Should We Really Determine a Reference Population for the Definition of Thyroid-Stimulating Hormone Reference Interval?

To the Editor:
In a recent report, Kratzsch et al. (1) reported new reference intervals for thyrotropin [thyroid-stimulating hormone (TSH)] and thyroid hormones, based on National Academy of Clinical Biochemistry (NACB) criteria. Although the report deals with defining reference intervals for TSH and for thyroid hormones, the major point of discussion is the reference interval for TSH. The discrimination of subclinical thyroid dysfunction from euthyroidism has major therapeutic consequences, especially in elderly and/or comorbid patients. With the improved sensitivity of current TSH methodology, TSH measurement has replaced free thyroxine testing as the first-line test for screening and finding thyroid dysfunction. Current 3rd-generation assays (lower limit of detection ~0.01 mIU/L) now allow the detection of subclinical hyperthyroidism (2, 3).

There is consensus regarding the lower limit of the TSH reference interval (0.3–0.4 mIU/L). In contrast, however, the upper limit of the TSH reference interval is currently under discussion. In recent guidelines, the NACB recommended the use of ~2.5 mIU/L, rather than ~4 mIU/L, because reference populations, on which the definition of the reference interval is based, contain individuals experiencing an initial phase of autoimmune thyroid disease (4), thus skewing the upper reference limit of TSH (5). Ultrasonography, in addition to measurement of thyroid autoantibodies, should be used to exclude these individuals (6, 7). From a whole study group of healthy blood donors (n = 870), Kratzsch et al. (1) defined a constraint group (n = 453) exclusive of individuals with family history of thyroid disease, positive autoantibodies to thyroid peroxidase (TPO) and/or thyroglobulin (Tg), increased free triiodothyronine and/or free thyroxine, and sonographically assessed abnormalities of the thyroid. Interestingly, the upper limit (97.5th percentile) was in the same range for the constraint group as for the whole study population (3.63 mIU/L vs 3.77 mIU/L). Both values were higher than the NACB recommendation (~2.5 mIU/L). Our own data (8) confirm these results. Jensen et al. (9) also reported an upper limit of 4.1 mIU/L in 987 healthy volunteers selected from a total population of 1512 persons. They found that 250 individuals had at least 1 thyroid autoantibody, 121 were taking medications other than estrogens and occasional analgesics, and 105 reported a family history of thyroid disease. Furthermore, the 987 healthy adults included both women and men between 17 and 66 years of age. In our study, the 97.5th percentiles were 3.35 mIU/L for the constraint group (n = 713) and 3.34 mIU/L for the whole group (n = 1442, Fig. 1). As Kratzsch et al. (1) also found in their study, the lower reference limit was higher in our constraint group than in the whole group (0.30 mIU/L vs 0.11 mIU/L). Völzke et al. (10) presented the well-known inverse correlation between TSH and age, as also mentioned by Kratzsch et al. (1) and Jensen et al. (9). According to our data, the upper limits of the disease-free group (n = 1488) and the whole study population (n = 4298) were in the same range. We therefore question whether we really need a reference population selected according to NACB criteria for assessment of TSH reference values.

There are several possible explanations for these results. In our opinion, the most important influence is the iodine status of the population investigated. Whereas the National Health Nutrition and Examination Survey (NHANES) III study (11) was carried out in a region of sufficient iodine intake, the European studies were performed in regions with mild or moderate iodine deficiency. Only Jensen et al. (9) compared the iodine intake of individuals from different regions. They showed a lower median and reference interval in persons with mild iodine deficiency compared with those with moderate iodine deficiency. Furthermore, the lower 2.5th percentile in the constraint group of older individuals may have been a result of their longer exposure to iodine deficiency, which could lead to a higher risk of having an initial state of subclinical hyperthyroidism, e.g., disseminated autonomy (12). In contrast to Kratzsch et al. (1), we would favor this reason more than their claim that the lower comorbidity of healthy blood donors would be responsible for the difference.

Several studies indicated that the currently available commercial as-

![Fig. 1. Histograms showing the distributions of TSH concentrations in the reference population (thin dashed line; n = 713), all participants (thin solid line; n = 1442), TPOAb- and/or TgAb-positive persons (thick dashed line; n = 216), and persons with a hypoechoic pattern in thyroid ultrasonography (thick solid line; n = 66).](image-url)
says are too insensitive to detect thy-
roid autoantibodies (TPOAb and TgAb) in an early state of autoim-
mune thyroid disease (1, 4, 5, 8, 10).
Therefore, thyroid ultrasonography is recommended to exclude these in-
dividuals. Obviously, however, ul-
trasonography is not sufficient in
populations with lower iodine in-
take.

A third possible explanation for
these findings is that the microhet-
erogeneity of the antigen TSH itself
leads to differences in the epitope
spectrum. As a result, the interaction
of TSH with the assay-specific anti-
bodies differs among assays, or bet-
ter, among manufacturers (2, 13, 14).
The analysis of external quality con-
trols—which is mandatory for each
laboratory in Germany—gives in-
sights into this possibility (15). Some
assays slightly underestimate and
others overmeasure the control sam-
ple consistently, although all manu-
facturers calibrate their assays to
International Reference Preparation
(IRP) 80/558. Of course, the intra-
method variation is acceptable.

In conclusion, it seems useful to
redefine the upper limit of the TSH
reference interval to a value lower
than ~4.0 mIU/L, following the
NACB criteria. Despite a family his-
tory of thyroid disease, thyroid ultra-
sonography, and sensitive thyroid autoantibody measurement, the io-
dine status of the reference popu-
lation should be known to define a
representative TSH reference in-
terval usable for therapeutic deci-
sions, especially in elderly patients.
Thyroid-releasing hormone testing
might be helpful in central hypo-
thyroidism, as recommended by the
NACB (4, 6).

Considering the diversity of prob-
lems that impact the establishment of
reference intervals for TSH, which
were mentioned in the reports of
Kratzsch et al. (1), Voelzke et al. (10),
and in our own (8), we question
whether it makes sense at all to de-
fine a common upper limit for TSH
determinations.

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Serum Creatinine Values in Elite
Athletes Competing in 8 Different
Sports: Comparison with Sedentary
People

To the Editor:
The concentration of creatinine in
serum is the most widely used and
commonly accepted measure of renal
function in clinical medicine. Refer-
ence values of biochemical variables
specific for sportsmen have never
been defined, and those used for the
general population are also applied
to athletes. The common reference
interval for creatinine in the general
population corresponds to 62–115
μmol/L (0.7–1.3 mg/dL) for adult
males (1). In our experience with
athletes, we frequently observed
high creatinine values, near or higher
than 115 μmol/L (1.3 mg/dL). We
studied 220 elite athletes: 15 triath-
letes of the Italian National Team, 29
basketball players of an Italian First
Division team, 35 cyclists from 2 pro-
fessional teams, 13 racing motocyc-
lists of a professional team, 27 soc-
cer players of an Italian First Division
team, 23 sailors of an America’s Cup
yacht, 34 alpine skiers of the Italian
National Team, and 44 rugby players
of the Italian National Team. The
athletes were all males, and the age
range was 17–36 years. Serum was
always analyzed within 5 h from
blood drawing on an Aeroset c8000

People