The effects of postdischarge nutrition on growth, body composition, and bone development of preterm infants

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2014

document version
Publisher's PDF, also known as Version of record

SUMMARY

During the extrauterine third trimester, preterm infants develop nutritional deficits as postnatal morbidity increases nutritional demands, which are not reached because of limited feeding possibilities. Consequently, many preterm infants experience extrauterine growth restriction (EUGR) followed by accelerated growth. Nutritional deficits may also lead to decreased bone accretion, micronutrient deficiencies, and neurodevelopmental impairment. The quantity and quality of prenatal and postnatal growth of preterm infants are important with respect to metabolic and cardiovascular consequences in later life. In-hospital feeding regimens aim to prevent cumulative postnatal nutritional deficits in preterm infants. To date, however, in-hospital regimens cannot fully prevent cumulative nutritional deficits or EUGR in preterm infants. Therefore, specialized postdischarge nutrition has a key role in the nutritional management of preterm infants after discharge to improve growth and bone accretion and to limit fat accumulation, which is associated with long-term cardiovascular and metabolic consequences. The background of this thesis is further addressed in **Chapter 1**.

This thesis is based on a single-blinded randomized controlled trial in 152 preterm infants that compared the effects of an isocaloric, protein- and mineral enriched postdischarge formula (PDF), a standard term formula (TF), and human milk (HM) on growth, body composition, bone accretion, and micronutrient status between term age and six months corrected age (CA). **Chapter 2** describes the study design and the main results of the randomized controlled trial. In short, preterm infants fed PDF had higher protein intake and similar growth with less fat accumulation compared to those fed TF during the first half of infancy. This thesis evaluates the effects of prenatal growth, early postnatal growth, and postdischarge nutrition on growth, body composition, and bone accretion of preterm infants during the first half of infancy, as stated in **Chapter 2**.

The first part of this thesis focuses on postnatal growth regulation and on the effects of prenatal growth and early postnatal growth on body composition and bone accretion of preterm infants. **Chapter 3** demonstrates that insulin-like growth factor type I (IGF-I) and insulin are important for growth regulation of preterm infants during the first six months post-term, independent of nutritional intake. In addition, the lack of association between IGF-I and insulin at six months CA suggests that growth regulation shifts towards growth hormone (GH) dependency at six months CA due to a gradual maturation of the GH/IGF-I axis.

Prenatal growth and early postnatal growth are important for body composition and bone accretion. **Chapter 4** reports that small-for-gestational-age (SGA) preterm infants and preterm infants with EUGR before term age (early EUGR) remained smaller and had

a lower percentage of body fat during the first six months post-term, despite increased relative growth and higher energy and macronutrient intakes. It might be hypothesized that accelerated infant growth without increased adiposity favors later metabolic health. However, the optimal nutritional requirements of preterm infants needed to achieve accelerated growth without excessive fat deposition have to be elucidated.

Chapter 5 describes that SGA preterm infants had lower gain in bone mineral content (BMC) during the first six months post-term, independent of gain in body size. In addition, **Chapter 6** shows that SGA preterm infants had higher collagen type I synthesis during the first half of infancy, which may reflect increased relative growth. Although collagen type I is predominantly found in bone matrix, higher collagen type I synthesis did not lead to increased gain in BMC in SGA preterm infants. This may be explained by insufficient bone mineralization. Since the lower bone mass of SGA preterm infants is a risk factor for osteoporosis, it is important to focus on nutritional interventions, for example with calcium, phosphorus, and vitamin D, that may stimulate bone accretion in these infants.

The second part of this thesis focuses on the effects of postdischarge nutrition on bone accretion, growth, and micronutrient status. **Chapter 7** describes that PDF enhanced gain in BMC of preterm infants during the first six months post-term, independent of gain in weight and length. Higher BMC of preterm infants during infancy, as a result of PDF, may track to higher adult bone mass, which decreases the risk of osteoporosis in later life.

Chapter 8 relates growth of preterm infants to long-chain polyunsaturated fatty acid (LC-PUFA) levels, namely docosahexaenoic acid (DHA) and arachidonic acid (AA). During the first six months post-term, PDF fed preterm infants had higher red blood cell (RBC) DHA and AA concentrations. RBC-DHA was positively associated with gain in weight and length and negatively with gain in head circumference. RBC-AA was positively associated with gain in head circumference and negatively with gain in weight and length. These findings suggest that the dietary supply of DHA and AA by PDF, which was within the targets of term infants fed human milk, may be related to balanced growth of preterm infants.

Chapter 9 shows that, in preterm infants, higher vitamin D intake with an isocaloric, protein- and mineral-enriched PDF resulted in a greater increase in serum 25-hydroxyvitamin D during the first six months post-term. Increase in serum 25-hydroxyvitamin D was positively associated with gain in BMC. This may suggest that, in addition to the availability of dietary protein, calcium, and phosphorus, higher vitamin D intake contributes to increased bone accretion in PDF fed preterm infants.

Chapter 10 demonstrates that iron deficiency was more frequent in preterm infants fed HM compared to those fed iron-fortified formula at three and six months CA. This

may be due to early cessation of additional iron supplementation in HM fed preterm infants. This might suggest that the importance of iron supplementation for HM fed preterm infants during the first half of infancy needs to be brought to the attention of Dutch pediatricians. In accordance with Dutch guidelines, iron-fortified formula appears to suffice to prevent iron deficiency between three and six months CA.

Chapter 11 discusses the growth regulating role of the endocrine factors IGF-I and insulin as well as prenatal growth and early postnatal growth in relation to growth, body composition, and bone accretion of preterm infants during the first half of infancy. In addition, this chapter discusses the benefits of an isocaloric, protein- and mineral-enriched PDF with regard to quantity and quality of growth, bone accretion, LC-PUFA status, and vitamin D status during the first six months post-term. Finally, the implications of the incidence of iron deficiency of preterm infants fed HM and iron-fortified formulae with regard to iron supplementation are discussed. Several suggestions for future research are described with a special interest in the nutritional intake between birth and term age and the long-term outcomes of preterm infants fed the isocaloric, protein- and mineral-enriched PDF described in this thesis.