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The Physiologic Development of Fetuin-A Serum Concentrations in Children

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ABSTRACT: Fetuin-A prevents tissue calcification by forming soluble complexes with calcium and phosphate. A pathological depletion of serum fetuin-A has been observed in children on dialysis or after renal transplantation but knowledge on physiologic age-related changes in serum fetuin-A is limited. We prospectively evaluated serum fetuin-A in 133 infants and children, ranging from very low birth weight infants to adolescents. Highest serum fetuin-A levels were present between 23 and 30 wk of gestation (1 ± 0.33 mg/mL). Thereafter, the values decreased. This decrease was linked to biological rather than chronological age. At 32 to 36 and 37 to 40 wk of gestation, the serum fetuin-A concentration was 0.63 ± 0.26 and 0.63 ± 0.21 mg/mL, respectively. Thereafter, the concentrations remained stable until adolescence at 0.58 ± 0.12 mg/mL. Intercurrent infections were associated with a transient decrease of serum fetuin-A levels. The high serum fetuin-A concentrations in preterm children suggest that fetuin-A is of high physiologic impact for the fetal and the preterm-born organism, showing extensive tissue formation. This might point to a new mechanism contributing to organ damage in these patients, comparable with children on dialysis. **(*Pediatr Res* 66: 660–664, 2009)**

Fetuin-A is a serum protein that stabilizes calcium–phosphate in a complex, which enables its clearing by the phagocytic system (1,2). It is constitutively produced in the liver (3) and down-regulated during the acute phase (4). In healthy adults, serum fetuin-A ranges between 0.4 and 1 mg/mL serum, dominating the alpha-2 band on serum electrophoresis (5).

The *in vivo* function of fetuin-A was deduced by gene knockout in mice (6). These animals develop widespread soft tissue calcifications with renal failure and myocardial dysfunction (7–9). Fetuin-A is, therefore, assumed to act as a mineral chaperon, primarily preventing pathological mineralization and calcification (7,10). Further functions may include modulation of TGF-beta activities (11) and insulin signaling (12). Furthermore, crude preparations of fetuin-A have multiple activities in cell culture, many of which may be due to fetuin-A-bound molecules (13).

According to animal studies, fetuin-A may attain the highest serum concentration during fetal life (14), accumulating in regions of increased tissue turn over, such as the brain, the immune, and the hematopoietic system of the intrauterine-developing organism (15,16). It is abundant in the fetal bovine serum and also shows high concentrations in cattle and pigs (17). In the fetal pig, high fetuin-A serum concentrations, combined with low albumin-, low transferrin-, and high alpha-1 (acid) glycoprotein concentrations, may provide a protective constellation for the growing organism (18). After the high prenatal serum fetuin-A, a decrease with age was reported (15,16,19).

Compared with animal studies, published data on fetuin-A in the fetus and in children have remained contradictory (Table 1). Studies on the fetal plasma suggest that intrauterine serum fetuin-A may range widely between adult levels and very high concentrations (2.3 mg/mL maximum). Comparable heterogeneous findings have also been reported for neonates born at term (17,20,21). For children between 5 and 18 y, an increase in serum fetuin-A with age has been suggested (22,23). Although low serum fetuin-A have been reported in infected and malnourished children (24), defective glycosylation of fetuin-A was found in neonates with intrauterine growth restriction (25). Total fetuin-A concentrations, however, may be similar in healthy and growth-restricted term-born neonates (20).

Complete congenital fetuin-A deficiency is unknown in humans, but secondary fetuin-A deficiency in adults on dialysis is associated with increased mortality and morbidity as well as an increased small vessel calcification (9,26). This deficiency may, in part, be caused by subchronic inflammation associated with dialysis (27). Similarly, children on dialysis with cardiac calcifications have lower serum fetuin-A than those without (22). In children with renal transplantation, low serum fetuin-A were found although no correlation between serum fetuin-A and carotid artery vascular properties was established (28).

To specify the role of fetuin-A in distinct childhood diseases, more detailed knowledge on its physiologic concentration is required. Therefore, this prospective study aimed at studying the physiologic course of serum fetuin-A in children of different ages. To assess the potential impact of low serum fetuin-A in preterm infants, a group of very low birth weight infants was included and studied serially for several weeks.

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Abbreviations: CRP, C-reactive protein; **PVL,** periventricular leukomalacia

Table 1. *Literature data on fetuin-A serum concentrations in children of different ages*

Source	*N*	Age (mean ± SD)	Age range	Serum fetuin-A (mg/mL) (mean ± SD)	Additional remarks	Method used for analysis
Dziegielewska *et al.* (17)	6		14–19 wk	1.43 ± 0.26	Fetal blood	RID
Dziegielewska *et al.* (17)	8		20–3 wk	1.04 ± 0.14	Fetal blood	RID
Dziegielewska *et al.* (17)	6		Neonates	1.11 ± 0.07	Cord blood	RID
Abiodun and Olomu 1991 (21)	21		Neonates	1.06 ± 0.26		RID
Briana *et al.* (20)	20	38.4 ± 1 wk		0.42 ± 0.15	Healthy cord blood	ELISA (Biovendor)
Briana *et al.* (20)	20	38.4 ± 1 wk		0.43 ± 0.1	Healthy d 1	ELISA (Biovendor)
Briana *et al.* (20)	20	37.8 ± 1 wk		0.46 ± 0.76	IUGR cord blood	ELISA (Biovendor)
Briana *et al.* (20)	20	37.8 ± 1 wk		0.43 ± 0.12	IUGR d 1	ELISA (Biovendor)
Abiodun and Olomu (24)	16	23 ± 10 mo		0.82 ± 0.15		RID
Marhaug *et al.* (23)	20	Mean 9.3 y	5–12.8 y	0.3 (0.21–0.52)*		ELISA (Epitope)
Van Summeren *et al.* (28)	54	11.9 ± 3 y	6–18 y	0.52 ± 0.09		Nephelometry
Shroff *et al.* (22)	75	12.4 ± 4.1 y	5–18 y	0.41 ± 0.13	Increase with age	ELISA (Epitope)
Ziolkowska *et al.* (31)	43	13.7 ± 4.8 y	4.5–25 y	1.02 ± 0.12		ELISA (Biovendor)
Marhaug *et al.* (23)	24	Mean 14.5 y	14–17 y	0.39 (0.37–0.78)*	Increase with age	ELISA (Epitope)

Median (range).

* IGUR, intrauterine growth retardation; *N*, number of patients; RID, radial immunodiffusion.

PATIENTS AND METHODS

Patients. One hundred thirty-three patients treated at RWTH Aachen University Hospital during a 14-mo period were included prospectively. This included 31 preterm infants born between 23 and 36 completed weeks of gestation, six neonates born between 37 and 41 completed weeks of pregnancy, and 96 children of 3 wk to 17 y (6.3 ± 5.6 y).

For analysis of normal values, specimens were only included when no clinical signs of infections were present and when the C-reactive protein (CRP) serum concentrations were below 10 mg/L. In very low birth weight infants, isolated respiratory distress at birth was not the exclusion criteria. The patients studied after the neonatal period included children admitted for routine diagnostics or elective surgery with no overt infections, no immunologic disease, and no history of organ calcifications. In addition, serial measurements (total = 113; mean = 6 measurements/child) were taken in 18 preterm infants born between 23 and 30 wk of gestation.

All blood samples were drawn in the course of clinically confounded routine diagnostics. The study was approved by the ethics committee of RWTH Aachen University Hospital. Written parental consent was given for all patients.

Methods. Serum samples were snap frozen and stored at −80°C. Serum fetuin-A concentrations were determined as published previously (29,30). In brief, the thawed serum samples were cleared by centrifugation (1 h, 4°C, 14000 × g). Ten microliter of the interface was added to 30-μL dilution buffer (S2005, DAKO) and vortexed. Ten microliter of the resulting solution was added to 20 μL of diluted rabbit anti-fetuin-A antibody (Dade Behring, Marburg, Germany) and 200 μL of reaction buffer (S2006; DAKO). The samples were analyzed using a Minineph nephelometer (The Binding Site, Heidelberg, Germany). All samples were studied in triplicate and accepted only if the SD was within 10%. The mean was used for further data analysis. A standard curve was established with purified human fetuin-A (Dade Behring, Marburg; >98% purity). Pooled serum from five healthy adults served as an external control and was measured every 10 samples.

Statistics. Data are commonly reported as mean ± SD. Statistical differences between groups were assessed by the unpaired *t* test. Coefficients of determination were calculated using EXCEL software (Microsoft).

RESULTS

Fetuin-A concentrations in preterm and term neonates. Serum fetuin-A measured immediately after the birth may reflect intrauterine levels. Therefore, serum fetuin-A was measured in 32 neonates within 4 days (0.8 ± 1.2 d) after birth. The children born after 24 to 40 completed weeks of pregnancy showed CRP values below 10 mg/L and had no clinical signs of infections. Highest serum fetuin-A was found among the 13 preterm neonates of 24 to 30 wk of gestation, displaying fetuin-A values of 1 ± 0.33 mg/mL. Serum fetuin-A concentrations above 1 mg/mL were only recorded in this patient group. Children born between 32 to 36 ($n = 13$) and 37 to 40 ($n = 6$) weeks of pregnancy, respectively, showed serum fetuin-A of 0.63 ± 0.26 and 0.63 ± 0.21 mg/mL, respectively (Fig. 1).

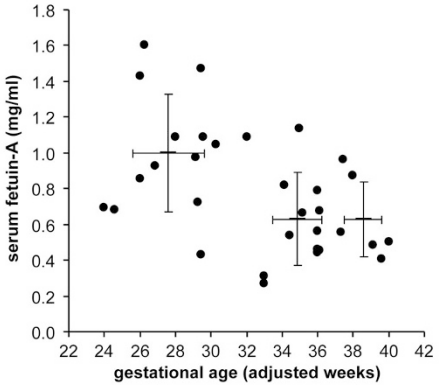

Figure 1. As an estimate of intrauterine concentrations, serum fetuin-A levels of 32 newborns born between 24 and 40 completed weeks of pregnancy, not showing any signs of infections and tested within 4 days after birth, are summarized (24–30 wk, $n = 13$; 32–36 wk, $n = 13$; >36 wk, $n = 6$). Highest serum fetuin-A was recorded among children born between 24 and 30 completed weeks of pregnancy compared with children born later ($p < 0.001$, *t* test). Each dot represents one different patient. The bars represent means and standard deviations for serum fetuin-A levels and adjusted gestational ages of the three patient groups.

Longitudinal fetuin-A studies in children born between 23 and 30 wk of pregnancy. To study the longitudinal development of serum fetuin-A in preterm children, 18 children born between 23 and 30 completed weeks of pregnancy (including the above-mentioned 13 children) were studied. Only samples obtained at times without clinical or laboratory signs of acute infections were included. Finally, 113 measurements were available for analysis. As already shown earlier, serum fetuin-A above 1 mg/mL was only recorded in samples taken before an adjusted gestational age of 37 wk (Fig. 2). Thereafter, serum fetuin-A reached adult levels. Hereby, intraindividual changes of serum fetuin-A in preterm children followed a similar time course as suggested by the early postpartal

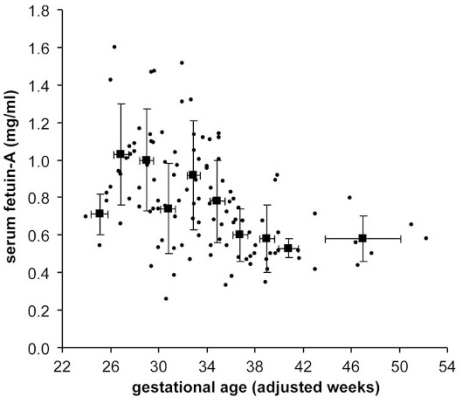

Figure 2. Longitudinal development of serum fetuin-A levels in preterm children. To provide an impression on time-related changes of serum fetuin-A in preterm children, serum fetuin-A concentrations were determined in 113 samples serially collected from 18 children born between 23 and 30 wk of gestation, at times with no acute infection. The ages were adjusted for biological age. The dots display distinct measurements, whereas the bars indicate the means and standard deviations for serum fetuin-A and age-adjusted gestational ages at distinct age groups using the same data. The time course of serum fetuin-A in these children closely mirrors the results obtained during early postpartal measurements displayed in Figure 1. Again, serum fetuin-A above 1 mg/mL is only present in premature infants. Note that individual serum fetuin-A levels of each child decreased slowly and the curves of the 18 children fitted better after adjustment for gestational age than for the time after birth suggesting that the development of serum fetuin-A levels is related to biological age.

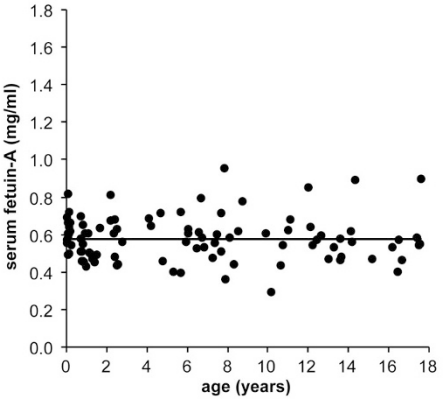

Figure 3. Age-related changes of fetuin-A serum concentrations during infancy and childhood. Fetuin-A concentrations in 96 children with ages ranging from 3-wk-old neonates to 17-y-old adolescents. During this time, fetuin-A concentrations remain stable at 0.58 ± 0.12 mg/mL (coefficient of determination = $R^2 = 0.000001$; R = Pearson's product-moment correlation coefficient).

measurements (Fig. 1), again suggesting that serum fetuin-A concentrations are closely linked to biological age.

Fetuin-A serum concentrations are stable between 3 wk and 17 y of life. Fetuin-A concentrations were also studied in 96 children and adolescents between 3 wk and 17 y (Fig. 3). In contrast to previous studies, serum fetuin-A remained stable during the whole time period (0.58 ± 0.12 mg/mL).

Intercurrent infections cause a decrease of fetuin-A serum concentrations. As fetuin-A is a negative acute phase protein, its serum concentration may decrease during intercurrent infections. Therefore, serum fetuin-A levels obtained at times of intercurrent infections in preterm children ($n = 22$), as suggested by increased CRP concentrations (≥10 mg/L), were compared with the data displayed in Figure 2. Overall, independently from adjusted gestational age, values obtained at times of infections were significantly lower than values obtained at times without (0.58 ± 0.21 mg/mL, $n = 22$ *versus* 0.78 ± 0.28 mg/mL, $n = 113$; $p < 0.002$, t test). As further suggested from Figure 4, the most profound infection-related decrease may occur in children below 34 adjusted weeks of gestation. To further illustrate this relationship, Figure 5 displays the serum fetuin-A concentrations in a patient with two episodes of intercurrent infections; both episodes leading to a transient decrease of fetuin-A.

Serum fetuin-A concentrations and total serum protein concentrations are not related. Low total serum protein concentrations are frequent in preterm children and may be related to immature metabolic functions. Total serum protein concentrations routinely determined in 108 samples out of the

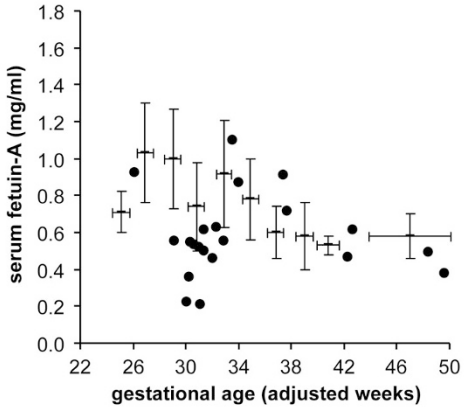

Figure 4. Serum fetuin-A obtained during serial measurements in preterm children born between 23 and 30 wk of pregnancy. Values obtained at times without infection (113 measurements in 18 children; data transferred from Fig. 2) are indicated by vertical and horizontal bars. Values obtained at times of infection are indicated by single dots (22 measurements in nine children, 0.58 ± 0.21 mg fetuin-A/mL). Values obtained at times of infections are significantly lower than values obtained at times without. This effect may be most prominent in children below 34 adjusted weeks of gestation ($p < 0.002$; t test).

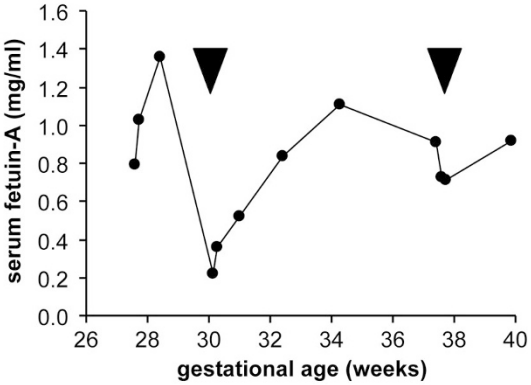

Figure 5. Longitudinal analysis of fetuin-A serum concentrations in a child born at 26 completed weeks of pregnancy suffering two infectious episodes at 30 and 38 adjusted weeks of gestational age, respectively (*arrows*). During the infections, serum fetuin-A decreased rapidly but reincreased during follow-up.

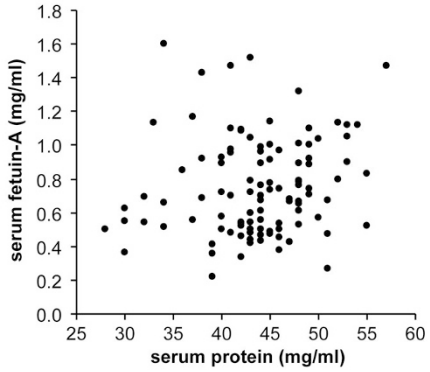

Figure 6. Comparison of paired fetuin-A/total serum protein concentrations in 108 samples deriving from 18 preterm children born between 23 and 30 wk of gestation shows no significant relationship, indicating that serum fetuin-A is no simple function of total serum protein (coefficient of determination = $R^2 = 0.027$; R = Pearson's product-moment correlation coefficient).

above-mentioned 18 preterm children born between 23 and 30 wk of pregnancy were compared with the respective serum fetuin-A. However, no correlation was found (Fig. 6), suggesting that fetuin-A is regulated independently from total serum protein concentrations. In a similar fashion, no correlation between total serum protein and serum fetuin-A was found in children studied after the neonatal period (data not shown).

DISCUSSION

This study delineates the physiologic changes of serum fetuin-A in children including the complete pediatric age spectrum from very low birth weight infants to adolescents. Our main results were that immature preterm infants show the highest serum fetuin-A, frequently exceeding 1 mg/mL (Figs. 1 and 2). The ensuing decrease to adult values seems to be closely related to the increase in biological age, suggesting a slow maturation process rather than a rapid adaptation to the extrauterine environment. Term-born children, in contrast, do already show similar serum fetuin-A as older children who, in turn, show stable values between 1 and 17 y of life.

Our findings on preterm infants complement previously published data deriving from studies on fetuses of 14 to 37 wk of gestation, showing maximum serum fetuin-A of 2.4 mg/mL (Table 1) (17). These findings, however, were based on few samples, no clear relationship between gestational age and serum fetuin-A was established and it had remained uncertain whether low fetuin-A concentrations in distinct samples were due to an acute phase reaction (17). The data reported here confirm high intrauterine serum fetuin-A and further demonstrate that serum fetuin-A is not continuously increased during pregnancy but decreases with gestational age.

Previously published studies reported that serum fetuin-A in later childhood were higher than (31) or similar to adult levels (22,23,28), some also suggesting a slight increase with age (22,23). Among healthy newborns, marked differences in fetuin-A concentrations were found (17,20,21) (Table 1). Two factors may explain this inconsistency: inadvertent measurement of acute phase serum samples and assay variations. To rule out an acute phase reaction, we strictly excluded children with a history of infectious disease and/or increased CRP concentrations. This may have especially affected the group of young children in whom frequent recurrent infections may result in lower values.

Assay variation is currently a serious shortcoming of fetuin-A serum level measurements, so that at this current time, serum measurements of fetuin-A can only be compared in relative, not in absolute terms. Even the results between studies applying the same test system in the same age group may differ markedly (Table 1). Moreover, older assays based on radial immunodiffusion or rocket immunoelectrophoresis showed a high specificity but lower precision than ELISA systems. This all may have contributed to very heterogeneous findings (Table 1) (17,20,21). We have used ELISA (26) and nephelometry (30) in several studies with a total of well more than 1500 samples with replicate variation and interassay variation of a maximum of 10%. According to our experience, to compensate for the problems related to assay variation, control sera for interlaboratory comparisons would be highly desirable.

Nevertheless, the base levels of serum fetuin-A determined in this and in previous studies consistently showed that the highest fetuin-A serum concentrations were always measured during fetal life (14,17). It is reasonable, therefore, to assume that high fetuin-A levels are essential during these periods of extensive tissue formation and remodeling.

Importantly, the continuous intrauterine decrease of fetuin-A serum concentrations to adult levels and the finding of similarly low fetuin-A concentrations from early infancy to adulthood are not necessarily related to a decrease of fetuin-A synthesis. Bone mineralization starts *in utero* and in parallel to these mineralization processes intrauterine serum calcium concentrations continuously increase during the last trimester, leading to highest serum calcium concentrations immediately before birth (32). Soon after birth, during the first year of life, characterized by rapid bone growth and mineralization, the human body shows the fastest increase of calcium content in relation to body size compared with any other year of life and the calcium $\times$ phosphate product reaches highest values especially during the first 6 months of life. Simultaneously, infants show the lowest urinary calcium excretion, the highest daily net calcium absorption, and the highest calcium retention when calculating uptake *versus* excretion (33). During this time, fetuin-A may be critically required as a mineral chaperone, not only to counteract pathological mineralization but also to foster physiologic bone mineralization while being incorporated into the new bone. In a comparable fashion, fetuin-A consumption has been reported for diseases associated with increased bone metabolism such as Paget's disease or bone neoplasms (34,35).

As already known from older children and adults, intercurrent infections also lead to an acute phase reaction with a decrease of serum fetuin-A concentrations in preterm children (Figs. 4 and 5). At present, it remains speculative whether this decrease might be harmful or protective for the growing organism. In our opinion, as hypothesized below for the pathogenesis of periventricular leukomalacia (PVL), a contribution to organ damage seems likely. The crucial event in the development of PVL is the destruction of oligodendrocytes of

the periventricular white matter. Oligodendrocytes derived from the immature brain express calcium-permeable AMPA/kainate receptors which, on oxygen-glucose deprivation and glutamate stimulation, mediate strong, sustained, and deleterious calcium influx into the cell (36). In a similar fashion, exposure of the immature brain to lipopolysaccharide derived from bacterial pathogens also causes a delayed and lethal rise of the intracellular calcium concentration (37). This increase of intracellular calcium concentration may activate various enzymes (phospholipases, proteases, and endonucleases), leading to apoptotic and/or necrotic cell death (38). For oligodendrocytes, the resulting damage can be prevented *in vitro* by decreasing the extracellular calcium concentration, which underlines the central role of calcium in this process and suggests that changes in the extracellular Ca-binding capacity might influence the extent of Ca-mediated tissue damage. Considering the high expression of fetuin-A in the developing brain (15,16), several potential connections between the pathogenesis of PVL and fetuin-A metabolism can be depicted. First, fetuin-A might counteract the noxious consequences of calcium influx into damaged cells by its Ca-binding ability, thus reducing the extent of oligodendrocyte death. Second, intercurrent infections with release of lipopolysaccharide might not only directly affect oligodendrocyte survival but also lead to a decrease of protective serum fetuin-A. Third, fetuin-A with its binding capability for TGF-beta superfamily members might contribute to the regulation or rather the bioavailability of TGF-beta, which is expressed in astrocytes during the reparative stage of PVL (39).

Fetuin-A seems to be an underestimated but emerging molecule. Its contribution to organ growth, function, and dysfunction between preterm birth and adolescence warrants further research.

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