Young adult reference ranges for thyroid function tests on the Centaur immunoassay analyser

M. ALQAHATANI*, W. TAMIMI†, M ALDAKER‡, F. ALENZI§, H. TAMIM¥ and A. ALSADHAN†

Pediatric Department, King Fahad Hospital of the University, Alkhobar; †Department of Pathology and Laboratory Medicine, and ‡Department of Internal Medicine, King Fahad National Guard Hospital, Riyadh; §Department of Medical Laboratory Sciences, College of Applied Medical Sciences, King Faisal University, Dammam; and ¥College of Medicine, King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia

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ABSTRACT

This study aims to establish reference ranges for thyroid tests in young Saudi adults using the Centaur immunoassay method. Physical examination is performed and thyroid function tests include thyroid stimulating hormone (TSH), free thyroxine (FT4) and free triiodothyronine (FT3). These are performed on 291 young Saudi adults (182 [63%] females and 109 [37%] males; average age: 27 years [range 18–50]). Clinical thyroid abnormality, related symptoms and/or abnormal thyroid function tests exclude a person from the study and thus a total of 276 subjects (171 [62%] females and 105 [38%] males) are used to establish the new reference ranges. Combined female and male ranges for TSH, FT4, and FT3 were found to be 0.48–6.30 miu/L (9.00–18.62 pmol/L and 3.39–6.85 pmol/L, respectively). Mean TSH and FT4 levels were significantly different ($P<0.0001$) from those quoted by the manufacturer. Ranges for TSH were 0.48–6.30 miu/L (female) and 0.52–4.89 miu/L (male) ($P=0.08$). Female ranges for FT4 and FT3 were 9.00–17.15 pmol/L and 3.39–5.82 pmol/L, respectively. Male ranges were 9.92–18.62 pmol/L ($P=0.0001$) and 4.36–6.85 pmol/L ($P<0.0001$). The range of TSH levels in the young local Saudi population proved to be higher than that quoted by the manufacturer. FT4 range was lower and narrower than that quoted by the manufacturer. Significant differences between female and male populations suggest that partitioning of the reference ranges by gender is necessary.

KEY WORDS: Reference values. Thyrotropin. Thyroxine. Triiodothyronine.

Introduction

A common problem seen in clinical endocrine practice is the abnormal thyroid function test. This problem affects 5–10% of the population[1] and, due to the non-specific nature of thyroid disease symptoms,[2,3] the laboratory assessment of thyroid function tests is the preferred means to diagnose and monitor patients with suspected thyroid illness.

Subclinical thyroid disease is present if thyroid stimulating hormone (TSH) level is abnormal (high or low), while free thyroxine (FT4) and/or free triiodothyronine (FT3) levels are within the laboratory reference ranges. However, these ranges are population-based and are usually wide, due to large differences in thyroid function among normal subjects.[4,5]

Many patients attending adult endocrinology clinics in Saudi Arabia show a low FT4 level, while TSH falls within the reference range. These observations suggest that the local population could have different reference ranges to those quoted in analyser/assay literature.

In addition, the International Federation of Clinical Chemistry (IFCC) has recommended that each laboratory should estimate its own reference range.[6–10] However, the selection of healthy reference subjects and the determination of reference values are time-consuming processes. Therefore, many laboratories use reference ranges obtained from the scientific literature or provided by the manufacturer.

This study aims to establish local reference ranges for thyroid function tests among the Saudi population.

Materials and methods

This study was undertaken in the laboratory and the blood donor centre of the King Fahad Hospital, National Guard Health Affairs, Riyadh, Saudi Arabia, during 2004.

A total of 291 young Saudi adult volunteers, originating from the central region of the Arabian Peninsula, were included. Most were students and staff of the Nursing School of King Abdulaziz Academy, National Guard, Riyadh, Saudi Arabia, and staff and students of the Institute of Public Administration, Riyadh, Saudi Arabia. The initial study population comprised 182 females and 109 males (age range: 18–50 years; average age: 27 years).

Informed consent was obtained and health assessment was performed using the standard blood donor procedures.[11] All physical examinations and vital signs including blood pressure, respiratory rate, pulse rate, temperature and demographic data were taken for all subjects. Pregnant women were excluded from the study.

Blood samples were collected using Vacutainer gel separator tubes (Becton Dickson, USA) and left to clot for 30 min at room temperature before centrifugation at 3000 x*g* for 15 min. Primary sample tubes were transferred immediately to the ADVIA Centaur immunoassay analyser (Bayer Diagnostics, Tarrytown, NJ, USA) and TSH, FT4 and FT3 analyses were performed.[12,13] Following analysis, the

Correspondence to: Dr. Waleed Tamimi
Department of Pathology and Laboratory Medicine, King Fahad National Guard Hospital, PO Box 22490, Riyadh 11426, Saudi Arabia
Email: tamimiw@ngha.med.sa

serum was separated in secondary plastic tubes and stored frozen (–70°C) for future analytical testing.

Thyroid function tests were used as the first-line assessment in evaluating the subjects included in the study. Any subject with physical abnormalities and/or thyroid function test abnormality was excluded from the study. Fifteen subjects (11 females and four males) were excluded from the study and referred to the adult endocrinology clinic.

Reference ranges were established from samples from the remaining 276 subjects (171 [62%] females and 105 [38%] males). Samples were also tested for total cholesterol, triglyceride, low-density lipoprotein (LDL) and high-density lipoprotein (HDL) to ensure no lipid abnormalities were present among the subjects (data not shown).

Data for TSH, FT4 and FT3 were summarised by calculating the mean, standard deviation and ranges for each parameter. In addition, the results were compared with manufacturer reference information using the two-tailed *t*-test. FT4,[12] FT3[14] and TSH[15] were tested by similar methods in apparently healthy cohorts of adult Western populations comprising 388, 594 and 404 people, respectively. The NCCLS guidelines for determination of reference ranges were followed.[16] Data management and analyses were performed using SAS (version 8.0) statistical software.[17]

Results

Table 1 shows the determined and manufacturer reference ranges for the thyroid function tests (TSH, FT4, FT3). Study by the manufacturer for thyroid reference ranges were conducted on the old version of its technology (ACS 180) and then correlated to the new version (ADVIA Centaur). However, the manufacturer's study does not show the gender-specific reference ranges.[13–15] The mean and standard deviation for the local population and that used by the manufacturer were compared and found to be 1.83±0.94 and 2.92±1.29 ($P<0.0001$) for TSH, 12.91±1.72 and 17.10±2.80 ($P<0.0001$) for FT4, and 4.99±0.60 and 5.00±0.70 ($P=0.86$) for FT3.

Table 2 shows the calculated mean, standard deviation and ranges for the local Saudi female and male populations for TSH, FT4 and FT3. The mean of each group was compared and *P* values were found to be 0.08, 0.0001 and <0.0001, respectively.

Discussion

The present study shows that TSH and FT4 reference ranges for a Saudi young adult population, based on a 95% confidence interval, are 0.49–6.30 miu/L and 9.00–18.62 pmol/L, respectively. The TSH range is slightly higher than the manufacturer's range (0.35–5.50 miu/L). The FT4 range is lower and narrower than that quoted by the manufacturer (11.5–22.7 pmol/L), which was based on a Western population.[13] However, the range for FT3 is similar to that quoted by the manufacturer.

No other local studies have been undertaken on thyroid function reference levels among Saudi adults. However, a recent study by Henry *et al*. conducted on Saudi newborns shows that FT4 is slightly lower in that population than in internationally published data.[18]

Table 1. Local and manufacturer's reference ranges for TSH, FT4 and FT3.

	Local range (*n*=277)	Manufacturer's range (*n*=388)	*P* value
TSH (miu/L)	0.48–6.30 Mean=1.83 SD=0.94	0.35–5.50 Mean=2.92 SD=1.29	<0.0001
FT4 (pmol/L)	9.00–18.62 Mean=12.91 SD=1.72	11.50–22.70 Mean=17.10 SD=2.80	<0.0001
FT3 (pmol/L)	3.39–6.85 Mean=4.99 SD=0.60	3.50–6.50 Mean=5.00 SD=0.7	0.86

SD: Standard deviation.

Table 2. Reference ranges partitioned according to gender.

	Female (*n*=172)	Male (*n*=105)	*P* value
TSH (miu/L)	0.48–6.30 Mean=1.75 SD=0.93	0.52–4.89 Mean=1.95 SD=0.95	0.08
FT4 (pmol/L)	9.00–17.15 Mean=12.58 SD=1.47	9.92–18.62 Mean=13.45 SD=1.96	0.0001
FT3 (pmol/L)	3.39–5.82 Mean=4.68 SD=0.43	4.36–6.85 Mean=5.50 SD=0.49	<0.0001

SD: Standard deviation.

Hubner *et al*. reported continuous age-dependent reference ranges for thyroid hormones in neonates, infants, children and adolescents by the same method used in the present study. Their FT4 range (10.7–18.7 pmol/L) among adolescents was similar to the adult population studied here. Similarly, their female TSH (0.56-4.53 miu/L) and overall FT3 (3.57–6.65 pmol/L) ranges were similar.[19] This may indicate that analytical variation rather than biological variation contributed to this lower FT4, as the reference range shows clear dependence on applied immunoassay due to different immunoassay architecture and a lack of international standardisation. An international reference standard is only available for TSH.[20]

The differences in TSH and FT4 ranges in the Saudi population studied and in that quoted by the manufacturer can also be attributed to the improvement in technology, as established thyroid reference ranges were complied using a previous version of this technology (ACS 180).[13–15] Clearly, new thyroid reference ranges based on the use of the latest technology are required. Other manufacturers have reported a lower FT4 range using different instrumentation but the same immunological principle.

In the present study, the age of the investigated group (18–50 years) may be regarded as low and this may also account for the difference in the Saudi population range and that quoted by the manufacturer. Thus, a larger-scale study may be necessarily.

Bruchert *et al*. report that low FT4 is a risk factor for

atherosclerosis in male subclinical hypothyroidism patients.[21] In the present study, neither male nor female populations were found to have lipid abnormality. This may reflect the low age range of the populations studied.

As there was a statistically significant difference between male and female levels for each of the thyroid tests undertaken, partitioning of the reference ranges according to gender was performed according to NACB guidelines.[22] In addition, as pregnant females have a different reference range,[23] the present study did not include this group.

LoPresti *et al*. suggest that the difference in their population reference ranges may be attributed to the fact that individuals have their own FT4-TSH set-point, whereby any deviation from this genetically determined relationship changes both levels.[24] This suggests that the present study population is genetically different from other populations and may explain the lower and narrower FT4 range. However, a genetic study is needed to test this hypothesis.

In conclusions, the TSH range in the Saudi young adult population study is higher than that quoted by the manufacturer of the equipment used ($P \leq 0.0001$), and the range for FT4 is lower and narrower ($P \leq 0.0001$). The latter may reflect a genetic influence rather than reduced thyroid hormone action.

The results of this study provide normal reference ranges for the interpretation of thyroid function tests in 'young' Saudi adults (age range: 18–50 years) and may not be applicable to the general Saudi population. □

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