Biological reference values

Gérard Siest
Centre de Médecine Préventive
Université Henri Poincaré
Nancy

The reference values concept has been adopted by health care professionals, including clinical chemists, laboratory scientists and clinicians and simultaneously by all the official organizations in charge of the establishment of legislation. But the estimation of reference limits and the evaluation of biological variability need to be improved at the level of the procedures, which are currently too long and too expensive and not feasible easily for all laboratories. Recently, a group of experts started a revision process (1).

The procedures for obtaining reference values, if we follow the original documents, are complex, and that is the main reason that clinical chemists or diagnostic kit manufacturers have not used them systematically. More than that, when the laboratory scientists try to use the papers describing the concept, they do not supply enough details and do not use them as rigorously as they should. There is also now a clear confusion between the notion of reference values and reference limits and that of decision limits. And finally the methods used for determining these limits are not sufficiently defined.

It is now time to examine if the use of reference limits can be improved by making new practical guidelines.

The first step is to better define the knowledge and the use of major sources of variation of biological quantities. Sources of variation could be classified according to different systems proposed in the early 70s by the North American, Scandinavian and French groups. Different classification systems have been proposed.

The first one details the different sources of variation:

A Metrological and pre-metrological
- Intra-individual: including physiological regulatory mechanisms and aging.
- Inter-individual: all variations observed within a population

The second takes into account:

B. Exogenous or endogenous factors
- Genetic or acquired factors
- Metabolic factors and regulation
There is no comprehensive list of factors. Each quantity may be influenced by one or many factors. Table 1 proposes for discussion a list of factors that may affect biological quantities.

Methods to determine biological variability have evolved from the empirical approach of comparing population means or medians with parameters of a control population, to the multiple regression analysis of all factors studied. It is the responsibility of clinical chemists to consider all pertinent sources of variation for a given quantity; this requires knowledge of physiology and pathophysiology as well as potential environmental factors. Depending on the magnitude of their effect, factors should be considered on the basis of their clinical significance.

Special emphasis should be put on variability as a function of age. Until recently reference values for older age groups were not produced, mainly because of the multiple medication status of these groups. Nowadays, with longer life expectation and improvement of the global health status of the elderly, it is becoming necessary to produce reference values for elderly people.

**Producing reference values for the elderly is challenging.**

How to differentiate a physiologic variation due to age from one due to pathologic aging process? Is the classical approach to reference values production still applicable? The concept of healthy elderly is not clearly defined. Many biological, physiological and psychological criteria remain to be defined. Should medication be taken into consideration? To what extent? Should chronic benign conditions be accepted? Should reference values be produced for those elderly defined to be in an acceptable state of health by clinicians? Should reference values be produced not only for “supposed” healthy people according to idealistic criteria, but also for some non fatal disease groups?

Defining preventive health strategies may lead to modification of the original concept of reference values. People do live longer and healthier as a result of better medical care and appropriate medication, e.g. women on hormone replacement therapy have less osteoporosis. Reference values should be available for post-menopausal women with and without HRT. The same would probably apply to normotensive people with and without antihypertensive medication. The subject of elderly reference values is a moving target and should be reexamined periodically to adjust if judged necessary.

Asymmetry, bimodality of distributions and the presence of outliers will be more frequent as a result of heterogeneous populations. Hence, quantiles 10, 20, 50, 80, 90, 95, 97.5 would probably better describe the distributions than the traditional central 95% interval.
Coming back to a first practical guideline

Between the different biological variations factors that affect the value of a biological quantity, only those with clinical significant impact should be given and their effect quantified. They can be appreciated by analyses of variance followed by multiple regression analyses or available in the literature. In this last case the quality of the data must be carefully checked. In this category, the most important factors of biological variation must be documented such as age, gender, overweight, hormonal status, pregnancy, pill. The others should be collected separately and made available through publications including electronically (2). Genetic or geographical variations, environmental factors (ethanol and tobacco consumption, drugs, diet, etc.) must be included if necessary. Both significant and non-significant factors of biological variation should be listed. The group of experts should define the criteria for the selection of the reference individuals for each biological quantity taking this knowledge into account.

Bibliography


Table 1: Biological variation factors

<table>
<thead>
<tr>
<th>Age</th>
<th>Stress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Exposure to light</td>
</tr>
<tr>
<td>Menarche</td>
<td>Bed rest</td>
</tr>
<tr>
<td>Puberty</td>
<td>Cold</td>
</tr>
<tr>
<td>Menstrual cycle</td>
<td>Fasting</td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Nutrition deficiencies</td>
</tr>
<tr>
<td>Post-partum</td>
<td>Vegetarians</td>
</tr>
<tr>
<td>Lactation</td>
<td>Vitamin deficiencies</td>
</tr>
<tr>
<td>Menopause</td>
<td>Xenobiotics</td>
</tr>
<tr>
<td>Morphometry</td>
<td>Blood pressure</td>
</tr>
<tr>
<td>Ethanol consumption</td>
<td>Polymorphism</td>
</tr>
</tbody>
</table>
Coffee consumption	Ethnic factors
Tobacco consumption	Blood groups
Muscular exercise	Geographical variations

Intra-individual variation

Citació recomanada per a aquest document: