Infectious disease-related differences in the adaptation of glucose metabolism to fasting in children and the effect of age
Zijlmans, C.W.R.

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Summary

Chapter 1
Chapter 1 provides a short introduction to this thesis. Hypoglycemia is a common and serious complication in young children under five years of age during fasting and severe illness and it predicts mortality. The mortality rate increases four- to six-fold in young children with infectious disease complicated by hypoglycemia and children under three years of age are particularly at risk. Available data on glucose kinetics in children, with fasting, young age and infectious disease as well recognized risk factors for the occurrence hypoglycemia, are discussed resulting in the research questions that are addressed in this thesis. Furthermore the currently available methods to quantify glucose kinetics in children that are used in this thesis are described.

Chapter 2
In chapter 2 the scarce published data on the effect of age and fasting duration on glucose kinetics both in healthy children and in children with infectious diseases are reviewed. Differences between adults and children are addressed, since glucose kinetics are regulated differently in children than in adults. It is stressed that data are limited and therefore, in order to understand and thereby being able to anticipate on the occurrence of hypoglycemia in children, further research on glucose kinetics in this age group is required.

Chapter 3
Hypoglycemia is considered a major outcome predictor in children with falciparum malaria and it is particularly common in young children below the age of 3 years. Although hypoglycemia primarily is found in children with severe malaria, the risk for hypoglycemia in children with non-severe malaria may be increased in the presence of other risk factors such as prolonged fasting and young age. In chapter 3 glucose kinetics are measured in seventeen young (< 3 years of age) children and compared with seven older (3-5 years of age) children with uncomplicated malaria after an 8 hour controlled fast. Plasma glucose concentration was lower in the group of young children than in the older children. There were no differences in endogenous glucose production (EGP) and gluconeogenesis between the groups. These data confirm the higher risk of hypoglycemia in young children with uncomplicated malaria during an 8 hour fast. Since EGP was not impaired after such a fasting period, it is concluded that older children are better capable of reducing glucose utilization.

Chapter 4
In chapter 4 the influence of severity of infection and prolonged fasting on glucose metabolism in children 1-5 years of age with malaria is studied. Plasma glucose
concentration, EGP and gluconeogenesis were measured in 12 children with severe malaria and compared with 16 children with non-severe malaria during a 16 hour controlled fast. Glucose concentration and EGP were comparable after 8 hours of fasting and decreased in both groups with an extension of the fast up to 16 hours. Glucose concentration decreased faster in the non-severe group than in the severe group. The decrease in EGP was not different between groups. These findings confirm that prolonged fasting predisposes for hypoglycemia in young children with falciparum malaria. Contrary to the general opinion, hypoglycemia due to fasting develops later in young children with severe malaria than in children with non-severe malaria. This is most likely due to a difference in peripheral uptake of glucose, indicating that children with severe malaria possibly are more insulin resistant than children with non-severe malaria.

Chapter 5

In chapter 5 a similar study design as in chapter 4 was applied to measure the influence of prolonged fasting and age in children with severe pneumonia. Plasma glucose concentration, EGP and gluconeogenesis were measured in 12 children with severe pneumonia, 6 young children (< 3 years) and 6 older children (3-5 years), during a 16 hour controlled fast. On admission glucose concentration was comparable in both groups and decreased during the first 8 hours of fasting in the young children only. EGP was comparable in both groups. Between 8 and 16 hours of fasting glucose concentration and EGP decreased comparably in both groups. Gluconeogenesis decreased in young children but not in the older children. It is concluded that during fasting children below 3 years of age with severe pneumonia initially have a higher risk for developing hypoglycemia than children 3-5 years of age in spite of high plasma concentrations of glucoregulatory hormones and free fatty acids. The age difference in the rate of decline of plasma glucose exists only in the early few hours of the fast indicating that glucose metabolism in children younger than 3 years of age with severe pneumonia adapts adequately albeit slower to fasting than in older children. Like in malaria fasting predisposes to hypoglycemia in children with severe pneumonia, but its mechanism differs from that in malaria.

Chapter 6

Prolonged fasting is an important factor in the induction of hypoglycemia in children with malaria or pneumonia, and young children are more at risk than older children. Impaired EGP due to smaller liver glycogen stores in young children is presumed to be the underlying cause. To be able to stimulate glycogenolysis sufficient amounts of glycogen are needed. The change in EGP induced by a glucagon bolus is considered to be an indicator of glycogen content. In chapter 6 the effect of a bolus glucagon on EGP and plasma glucose concentration is measured in 18 Surinamese children before and after a bolus glucagon after a 16 hour controlled fast. Six children 1-5 years of age had severe malaria and 12 children had severe pneumonia, 6 were young (1-3 years) and 6 were older (3-5 years). Basal glucose concentration and EGP were higher in children with malaria.
Glucose concentration and EGP increased after glucagon in both groups. The peak in glucose concentration and in EGP was higher in children with malaria. There were no differences between young and older children with pneumonia. These findings suggest that hepatic glycogen stores in children with severe pneumonia are smaller than those in children with severe malaria after a 16-hour fast. Glycogen stores in young and older children with pneumonia are equally diminished.

Chapter 7

Chapter 7 provides a perspective of disease-related differences in the adaptation of glucose metabolism to fasting in young children by combining and comparing data of studies in children with malaria and pneumonia. It is shown that there are age-related differences in the rate of decline of plasma glucose since glucose concentrations decline faster in children under three years of age than in children 3-5 years of age in the early 8 hours of fasting. During prolongation of the fast the risk of hypoglycemia concerns all children 1-5 years of age. The glucoregulatory mechanism used to maintain plasma glucose concentration differs between young and older children. Next, fasting indeed proves an important risk factor for hypoglycemia in children under five years of age. Hypoglycemia in these children is induced by impaired EGP; infectious disease is a risk factor that further compromises EGP. This is in contrast with adults with infectious disease because adults are better capable of maintaining plasma glucose concentration within normal limits by regulation of peripheral glucose uptake. Furthermore, disease-specific differences in the adaptation of glucose metabolism in young fasting children with different infectious diseases are revealed and several assumptions are made as to the underlying cause of these differences. First, disease-related differences in the hormonal response to fasting lead to changes in the contribution of gluconeogenesis and glycogenolysis to EGP. Second, differences in hepatic glycogen content may lead to earlier depletion of glycogen stores in children with certain infectious diseases thereby compromising glycogenolysis and hence EGP. And third, enzymes, transcription factors and cytokines may play a role in regulation of glucose metabolism in young children with infectious disease, its potential influence needs to be investigated in future studies. Finally, recommendations are given for the approach towards all young children with severe infectious illnesses in clinical practice in order to prevent hypoglycemia.