Tidsskriftet Tidsskrift for Den norske legeforening

Paediatric reference intervals – an update

FROM THE LABORATORY

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Children are not small adults, including when it comes to reference intervals. As reference intervals can vary considerably with age, sex and stage of development, it is important to use the correct reference intervals and decision limits in order to ensure optimal diagnostics. Norway's national user manual in clinical chemistry has now been updated to include paediatric reference intervals.

The greatest changes in biochemical analytes occur during the neonatal period, in infancy and during puberty. In the first 3–4 months after birth, haematological parameters change considerably. Fetal haemoglobin is replaced by adult haemoglobin, and large fetal erythrocytes are replaced by small erythrocytes, which gradually increase in size until puberty. Infants have high creatinine concentrations in the first weeks of life, followed by nadir values at 2–7 months and then gradually rising concentrations due to increased muscle mass (1).

Bone growth is pronounced in the first years of life and during puberty, which is reflected in the large fluctuations in the concentration of alkaline phosphatase (Figure 1) (2). Maturation of the adrenal cortex and gonadal function leads to major hormonal changes during puberty. The onset of puberty varies, and a child's level of development must therefore be taken into account when assessing reference intervals for several analytes.

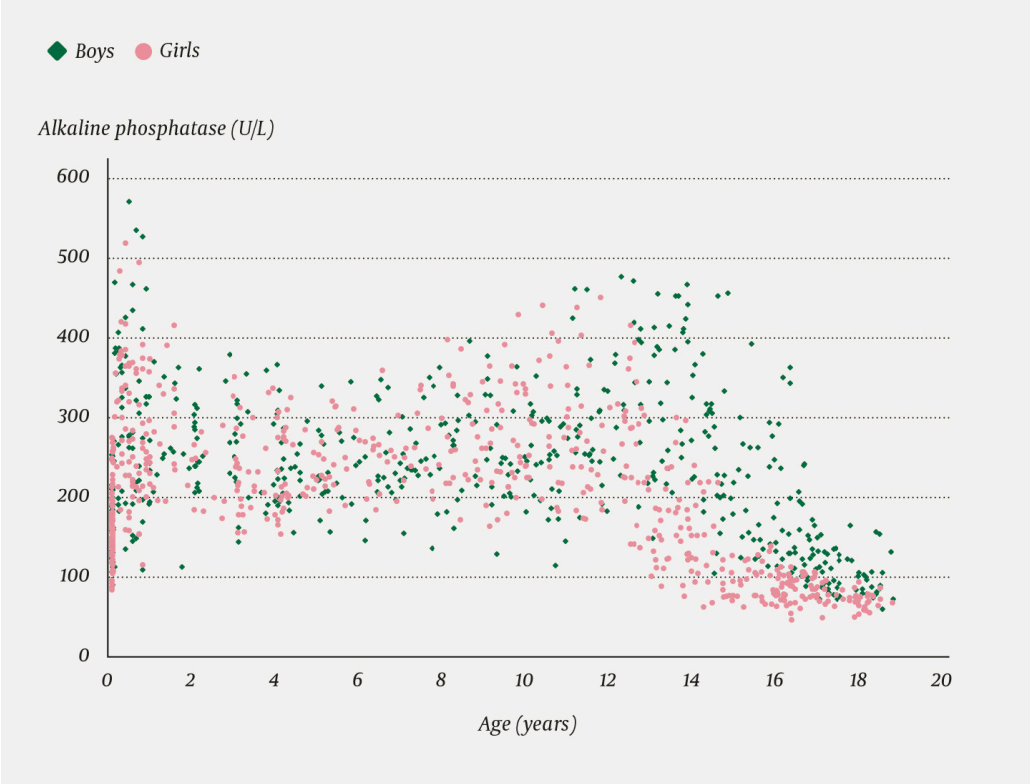

Figure 1 Change in serum concentration of alkaline phosphatase by age. Reproduced with permission (2).

Nordic collaboration

Historically, paediatric reference intervals have largely been based on patient data, but studies have recently been published based on data from healthy children. In a Nordic collaboration, reference intervals for 18 common biochemical analytes were determined in almost 2000 children aged 6 months to 18 years (3). In a multi-centre Canadian collaboration, reference intervals for over 170 analytes were determined in more than 10 000 children aged 0–18 years (4, 5). Similar studies have been conducted in Germany (6) and the United States (7). Reference intervals for endocrine analyses for children aged 6–16 years with associated Tanner staging have been determined in a Norwegian study (8, 9).

In collaboration with the Norwegian Society of Paediatricians, a working group in the Norwegian Society of Medical Biochemistry (NSMB) has updated Norway's national user manual in clinical chemistry (10) to include paediatric reference intervals and clinical decision limits. The reference intervals are mainly based on the aforementioned Nordic, Canadian and Norwegian studies.

For all laboratories

All laboratories should have paediatric reference intervals. As it is ethically problematic as well as time-consuming for laboratories to establish their own intervals, we suggest that the information in the user manual is used instead. Note that analyses may be performed using different methods, and laboratories must consider whether the reference intervals should be changed to align with their own method. In the manual, methodological differences are discussed under the heading *For the laboratory*.

Traditionally, reference intervals describe the central 95 % of reference values in a population. Such reference intervals are only for guidance and must be interpreted with caution. For some analytes, reference intervals can skip age levels, which does not reflect the actual, gradual physiological changes. For many analytes, there are significant individual age variations depending on the growth phase and degree of maturity. Reference intervals for vitamins and minerals will vary in relation to intake and do not indicate optimal status. For such analytes, clinical decision limits have been introduced based on updated literature and the use of own data.

NSMB's working group 'Paediatric reference intervals' consists of Ingrid Hardang, Per Thorsby, Maria Averina, Claus Klingenberg, Thomas Hundhausen, Trine Lauritzen, Ann Helen Kristoffersen, Paul Kjetel Lillemoen, Pétur Júlíusson, André Madsen, Ingrid Alsos Lian and Anne-Lise Bjørke Monsen.

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Publisert: 14 June 2022. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.22.0073