Clinical Biochemistry 47 (2014) 27–32

Contents lists available at ScienceDirect

Clinical Biochemistry

journal homepage: www.elsevier.com/locate/clinbiochem

Redefining normal bone and mineral clinical biochemistry reference intervals for healthy infants in Canada ☆,☆☆

Sina Gallo [a,c], Kathyrn Comeau [a], Atul Sharma [b,d], Catherine A. Vanstone [a], Sherry Agellon [a], John Mitchell [b], Hope A. Weiler [a,1], Celia Rodd [b,d,*,1]

[a] School of Dietetics and Human Nutrition, McGill University, Montréal, Québec H9X 3V9, Canada
[b] McGill University Health Center, Montréal, Québec H3G 1A4, Canada
[c] Nutrition and Food Studies, George Mason University, Fairfax, VA 22030, USA
[d] Winnipeg Children's Hospital, University of Manitoba, Winnipeg, Manitoba R3E 0Z2, Canada

ARTICLE INFO

Article history:
Received 10 April 2014
Received in revised form 12 July 2014
Accepted 15 July 2014
Available online 23 July 2014

Keywords:
Normative
Breastfed
Infants
Minerals
Calcium
Phosphate
Creatinine
Growth

ABSTRACT

Background: Few normative data exist for routine clinical chemistry in healthy term infants, that is, during a time of rapid development. Biochemical markers are significantly affected by these physiological changes and the lack of appropriate reference intervals may impede diagnostics in infants.

Objective: To define reference intervals for calcium, phosphate, creatinine, and alkaline phosphatase in infants from 1 to 12 months of age.

Design and methods: This was an unblinded secondary analysis of 132 breastfeeding infants participating in a vitamin D_3 supplementation trial (400–1600 IU/d) followed prospectively until 1 year of age (NCT00381914). Serial non-fasting capillary and spot urine samples were collected for the measurement of plasma calcium, phosphate, creatinine, and alkaline phosphatase; urinary calcium, phosphate and creatinine (DxC600 Beckman Coulter); and whole-blood ionized calcium (ABL 725 Radiometer). All visits were conducted at McGill University in Montréal, Canada.

Results: All analytes changed significantly over time ($p < 0.05$), but there was no effect of sex. From 1 to 12 months, values decreased for whole-blood ionized calcium; plasma calcium, phosphate, and alkaline phosphatase; and urinary calcium:creatinine. Plasma creatinine increased. For some analytes, particularly calcium and alkaline phosphatase, values were often above the 'typical' adult or older child reference limits. Smoothed centile curves (LMS method) were developed to fill existing gaps in normative data for these analytes.

Conclusions: Most analytes showed a significant change from 1 to 12 months, confirming the need for age-specific reference values. These data can assist in the generation of new reference intervals for healthy term infants and ultimately improve the care of children.

© 2014 The Canadian Society of Clinical Chemists. Published by Elsevier Inc. All rights reserved.

Introduction

Providing standard-of-care health services requires access to laboratory facilities and age- and sex-specific reference intervals [1,2]. Pediatric health care providers have long been disadvantaged relative to adult health care providers because of the relative paucity of norms; data for some age groups – e.g. infants – have been particularly limited even for routine clinical chemistries [2]. Moreover, the biologic samples used to develop reference intervals have often been derived from hospitalized children or leftover material from specific outpatient clinics [3–5].

Ideally, more than 120 specimens are required to construct each confidence reference interval as per the Clinical and Laboratory Standards Institute (CLSI) [6]. Additional information such as ethnicity, age and sex is desirable for association analyses [7]. Because of rapid maturation in the pediatric age range [8], the biochemical analyses are frequently partitioned by age (usually graphically).

Abbreviations: d, day; mo, month; n, number; y, year; 25(OH)D, 25-hydroxyvitamin D; CV, coefficient of variation; CLSI, Clinical and Laboratory Standards Institute; CALIPER, Canadian Laboratory Initiative on PEdiatric Reference Intervals; GAMLSS, Generalized Additive Models for Location, Scale and Shape; SAS, Statistical Analysis System; LMS, lambda–mu–sigma = L curve (Box–Cox power to remove skewness), M curve (median) and S curve (coefficient of variation); LOQ, limit of quantification; WHO, World Health Organization.

☆ Disclosure: HAW is a Canada Research Chair with infrastructure funding from the Canadian Foundation for Innovation.

☆☆ Previous presentations: As a poster at the 2008 Experimental Biology and 2012 Clinic Chemistry meetings.

* Corresponding author at: Section of Pediatric Endocrinology & Metabolism, Winnipeg Children's Hospital, 685 William Avenue, Room FW302, Winnipeg, Manitoba R3E 0Z2, Canada. Fax: +1 204 787 1655.
E-mail address: crodd@hsc.mb.ca (C. Rodd).
[1] Senior authors.

http://dx.doi.org/10.1016/j.clinbiochem.2014.07.012
0009-9120/© 2014 The Canadian Society of Clinical Chemists. Published by Elsevier Inc. All rights reserved.

Often, all infants are grouped as a single category despite infancy being a notable period of growth. The CALIPER group (Canadian Laboratory Initiative on PEdiatric Reference Intervals) [7,9] has helped this field by developing reference intervals for some common pediatric clinical chemistry analytes on at least 2 platforms (Abbott ARCHITECT, Roche Cobas) [7,9]. Although data are available for >2000 pediatric participants (newborn to 18 y), the data are pooled for infants (0–365 d) and the 'n' in this age ranges from ~100 to 250 per analyte. Understandably, partitions in infancy have been difficult to implement given the limited access to samples from healthy individuals. Notwithstanding these major advances, significant lacunae still exist. For example there are few normative data for ionized calcium concentrations between the ages of 7 d and 12 mo of life [10–13].

The objective of this report was to assist in generating normative reference data for healthy infants for several routine analytes, with emphasis on determining whether age-specific partitions were required from 1 to 12 mo of age. Measured values for whole blood ionized calcium; plasma calcium, phosphate, creatinine, and total alkaline phosphatase; and urinary calcium, phosphate and creatinine were tabulated from a cohort of healthy, breastfed, appropriate-for-gestational age infants followed longitudinally and prospectively as part of a vitamin D dose–response trial from 1 to 12 mo of age [14].

Materials and methods

As described in Gallo et al. [14], in a vitamin D_3 dose–response trial (400, 800, 1200 or 1600 IU/d), 132 healthy predominately breastfeeding infants from Montréal, Québec, Canada were recruited between 2007 and 2010 (ClinicalTrials.gov # NCT00381914). All infants were closely monitored by a safety monitoring officer and vitamin D supplementation was stopped if plasma 25(OH)D concentrations exceeded 250 nmol/L and then vitamin D supplements were re-initiated when 25(OH)D was <100 nmol/L (see [14]). Vitamin D supplementation for the 1600 IU/d group was discontinued because of high plasma 25(OH)D on screening, resulting in the lower sample size in this group (see [14]); the data from this group were included in this study. Healthy, term, singleton infants, born appropriate-for-gestational age (between the 5th and the 95th percentile, 2000 Centers for Disease Control growth charts) and breastfeeding (consuming >80% of total milk volume) were included. Infants of mothers with gestational diabetes, hypertension in pregnancy, chronic alcohol use, or malabsorption syndromes were excluded. Serial visits took place at approximately 1, 2, 3, 6, 9 and 12 mo of age. At each visit, weight, length, and head circumference were taken and mothers were asked if they continued to breastfeed. Any breast milk was defined as 'breastfeeding' and a combination of breast-and-formula feeding and/or formula-only feeding were considered as 'mixed/formula feeding'.

Capillary blood samples, in the fed state, were collected at each visit by heel lance or finger prick. Whole blood ionized calcium was analyzed (ABL 725 series blood gas analyzer; Radiometer America) within 4 h of collection at the Montréal Children's Hospital. Blood was centrifuged at 2235 ×*g* for 20 min at 4 °C; plasma total calcium (indirect ion selective electrode method), phosphate (phosphomolybdate method), total alkaline phosphatase (AACC reference method) and creatinine measurements were performed, on the same day within 4 h of collection, using a Beckman Coulter UniCel DxC600 auto-analyzer. Creatinine was initially measured using the Jaffe method and switched to an enzymatic method in June 2009; calibration was traceable to an isotope dilution mass spectrometry (IDMS) reference procedure [15–17]. An equation (pl. creatinine × 1.04 − 20.4) was developed to reconcile differences between the two methods, with r = .99 [15–17]. A spot urine sample was collected for the assessment of calcium, creatinine and phosphate (Beckman Coulter UniCel DxC600). Values below the assay limit of quantification (LOQ) for all analytes were not included [18,19] and all values above the LOQ were reported separately. The Montréal Children's Hospital laboratory participates 3 times per year in a proficiency testing program organized by the Laboratoire de Santé Publique du Québec. For the Radiometer, the intra-individual % CV was <2.2% and the inter-individual % CV was <4.2% based on internal quality controls for ionized calcium. For the Beckman Coulter analyzer, the intra-individual % CV was <3.8% and the inter-individual % CV was <5.5% based on external controls for calcium, phosphate, alkaline phosphatase and creatinine (Bio-Rad Laboratories, Inc.). Remaining plasma was stored frozen at −80 °C for batch analysis of 25-hydroxyvitamin D (25(OH)D) measured using liquid chromatography tandem mass spectrometry (Warnex Bioanalytical Services) [14]. As the primary driver of calcium homeostasis is parathyroid hormone (PTH), samples were batched for analysis using an ELISA (Immutopics International). However, these results are presented elsewhere [14].

Ethics

The original research study was approved by the Institutional Review Board of McGill University and permission for secondary analyses (present study) was approved by McGill, George Mason University, and the University of Manitoba.

Statistical analyses

All analytes are expressed as median and range (minimum, maximum) at each time point. Given the design of the dose–response study, associations with 25(OH)D, time, and sex were explored for each analyte using a mixed effects model with a random subject effect to account for repeated measures over time (Statistical Analysis System, SAS, Proc Mixed). Feeding status (breast vs. mixed/formula feeding) was also explored as a possible covariate although the sample size in the mixed/formula fed group was limited by study design. Regression assumptions for the mixed effects models were checked by standard diagnostic methods. Overall statistical significance was set at $p \leq 0.05$ (two-tailed). Data were analyzed using SAS version 9.2 (SAS Institute Inc., Cary, NC). Reference curves were generated for all analytes using the LMS method [20] in the Generalized Additive Models for Location, Scale and Shape (GAMLSS) [21] statistical package. The LMS method fits a 3 parameter skew normal distribution at each time, with cubic splines used to smooth the resulting curves [20,22]. The 3 parameters represent the median (M), the coefficient of variation (S), and the power in the Box–Cox transformation (L) that vary as a function of age, with centiles calculated using the following formula: $M(1 + L \cdot S \cdot Z)1 / L$ [20,22], where L, M, and S are age-specific and Z is the Z-score that corresponds to a given percentile. Model fit was verified through standard diagnostic procedures and comparison with empiric centiles [23].

Results

Samples from 56 female and 76 male infants were collected prospectively over the first year of life [range 24–390 d]; attrition was 26% (see [14]). Fewer samples were available for some analytes secondary to insufficient volume. Sample sizes ranged from 89 to 132 (Tables 1–2). Demographic characteristics were previously described [14]. In brief, the large majority of parents were white (82% of mothers and 81% of fathers). Infants were all breastfed from birth (receiving 80% of their total needs from breast milk); 88% were still receiving some breast milk to 6 mo and 35% to 12 mo. All infants were healthy and growing: mean weight-for-age and weight-for-length Z-scores at each time point were within ±0.5 Z-score from the WHO growth standard [14].

All plasma analytes had values within the quantification limits of the assay except for creatinine (LOQ = limit of quantification = 7 μmol/L; % < LOQ: 1 mo: 16%, 2 mo: 5%, 3 mo: 8%, 6 mo: 6%, 9 mo: 2% and 12 mo: 0%, which were not included in analyses). Similarly, urinary samples with values for calcium < LOQ (<0.5 nmol/L) or creatinine

Download English Version:

https://daneshyari.com/en/article/1969088

Download Persian Version:

https://daneshyari.com/article/1969088

Daneshyari.com