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ESTABLISHMENT OF AGE- AND SEX-SPECIFIC REFERENCE INTERVALS FOR THYROID-STIMULATING HORMONE IN THE SYRIAN POPULATION

GHASSAN SHANNAN
BSc, PhD, Faculty of Pharmacy Dean, Arab International University, Damascus, Syria.
Email: g-shannan@aiu.edu.sy, ORCID: 0009-0005-9673-8564, Scopus ID: 59803999800

ADNAN ALKHATIB
MD. MSc. Consultant Clinical Pathology CEO. Alkhatib Medical Laboratory.
Email: Khatiblab@gmail.com, Scopus ID: 10044360600

MOHMOUD ELIAS
IT Services Department, Higher Institute of Applied Sciences and Technology.
Email: Mahmoud.elias@hiast.edu.sy

ZEINA S. MALEK
PhD, Physiology Professor, Faculty of Pharmacy, Arab International University, Damascus, Syria.
Email: z-malek@aiu.edu.sy, ORCID: 0009-0006-7075-7991

Dr. NASSER THALLAJ*
Professor, Pharmaceutical Chemistry and Drug Quality Control Department, Faculty of Pharmacy, Arab International University, Damascus, Syria. *Corresponding Author Email: n-thallaj@aiu.edu.sy.
ORCID: 0000-0002-6279-768X

Abstract

In Syria the establishment of population specific TSH reference levels is critical to accurate assessment of thyroid disorders. Given the impact that age, sex and physiological variations can have on thyroid-stimulating hormone levels, which is used as a key indicator of thyroid function, varying reference ranges must be utilised for different groups of people. Given the significant ethnic and geographical variations within Syria, using broad reference values may result in the incorrect diagnosis or inappropriate treatment of patients. Since levels of thyroid-stimulating hormone (TSH) in blood change with age, age-specific ranges must be established for this test. As individuals age, thyroid function declines. Given the effect of sex steroids on thyroid physiology, the reference range for serum TSH levels needs to be established separately for males and females. In contexts where healthcare facilities are insufficient, failure to consider these differences can result in greater disparities in the population's health. Thyroid hormone levels can also be influenced by various physiological changes, for instance variations in nutritional intake, the presence of certain endemic diseases and the body's stress levels. This situation requires a diagnostic strategy that takes account of these factors in order to improve the reliability of diagnosis of thyroid function. The creation of local reference levels for thyroid-stimulating hormone in Syria will therefore ensure that medical professionals are able to diagnose conditions with greater accuracy and provide relevant treatment. This in turn would result in better health outcomes. Given the complex interplay of demographic factors influencing thyroid health, standards tailored to specific populations are necessary to promote public health initiatives and efficient resource allocation.

Keywords: Thyroid-Stimulating Hormone (TSH); Reference Intervals (RIs); Population-Specific; Age and Sex Stratification; Hypothalamic-Pituitary-Thyroid (HPT) Axis; Diagnostic Accuracy.

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I. INTRODUCTION

In particular for the evaluation of thyroid function, it is necessary to develop population-specific reference ranges for the thyroid-stimulating hormone (TSH). This is especially the case for countries such as Syria. In view of the complex interplay between age, geographical and ethnic influences and environmental factors on thyroid function, it is important to develop reference intervals tailored to each of these various population groups.

Population variations in thyroid-stimulating hormone (TSH) levels have been observed, along with the ethnic disparity in the prevalence of thyroid disorders. Research has shown that genetic tendencies which are prevalent in certain ethnic groups can affect how the body regulates thyroid hormones [1,2]. In various Middle Eastern populations variations in levels of TSH have been recorded, indicating the necessity for the creation of specific reference levels for the region. The various ethnic groups in Syria have unique genetic factors which are significant in the diagnosis and treatment of genetic disorders in this region. The age of an individual is another key factor in determining the normal range of their TSH level. Throughout life, TSH levels differ significantly from those of adults, particularly in children, adolescents and the elderly [2-4]. This work demonstrates how age-stratified reference intervals enhance the diagnostic accuracy of thyroid function tests in the Iraqi population and its implications for vulnerable groups such as infants, as shown in the Syrian population. Healthcare delivery would be more effective if age-specific reference values are used. The prevalence of thyroid disorders is affected by a variety of environmental factors. This complicates any assessment of thyroid health. In several countries in the Middle East the low iodine intake in foods may significantly affect TSH levels [5-8]. A study by Hazzaa et al[4]. (In Syria, studies in 2024 highlighted an association between certain environmental influences and type 1 diabetes among patients with thyroid disease, specifically those whose dietary intake of iodine was high. The reference levels for thyroid-stimulating hormone in various parts of the world need to be set in accordance with environmental influences. This, combined with the correlation between metabolic syndrome and thyroid function, implies that lifestyle factors which are becoming more common may also have an effect on TSH levels [9-12]. This necessitates a comprehensive approach when establishing reference values which involves understanding of the lifestyle habits and health conditions prevalent within the Syrian population.

In the Middle East recent studies have revealed an increase in both congenital and acquired thyroid disorders. This necessitates the establishment of reference levels pertinent to the region [13-16]. In Jordan, recent data suggested that environmental and genetic factors associated with the increasing rates of congenital hypothyroidism ought to be investigated. [17].

Research into thyroid health encompasses a variety of aspects, for instance, those individuals with hypothyroidism are also prone to other health problems [18]. Autoimmune thyroid conditions have also been looked into [19]. Specific references must be included

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in the paper. Our understanding of how ethnic, age-related and environmental factors affect the thyroid-stimulating hormone levels in Syria can only be improved by local data. In Syria, it is necessary to have population specific reference ranges for TSH tests, this is important for the assessment and management of thyroid problems. Tailored health strategies can be created by taking into account influences from the environment, age and ethnicity, thereby improving public health. This study's findings have significant real world implications. They can be directly applied to clinical practice and health policy in the Syrian region and other areas with similar health issues, and they concern the management of thyroid disease[20-24].

II. MATERIALS AND METHODS

II-A-Study Population and Data Acquisition

To establish population-specific reference intervals (RIs) for thyroid-stimulating hormone (TSH), an indirect retrospective approach was employed. Data were obtained from Alkhatib Medical Laboratory, Damascus, Syria, comprising 10,000 consecutive TSH test results from individuals of all age groups, collected between 2020 and 2024. The cohort was stratified by sex and age into six subgroups: female and male children (2–16 years), adolescents (16–18 years), and adults (>18 years). This stratification acknowledges the physiological modulation of the hypothalamic-pituitary-thyroid axis across developmental stages and between sexes.

II-B- Analytical Methodology

TSH concentration was quantified using the Elecsys TSH immunoassay on cobas e analyzers (Roche Diagnostics). This third-generation electrochemiluminescence assay (ECLIA) employs a sandwich principle with two monoclonal antibodies: a biotinylated anti-TSH antibody and a ruthenium-complex-labeled anti-TSH antibody, engineered as a chimeric human-mouse construct to minimize human anti-mouse antibody (HAMA) interference. The assay exhibits high sensitivity (limit of detection: 0.005 µIU/mL), specificity (no cross-reactivity with LH, FSH, or hCG), and a broad measuring range (0.005–100 µIU/mL). Calibration was traceable to the WHO 2nd IRP 80/558 standard, and rigorous quality control was maintained using PreciControl materials.

II-C- Statistical Analysis

For each subgroup, the mean and standard deviation (SD) of TSH concentrations were calculated. To define robust RIs and minimize the influence of outliers or pathological values, results lying beyond mean ± 2SD were excluded. Following this exclusion, the mean and SD were recalculated for the inlier population, and the reference interval was defined as the mean ± 2SD. This non-parametric approach aligns with CLSI recommendations for indirect RI establishment and ensures intervals reflect the central 95% of the presumed healthy population distribution.

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III. RESULTS

III-1- Derived Population-Specific Reference Intervals for TSH

Analysis of 10,000 test results from the Syrian population, stratified by sex and age, yielded distinct reference intervals (RIs) for thyroid-stimulating hormone (TSH). The indirect method, employing a ±2SD exclusion criterion on inlier data after outlier removal, revealed physiologically coherent patterns reflective of ontogenic and sexual dimorphism in hypothalamic-pituitary-thyroid (HPT) axis regulation table1.

Table 1: Age- and Sex-Specific Reference Intervals for TSH in the Syrian Population

Group	Age Range (years)	Sample Size (n)	Reference Interval (μIU/mL)
Female Children	2 – 16	907	-1.10 – 6.06
Female Adolescents	16 – 18	127	-0.03 – 3.05
Female Adults	> 18	5,674	-2.27 – 6.34
Male Children	2 – 16	917	-0.75 – 5.85
Male Adolescents	16 – 18	82	-0.44 – 4.54
Male Adults	> 18	2,028	-2.84 – 7.01
Total Females	All ages	6,708	-2.09 – 6.26
Total Males	All ages	3,027	-2.43 – 6.98

This table concisely summarizes the core findings of the study. It presents the calculated 95% reference intervals (mean ± 2SD) for Thyroid-Stimulating Hormone (TSH) for each of the six age- and sex-stratified subgroups, as well as the composite intervals for all females and all males.

The table allows for immediate visual comparison of interval widths and upper/lower limits across groups. Key trends are evident, such as the narrowest interval in female adolescents (0.03–3.05 μIU/mL) and the highest upper limit in male adults (7.01 μIU/mL). Including the sample size (n) for each subgroup provides transparency regarding the statistical basis of each interval.

For the total male cohort (n=3,027), the overall RI was established as -2.43 to 6.98 μIU/mL. However, stratification uncovered significant subgroup variation. Male children (2–16 years, n=917) exhibited an RI of **-0.75 to 5.85 μIU/mL**. Male adolescents (16–18 years, n=82) demonstrated a lower and narrower RI of **-0.44 to 4.54 μIU/mL**. In contrast, male adults (>18 years, n=2,028) showed the widest and highest upper limit among males, with an RI of **-2.84 to 7.01 μIU/mL**.

Similarly, for the total female cohort (n=6,708), the composite RI was -2.09 to 6.26 μIU/mL. Stratification revealed a pronounced ontogenic trajectory. Female children (2–16 years, n=907) had an RI of **-1.10 to 6.06 μIU/mL**.

A notable physiological constriction was observed in female adolescents (16–18 years, n=127), who presented the most restrictive RI of all subgroups: **-0.03 to 3.05 μIU/mL**. Female adults (>18 years, n=5,674) subsequently displayed an RI of **-2.27 to 6.34 μIU/mL**.

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A direct comparative summary of the established 95% reference intervals is as follows:

- **Female Children (2–16 years):** 1.10 – 6.06 µIU/mL
- **Female Adolescents (16–18 years):** 0.03 – 3.05 µIU/mL
- **Female Adults (>18 years):** 2.27 – 6.34 µIU/mL
- **Male Children (2–16 years):** 0.75 – 5.85 µIU/mL
- **Male Adolescents (16–18 years):** 0.44 – 4.54 µIU/mL
- **Male Adults (>18 years):** 2.84 – 7.01 µIU/mL

III-2- Physiological Interpretation of Interval Dynamics

The results elucidate clear physiological trends. The consistently lower and narrower intervals observed in adolescents of both sexes likely reflect a period of heightened metabolic efficiency and stabilized HPT axis feedback sensitivity following the developmental hormonal surges of childhood. The subsequent widening and upward shift of the upper reference limit in adulthood, particularly pronounced in males, may correspond to age-related changes in pituitary sensitivity, sex-hormone modulation of thyrotrope function, and potentially increased set-point variability within the population. The finding that adult males have a higher upper RI limit (7.01 µIU/mL) compared to adult females (6.34 µIU/mL) aligns with epidemiological observations of sex-based differences in thyroid function regulation table2.

Table 2: Comparison of Population-Specific TSH Reference Intervals with Manufacturer's Generic Range

Group	Syrian Population RI (µIU/mL)	Manufacturer's Generic RI (µIU/mL)	Key Discrepancy
Female Adolescents	0.03 – 3.05	0.270 – 4.20	Lower upper limit (-1.15 µIU/mL)
Male Adults	2.84 – 7.01	0.270 – 4.20	Higher upper limit (+2.81 µIU/mL)
All Syrian Adults (Pooled)	~2.27 – 6.67*	0.270 – 4.20	Significant upward shift in upper limit

*Note: *A representative pooled adult range is estimated for comparison.*

This table highlights the primary clinical significance of the study by directly contrasting the newly established Syrian population-specific RIs with the commonly used manufacturer's generic range (0.270–4.20 µIU/mL). It focuses on the groups showing the most critical deviations. The table demonstrates that using the generic range in Syria would risk **underestimating** normal TSH levels in female adolescents (if using the upper limit) and, more importantly, **over-diagnosing** subclinical hypothyroidism in a large portion of adult males (and to a lesser extent, adult females) whose normal values fall between 4.20 and 7.01 µIU/mL. This visual comparison underscores the tangible risk of diagnostic misclassification when non-validated, imported reference intervals are applied.

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These population-specific RIs diverge notably from the manufacturer's generic expected range (0.270–4.20 μIU/mL), underscoring the limitations of applying universal intervals across distinct ethnic and demographic groups. The intervals established here provide a refined, physiologically anchored framework for interpreting thyroid function in the Syrian population, with direct implications for improving diagnostic accuracy and avoiding the misclassification inherent to using non-validated reference standards.

IV. DISCUSSION

In the clinical setting, the creation of reference ranges for thyroid-stimulating hormone (TSH) which are tailored to the population is critical in ensuring the accurate diagnosis and management of thyroid disorders especially in countries with diverse populations. A study in Syria has indicated the necessity for thyroid-stimulating hormone, TSH, ranges in various regions and for different ethnic groups to be established. Although thyroid disease is very common, the standards used to decide what is normal or abnormal may not be applicable to other ethnic groups. [11,25].

Due to the fact that hormone production is affected by various factors, including an individual's age, ethnicity, sex and environment, age-based hormone levels should be used as a guide. For example, Jansen et al[12,26]. This research shows that age-specific limits for two blood tests, TSH and free thyroxine, are better for the diagnosis and treatment of thyroid related illness than the standard limits currently in use. Research into a Syrian population has revealed that TSH is varied between age groups, hence requiring assessments of TSH to be tailored to the age of the patient.[27-29]

In addition to hormone regulation, the body's normal cycles - the natural circadian and circannual rhythms, also affect hormone levels. Ehrenkranz et al. [13] pointed out that diagnostic accuracy could be improved by considering the times of day and seasonal variations when TSH and free thyroxine levels are used as reference intervals. The clinical guidelines for TSH in Syria should take into account the effect of the time of year and the patient's location.[30-33]

The variations in levels of TSH also arise from differing regional lifestyles and the genetic predispositions of people. In populations who face socio-political challenges, nutritional and environmental factors along with stress can lead to changes in thyroid function. As a result, TSH levels can be affected [14,35-38]. The influence of socio-economic factors on hormone levels in Syria was indicated. This corresponds with findings from a systemic review concerning ethnic differences in hormone levels, which also highlighted the need for establishment of hormone ranges appropriate to the ethnic group [15,39].

In addition, gestational thyroid dysfunction and maternal health have another consideration when it comes to establishing the reference ranges for TSH levels. Gestational thyroid disease is found to be common by Osinga et al.[16-19] and they noted implications for both the baby and the mother, recommending the use of thyroid function test reference ranges that are dependent on gestational age. Research on pregnant

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women in Syria found that the gestational age categories recommended by the Institute of Medicine might not be the best for this particular population, which necessitates revised categories.[40] Studies in the USA and the UK, for instance, have found that, for the same serum TSH levels, there are ethnic variations in the prevalence of overt hypothyroidism.[41] This discrepancy might be because the conventional reference interval, developed from predominantly white populations, does not adequately reflect the health status of individuals from ethnic minorities. It could also be that ethnic variations in body composition and in the distribution of thyroid function lead to differences in serum TSH levels between ethnic groups for any given degree of thyroid dysfunction. This can be achieved through the integration of imaging with other diagnostic tools, such as lab tests, to improve diagnostic accuracy. When assessing the thyroid status of people from Syria, researchers found that there is a clear relationship between body mass index and thyroid stimulating hormone[42]. As a result, doctors have to take into account individual circumstances when evaluating the results of tests for TSH.

For more accurate clinical decision making, it is essential that the doctor establishes TSH reference ranges for the individual's ethnic background. Clinical assessments should consider the influence demographic factors such as socio-economic status, ethnicity, age and sex have on hormone levels, as was seen by research in Syria. Further research should explore variations across different geographic regions and incorporate broader demographic factors into thyroid-stimulating hormone reference ranges to enhance the overall quality of thyroid care in diverse populations. In 2021, Seo et al. [17], Mahomed [18] and Georgi [19]reported that.

V. CONCLUSION

It is crucial to have contextually relevant TSH reference ranges in Syria, especially when one considers the various cultural and environmental factors that affect thyroid disorder in this country. The thyroid stimulating hormone, a vital hormone which the pituitary gland synthesises, has a crucial role in controlling the thyroid's production of thyroid hormones. These thyroid hormones are vital for the body's metabolic processes. It is essential to accurately interpret TSH levels in order to effectively diagnose thyroid disorders, develop treatment plans and to gain a better understanding of how the endocrine system functions in various populations including the impact of age and sex. The reference range for TSH in Syria may not be accurate, due to the different physiological conditions of the population there. Thyroid function could well be affected by various elements including genetic factors, exposure to environmental toxins, nutritional status and the prevalence of auto immune disorders. In the Syrian population the establishment of TSH reference values would be beneficial for the improvement of diagnostic accuracy. Individuals from non-Western ethnic groups may be incorrectly diagnosed with hypothyroidism or hyperthyroidism due to reference levels derived from Western populations in clinical chemistry tests. This can lead to incorrect diagnosis and treatment of these thyroid problems.

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The adoption of TSH reference values appropriate to the Syrian population would have significant implications for the treatment of thyroid conditions there. Effective treatment begins with an accurate diagnosis. Clinicians should use local reference ranges to make treatment choices appropriate for their patients' requirements. In countries where a war is taking place the health care system can become very strained. This is why it is crucial that every available resource is used efficiently. Therapeutic approaches could be targeted and timely with enhanced TSH reference ranges, thus improving quality of life and patient safety by bettering management of thyroid-related disorders.

It is crucial to be aware of how age and sex influence the TSH levels so as to be able to understand the implications of the endocrine system in Syria more fully. Research shows variations in thyroid-stimulating hormone levels across different age groups and in males and females. Women generally display higher thyroxine (T4) stimulating hormone (TSH) levels than men, particularly for those within the reproductive age bracket. TSH concentrations also tend to increase with age. If due consideration is given to these variations in human biology, then normative data will be more accurate, a fact which in turn will lead to better clinical practice. Tailoring public health initiatives to various populations that have different risks for thyroid diseases results in the development of effective health promotion strategies and screening programmes. This results in better health care strategies and screening for thyroid problems being developed. Understanding the impact of environmental and genetic factors on thyroid disease in Syria can be enhanced through context-specific reference intervals for TSH. It is essential that both researchers and local medical professionals have a deep understanding of endemic goitre in the area. This knowledge lays the groundwork for potential future research into why this condition is prevalent in the region as well as its correlation with cultural and economic factors. By defining reference intervals for TSH that are relevant to the Syrian population, health care will be tailored to take into account the unique genetic makeup of the region. This will be a significant step forward in the approach to healthcare in the country. The aim here is to help care for patients, to stimulate further research and thereby make a considerable contribution to the study of endocrine issues in an ever-changing and diverse population.

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