largely overlooked.

2. Materials and methods

2.1. Data collection

All thyroid function test results were collected from patients (health check-ups as well as inpatient and outpatient visits) at Peking Union Medical College Hospital (PUMCH) from September 1st 2013 to August 31st 2016. Information for 339,985 subjects was downloaded from the Laboratory Information System (LIS). Basic information (ID number, name, age, gender, and history) and results of thyroid function testing TSH, free thyroxine 4 (FT4), free triiodothyronine (FT3), total thyroxine 4 (TT4), and total triiodothyronine (TT3) were collected. All information pertaining to patient identification was removed from the data prior to analysis. A schematic representation of our screening process is presented in Supplementary Fig. 1. The exclusion criteria were as follows: patients who visited the Department of Nuclear Medicine, Endocrinology, Obstetrics, or Neurosurgery; patients definitively diagnosed with thyroid cancer; and patients under 18 years of age. A statistical method was used to exclude abnormal outliers and patients with incomplete information. A total of 206,486 eligible subjects (77,808 males and 128,678 females) were included in our analysis. This study was approved by the Ethics Committee of Peking Union Medical College Hospital of the Chinese Academy of Medical Sciences (S−K441). As this study was retrospective in nature and the results were non-traceable to individual patients, informed consent for the use of samples was not needed.

2.2. Laboratory measurements

All blood was drawn by venipuncture, transported, and processed according to the Guidelines for the Collection and Transportation of Samples for Testing (PUMCHL-L-2-Q25b-04) program. Samples were drawn and centrifuged at 3000 rpm for 10 min before testing. Hemolysis and lipemia were treated as unqualified samples.

All thyroid hormones (TSH, FT4, FT3, TT3, and TT4) were evaluated using a Siemens ADVIA Centaur XP automatic chemiluminescence immunoassay analyzer and the needed reagents and calibrators. Calibration was performed appropriately, and quality controls (Lyphochek® Immunoassay Plus Control) were used before the analyses to monitor the precision of the instrument. Measurements were performed according to the standard operating procedure (SOP). To ensure the reliability of results, internal quality control (IQC) data were obtained during the study period. A total of four batches of quality controls K40261, K40281, K40301, and K40321 were used. The CVs of these controls were 6.4%, 5.7%, 6.0%, and 4.6%, respectively, indicating stable and reliable measurements. The instrument was calibrated and preventively maintained every year. In the past three years, we also participated in external quality assessments (EQAs) by the National Center for Clinical Laboratories and College of American Pathologists to guarantee the accuracy and reliability of our results.

2.3. Definition of seasons

The China Meteorological Administration defines average temperature above 22 °C and below 10 °C for five consecutive days as summer and winter, respectively. Average temperatures between this range indicate spring or autumn.

2.4. Statistical analysis

Data were analyzed using Excel 2010 (Microsoft Inc., USA), SPSS 20.0 software (SPSS Inc., Chicago, IL, USA), and/or Medcalc Statistical software 15.0 (Mariakerke, Belgium). Before evaluating the effects, we used Excel 2010 to identify and remove values that were more than four standard deviations (± 4 SD) from the rest of the results. The data distribution was measured using Kolmogorov-Smirnov (K−S). The normally distributed data are presented as mean ± standard deviation (SD), while the non-normally distributed data are presented as medians (quartiles). The interquartile range (IQR) was calculated by SPSS and $p < .05$ were considered statistically significant.

The daily median of TSH concentrations was calculated as the daily TSH moving median (grouped per eight days). Furthermore, the data were divided into four seasons, and the significance of the data was assessed using non-parametric analyses. Pearson correlation coefficients were used to explore the association between the median monthly TSH value and average temperature. Notably, r coefficients between 0.36 and 0.67 indicate modest or moderate correlations, whereas those between 0.68 and 1.0 represent strong or high correlations [14].

3. Results

3.1. Baseline patient data and characteristics

The patient data are shown in Supplement Table 1. A total of 206,486 subjects (77,808 males and 128,678 females) with a median age of 45.0 years (IQR: 35.0 to 55.0 years) were included in our analysis. When the data was grouped by gender, the average age of males was higher than that of females. The FT4, FT3, and TT3 levels were higher in males compared to females ($p < .001$), and the TSH and TT4 levels in males were significantly lower than in females ($p < .001$).

3.2. Seasonal fluctuations in TSH concentrations

Fluctuations in TSH concentrations were monitored over time (Supplement Fig. 2). During the study period, the peak TSH concentrations were observed in January/February, and these concentrations dropped to a minimum in August/September. Notably, both males and females showed peaks and troughs in the same time period. As shown in Fig. 1, when the data were grouped by season, the median TSH concentration was highest in winter (winter: 1.96 ± 0.128 μIU/L, spring: 1.88 ± 0.125 μIU/L, summer: 1.86 ± 0.111 μIU/L, autumn: 1.87 ± 0.114 μIU/L, $p < .001$). However, the range was the largest in winter and lowest in summer.

3.3. Seasonal fluctuations in TSH concentration after normalization

A time course of normalized TSH medians is shown in Fig. 2. The TSH data for each year were normalized to the lowest TSH median values, which was in summer each year (2013–2014: 1.58 μIU/L; 2014–2015: 1.63 μIU/L; 2015–2016: 1.68 μIU/L). The equation used to normalize these values is presented below:

Normalized TSH = (Daily moving median of TSH) / (Lowest TSH median values each year in summer).

After normalization, the TSH concentrations still peaked in