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ScienceDirect
Metabolism Clinical and Experimental 58 (2009) 1356–1365
Metabolism
Clinical and Experimental
www.metabolismjournal.com

Glucose metabolism in children: influence of age, fasting, and infectious diseases

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Received 8 February 2009; accepted 28 April 2009

Abstract

This review describes the occurrence of hypoglycemia in young children as a common and serious complication that needs to be avoided because of the high risk of brain damage and mortality. Young age, fasting, and severe infectious disease are considered important risk factors. The limited data on the effect of these risk factors on glucose metabolism in children are discussed and compared with data on glucose metabolism in adults. The observations discussed may have implications for further research on glucose kinetics in young children with infectious disease.

1. Introduction

Glucose is one of the major fuels to meet the energy requirements of the human body. In the healthy individual, the amount of glucose produced is regulated to the need of the body and more in particular to the need of its major user, the brain. Although the brain can also use lactate, ketone bodies, and certain amino acids, its primary fuel is glucose [1]. During fasting, more than 90% of its energy is provided by glucose, making the brain highly vulnerable to alterations in the plasma glucose level [2]. The child's developing brain is more susceptible to hypoglycemia compared with the adult brain [3-7]. Recurrent hypoglycemia may result in permanent neurologic damage [4-6]. It is therefore imperative to prevent the occurrence of hypoglycemia in children.

In the fasted state, the plasma glucose level is maintained within narrow limits by a delicate balance between endogenous glucose production (EGP) and glucose utilization. The metabolic adaptation of glucose metabolism during fasting differs between children and adults [8]. The traditional concept is that children have a limited tolerance of fasting because glycogen stores are less and therefore they are able to maintain a normal plasma glucose level for a fasting period of 12 hours only [9,10].

Starvation is an uncommon event in a healthy child's life. However, many infectious diseases are characterized by starvation due to disease-induced anorexia as well as by cultural customs and traditional habits in disease [11-13]. Hypoglycemia is a frequent but poorly explored feature of severe infectious diseases in children. This review gives an update of the available data on the effect of age and duration of fasting on glucose kinetics. In addition, differences between adults and children will be addressed to emphasize that data from studies with adult patients cannot be extrapolated to children.

2. Definition of hypoglycemia

The plasma glucose concentration is the resultant of a tightly regulated balance between EGP and glucose utilization. A disturbance in this balance will lead to hyper- or hypoglycemia. Hypoglycemia in children remains one of the most controversial issues with regard to its definition; the mechanism of adverse effect on the brain; and the practical approach to monitoring, management, and treatment [3,14]. The definition of hypoglycemia can be based on clinical manifestations, on the range of glucose values measured in epidemiologic studies, on metabolic and endocrine counter-regulatory responses, or on long-term neurologic outcome; but none has been entirely satisfactory [15]. *Hypoglycemia* in

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doi:10.1016/j.metabol.2009.04.020

neonates is often defined as a plasma glucose concentration less than 2.5 mmol/L (45 mg/dL) [16], whereas in older children, the threshold of 3.0 mmol/L is often used [17]—and in healthy adults, 3.9 mmol/L [18]—based on the initiation of the counterregulatory response [19]. Most studies in infants and children up to 10 years of age performed in tropical settings [16,20-26] use the World health Organization definition of hypoglycemia based on clinical and epidemiologic data: less than 2.2 mmol/L or 40 mg/dL [27].

3. The influence of age and fasting on glucose metabolism in healthy humans

3.1. Hypoglycemia

Age is a risk factor for hypoglycemia. Studies in both healthy [9] and sick children [20,21,25,26,28] suggest a relationship between age and plasma glucose concentration. In healthy children, fasting plasma glucose concentration increases progressively with age. In a study of 28 healthy children, aged 2 to 17 years, plasma glucose concentrations less than 2.7 mmol/L after a 24-hour fast were found only in younger children, whereas values of all children older than 10 years were in the normal adult range [9]. Hypoglycemia is known to be particularly common in the very young children less than the age of 3 years [25,27,28].

Fasting is considered a major risk factor for hypoglycemia in children. Healthy adults are able to maintain normal plasma glucose levels at up to 86 hours of fasting [29]. There are sex-related differences in the metabolic response to fasting in adults: plasma glucose concentrations are lower in women than in men after a 38-hour fast [30]. During a fasting period of only 24 hours, healthy prepubertal children show a significantly steeper decrease in plasma glucose concentration than adults; and they are not able to maintain a plasma glucose concentration greater than 3.0 mmol/L [8,31,32]. Indeed, several studies suggest that fasting is a major factor in the occurrence of hypoglycemia in children and in adults because an association between the occurrence of hypoglycemia and the time since the last meal has been found [20,21,25,26,28,33-35]. These studies indicate that young children probably have a higher risk for developing hypoglycemia when fasting compared with older children and adults.

This conclusion is supported by studies on lipolysis and ketogenesis. During fasting, lipolysis increases, thereby providing the body with alternative fuel and delaying the occurrence of hypoglycemia. This is reflected by elevation of plasma concentrations of free fatty acids and ketone bodies, for example, β-hydroxybutyrate and acetoacetate. After 30 hours of fasting, plasma concentrations of ketone bodies reach levels in children that are seen in women only after a 3-day fast and that are never seen in men [8,31]. This indicates that glycogen stores in children are depleted more rapidly than in adults and thereby their risk of developing hypoglycemia is increased.

In conclusion, young children are more at risk for developing hypoglycemia than older individuals especially in response to fasting.

3.2. Glucose production and utilization

Plasma glucose is derived from exogenous supply, for example, enteral or parenteral nutrition, or from endogenous production. Glucose is produced mainly (~90%) in the liver by gluconeogenesis and glycogenolysis and to a smaller extent (~10%) in the kidney by gluconeogenesis only [36]. Glucose can be oxidized and thereby used for energy supply in various tissues; it can be stored as glycogen in the liver and muscle or stored as triglycerides in adipocytes (Fig. 1).

During fasting, plasma glucose is dependent on glucose production that consists of glycogenolysis, the breakdown of glycogen, and gluconeogenesis, the production of glucose from lactate, glycerol, or several amino acids. Most studies on glucose kinetics in adults are performed after different periods of fasting, up to 86 hours. After an overnight fast, EGP in healthy adults is approximately 11 μmol/kg·min [30,37]. Prolongation of the fasting period from 16 to 22 hours results in a decline in EGP by approximately 20% [38], and it is further reduced to one third after 86 hours [10].

In healthy humans, EGP decreases from infancy toward adulthood [32,39-64] (Table 1). This decrease is related to the ratio of brain weight to body weight. The weight of the human brain increases 3.5-fold from birth (400 g) to adulthood (1400 g), whereas body weight increases more than 20-fold [31], which means a 6-fold decrease in the ratio of brain weight to body weight. Because the brain is a major user of glucose [65], young children meet up to these cerebral demands by producing relatively more glucose in relation to their body weight [17]. This relationship of EGP to brain weight is found to be linear throughout life [32].

Studies on EGP in young healthy children can only be carried out during a restricted fasting period for ethical and safety reasons. The first published data are on 35 children aged between 1 month and 14 years after an 8- to 9-hour fast: mean EGP was 38 ± 1.4 μmol/kg·min in children aged

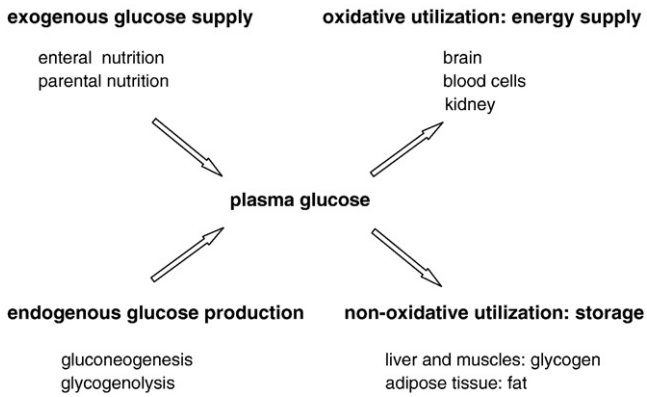

Fig. 1. Glucose production and utilization.

Table 1
Endogenous glucose production in healthy humans in relation to age

	Endogenous glucose production (μmol/kg·min)	References
Preterm infants	6-41	[39-49]
Term infants	8-33	[40,41,50-55]
Children aged 1 month to 6 years	28-40	[32,56]
Children aged 8 to 13 years	18-26	[57-60]
Adults	10-13	[38,61-64]

1 month to 6 years and 29 ± 1.5 μmol/kg·min in children aged 6 to 14 years [32]. Haymond et al [56] reported glucose production rates of 5 healthy children aged 4 to 8 years that declined from 35 to 23 μmol/kg·min after 14 and 30 hours of fasting, respectively.

In conclusion, EGP is approximately 10 to 11 μmol/kg·min in adults after an overnight fast and decreases to minimally 4 μmol/kg·min depending on the duration of the fast. No prolonged fasting studies are performed in children or neonates for obvious ethical reasons. Endogenous glucose production ranges from 23 to 38 μmol/kg·min following short-term fasting studies in infants and children. Age dependency of glucose production is the cause of this wide range.

3.3. Gluconeogenesis

Gluconeogenesis is the process in which glucose molecules are newly formed from lactate, glycerol, or gluconeogenic amino acids, especially alanine and glutamine. In the postabsorptive state, the estimated contribution of the gluconeogenic precursors to total glucose production is approximately 15% for lactate [66-70] and 2% to 4% for glycerol [71], which may increase to 22% after prolonged fasting due to accelerated lipolysis [72]. Alanine accounts for 6% to 12% of glucose production in the postabsorptive state [73-75]; and glutamine, the predominant substrate of gluconeogenesis in the kidney, contributes 5% to 8% [76-78].

Quantifying the contribution of gluconeogenesis to total glucose production is possible with techniques using stable isotopes [79]. Using the deuterated-water method, the contribution of gluconeogenesis to total glucose production in healthy adults has been estimated at 47% after 14 hours, 67% after 22 hours, and 92% after 42 hours of fasting [80]. The absolute rate of gluconeogenesis is more or less constant, indicating that the decrease in EGP is solely due to a decrease in glycogenolysis. In healthy lean and obese prepubertal children and adolescents, gluconeogenesis contributes 50% to 60% to EGP after an overnight fast, comparable with healthy adults [57,59,60].

During the first 86 hours of fasting, EGP is not dependent on precursor supply in healthy adults, unless precursor supply drops more than 50%, a value in general not reached during this period [10]. Studies measuring gluconeogenesis in nonfasted premature infants show that the availability of gluconeogenic substrates is not impaired [81].

In conclusion, during short-term fasting, the contribution of gluconeogenesis to EGP increases and is comparable in adults and older children. Because absolute gluconeogenesis is constant, the decline in EGP is merely caused by decreased glycogenolysis.

3.4. Glycogenolysis and glycogen content

Glycogen is a glucose polymer that is stored mainly in the liver and muscle. The kidney does not store glycogen [82-84]. Glycogenolysis or glycogen breakdown is the process of debranching glucose polymers to glucose. The liver is the major contributor to plasma glucose derived by glycogenolysis because myocytes lack glucose-6-phosphatase that dephosphorylates glucose-6-phosphate, an obligatory conversion enabling glucose to leave the cell and enter the blood [85]. The glucose formed by breakdown of glycogen in muscle tissue is used as fuel supply for the myocyte itself.

Quantification of glycogen stores can be done by liver biopsy [86], but its use in humans for research purposes is limited for practical and ethical reasons. In vivo measurement of liver glycogen content by using ^{13}C–nuclear magnetic resonance spectroscopy (NMR) is an alternative method [87]. Data on the NMR technique in young children are scarce, partially because of its practical limitations since the younger children especially need to be sedated or narcotized. Furthermore, measurements using the NMR technique require equipment that is available in only a few centers in the world [79]. The available data are mainly confined to nonfasted young children with disorders of carbohydrate metabolism [88-90].

A study in prepubertal children with type 1 diabetes mellitus reports that their ability to replenish glycogen stores after an overnight fast was as good as in healthy controls [91]. Direct measurements with ^{13}C -NMR in adults show that liver glycogen stores decrease concomitantly with the decrease in glycogenolysis [87,92]. These data indicate that glycogenolysis and liver glycogen content are correlated during fasting [93]. As mentioned earlier, in healthy adults, EGP decreases approximately 20% between 16 and 22 hours of fasting, which could not be contributed to a decrease in gluconeogenesis [94,95]. The decline is explained by a decrease in glycogenolysis, as was shown in healthy adults using the ^{13}C-NMR technique: glycogenolysis accounts for 45% of total glucose production during the first 6 to 12 hours of fasting [92], for 30% after 23 hours of fasting [96], and for 4% after 68 hours of fasting [87]. A limitation of the NMR method is that it may underestimate the contribution of glycogenolysis to glucose production because hepatic gluconeogenic flux into glycogen and glycogen turnover persist during fasting. Thus, the contribution of glycogenolysis to glucose production is greater than the measured net glycogen loss [97].

Because the liver biopsy and NMR technique cannot readily be used in children, data on liver glycogen and glycogenolysis in children have to be derived from indirect sources. A noninvasive approach to test the ability to release glucose from glycogen stores in young children is to measure the increase in EGP and plasma glucose concentration after a bolus glucagon, a method that is often used in clinical practice [98-101]. In adults, the response of EGP to a glucagon bolus is considered an indicator of glycogen content. A study measured the response of plasma glucose concentration to a glucagon bolus in healthy children aged 2 to 6 years after a 24-hour fast and showed that an increase in plasma glucose concentration of at least 50% in 30 minutes after the glucagon bolus is considered normal [102]. However, these results have to be interpreted with caution because a subnormal response of plasma glucose concentration to glucagon is not always indicative of impaired glycogenolysis. Because a change in the plasma glucose concentration is not necessarily a good parameter for a change in EGP, more insight in glucose kinetics must be obtained by combining the glucagon test with stable isotope studies [103]. This technique was used to measure EGP in response to glucagon in (preterm) infants [104-107] and in adults [97,108-110], showing a 4.5- and 9-fold increase in EGP, respectively. In children, merely case reports have been published on this subject [111,112].

In conclusion, measurements of glycogenolysis and glycogen stores in adults indicate that glycogenolysis and liver glycogen content are correlated during fasting. The decline in EGP during fasting is explained by a decrease in glycogenolysis ranging from 45% to 4% depending on the duration of the fast. The use of techniques to quantify glycogen stores in young children is limited and can best be done by combining the glucagon test with stable isotope studies; however, definitive data in children supporting this conclusion are scarce.

4. Glucose metabolism in malaria and other infectious diseases

4.1. Hypoglycemia in infectious diseases

In children with infectious diseases such as severe falciparum malaria, hypoglycemia is a common and serious complication [113-116]. Hypoglycemia occurs more frequently in children (up to 34%) [20,26,27,114,116] than in adults (8%) with malaria [117]. Hypoglycemia is an important feature in children with malaria because it predicts mortality [118,119]. The mortality rate increases 4- to 6-fold in children with malaria complicated with hypoglycemia [20,118,119]: 20% to 30% of the children admitted with malaria who had hypoglycemia do not survive [120], compared with a mortality rate of 3.8% in normoglycemic children [20]. Thus, hypoglycemia is considered to be one of the major outcome predictors in children with severe malaria.

The pathogenesis of hypoglycemia in malaria is still incompletely understood, although several possible mechanisms have been identified. Increased glucose consumption by the malaria parasites is considered to be a contributing factor. Parasitized erythrocytes consume up to 30 to 75 times the quantity of glucose that noninfected cells require [121]. Its contribution to total human glucose need however is thought to be relatively modest because the glucose demand of the severely ill patient is far greater than that of the parasites: glucose clearance rates increase 40% to 70% in severe malaria [122-124] and only 20% in nonsevere malaria [35,125]. Another well-known contributing factor is hyperinsulinemic hypoglycemia as a complication of quinine and quinidine in malaria treatment because quinine stimulates insulin release in vivo [126,127].

Hypoglycemia does not only occur in children with malaria but is also seen in children with other infectious diseases, such as pneumonia and diarrhea, both in tropical [20,21,24,25,28,113,115] and in Western countries [128,129]. In a Kenyan study, hypoglycemia occurred frequently in children with malaria (8.4%), but also in those with pneumonia (3.9%) and diarrhea (5.5%) [20]. In Tanzanian children, the frequency of hypoglycemia was similar in malaria (5.2%) and in other serious infectious illnesses (11.2%) [21], as was the case in Nigerian children where hypoglycemia occurred in 6.4% of children with malaria, septicemia, and pneumonia [28]. The mortality rate of children with other infectious diseases is similar to that of children with malaria (Table 2). Therefore, hypoglycemia may not be a disease-specific symptom but may be regarded as a serious metabolic complication in acute severe infections in young children [20,21,25,28,115,130-132].

In conclusion, hypoglycemia is a common and serious complication in young children with malaria and other infectious diseases and markedly increases mortality rates.

4.2. Glucose production and uptake in infectious disease

Hyperglycemia is a common finding in sepsis and other acute infections [133], caused by an imbalance between

Table 2
Mortality in hypo- and normoglycemic children with infectious diseases

Ref	Hypoglycemic %	Normoglycemic %	
Solomon et al, 1994 [25]	16.3	3.2	RR 5.8
Marsh et al, 1995 [118]	21.7	4.6	RR 3.6
English et al, 1998 [26]	28	7	$P = .003$
Schellenberg et al, 1999 [119]	12.4	3.0	OR 6.7
Osier et al, 2003 [20]	20.2	3.8	$P < .001$
Dzeing-Ella et al, 2005 [22]	25	8.9	OR 4.0
Elusiyan et al, 2006 [28]	28.6	4.2	$P < .01$
Huq et al, 2007 [115]	28	14	OR 2.4

RR indicates relative risk; OR, odds ratio.

alterations in glucose tissue uptake and glucose production [134-137]. In septic adult patients, EGP is doubled compared with that in healthy subjects [138,139]. However, the increase in EGP does not invariably lead to hyperglycemia. Plasma glucose concentrations are sometimes within the reference range despite increased glucose production rates in patients with sepsis [140] and in adults with falciparum malaria [124,125]. Infection with *Plasmodium falciparum* results in an increase in EGP in adult patients with both nonsevere and severe falciparum malaria [33,123,125,141]. In adults with nonsevere malaria, EGP increases by 20%; and plasma glucose concentration is higher (but in the normoglycemic range) compared with that in healthy controls [125,141]. In adults with severe malaria and adults with cerebral malaria, EGP is doubled; and plasma glucose concentration is approximately 40% higher than that in healthy controls [123,124]. In pregnant women, infection with *P falciparum* results in a 35% higher EGP after an overnight fast; but the plasma glucose concentration is comparable with that in healthy pregnant controls [33].

These findings indicate that peripheral glucose uptake is sometimes increased in adult patients with certain infectious diseases. This may be the result of increased tissue insulin sensitivity. Under healthy conditions, insulin inhibits hepatic glucose production by decreasing both gluconeogenesis and glycogenolysis and stimulates peripheral glucose uptake [142-144]. In most critically ill adult patients with sepsis and other acute infections, glucose metabolism is disturbed, resulting in hyperglycemia and insulin resistance rather than hypoglycemia [133,137,144-146]. *Insulin resistance* is defined as the relative inability of insulin to increase glucose uptake and utilization and/or to suppress glucose production [147] and typically presents with hyperglycemia despite "normal" or increased insulin levels [148], although during infections, seemingly low insulin levels have been reported [149]. During illness, these alterations in glucose metabolism may differ in children compared with adults [150]. For instance, in children with meningococcal sepsis and shock, hyperglycemia and inadequate low insulin levels were found, which are compatible with an insufficient insulin response [151,152], whereas in children with meningococcal sepsis without shock, insulin resistance was found [151]. This is in contrast with adults in whom normal or high insulin levels were found under those circumstances [153,154]. It is not clear whether children and adults can reduce insulin production as an adaptive response to severe disease or whether this is a direct effect of a specific critical illness [153].

Data on glucose kinetics in children with acute infectious diseases are scarce. There are 4 studies that report on glucose production rates in children, all with malaria. Glucose production rate in Ghanaian children with severe malaria aged 11 months to 10 years after a 9-hour fast was 56 μmol/kg·min [155], 2 to 5 times higher than that in fasted adults with severe malaria [123,124] and approximately twice the production in fasted children with nonsevere malaria [156]. The other 3 studies [156-158] report on Kenyan children with uncomplicated malaria and measured glucose production rates of 27 to 30 μmol/kg·min in children aged 2 to 10 years after 14 to 23 hours of fasting. Compared with healthy children, these values are in the reference range for age (Table 1).

Although data are limited and contradictory, glucose metabolism in children with malaria seems to be regulated differently than in adults. Severity of infection may be of influence on EGP, although a possible correlation between EGP and glucose concentration was not investigated in the children with severe malaria [155]. In children with uncomplicated malaria, a correlation between EGP and glucose concentration was found [157], indicating that hypoglycemia may be caused by limited glucose production capacity. This is in contrast with adults in whom peripheral uptake is more important [124,125]. In adults with malaria, peripheral glucose demands may increase considerably because of accelerated tissue metabolism [122,123], although there also is evidence of tissue insulin resistance in both uncomplicated and severe malaria [124].

In conclusion, the limited data in children with malaria suggest that EGP is an important determinant of plasma glucose concentration, indicating that hypoglycemia may occur as a result of impaired EGP. This is in contrast with adults in whom EGP is often increased during severe illness with glucose concentrations in the normoglycemic range, suggesting that peripheral uptake of glucose is facilitated.

4.3. Gluconeogenesis in infectious disease

Only 1 study measured EGP and gluconeogenesis in children younger than 5 years with an infectious disease: in Kenyan children aged 2 to 6.5 years with nonsevere malaria, fractional gluconeogenesis was 73% after 8 hours of fasting [156]. In comparison, gluconeogenesis contributed for approximately 87% of glucose production in Vietnamese adults with uncomplicated malaria after a 7-hour fast [125] and approximately 75% in pregnant women with uncomplicated falciparum malaria after a 24-hour fast [33]. In adults with cerebral malaria, EGP was completely (100%) derived from gluconeogenesis after a 20-hour fast [123]. These findings indicate that, in adults with malaria, the contribution of gluconeogenesis to glucose production increases with severity of disease [159] and makes impaired gluconeogenesis as a cause of hypoglycemia in adults with malaria unlikely. Studies measuring gluconeogenesis in children 2 to 7 years of age with uncomplicated malaria after a 15-hour fast [156] show that the availability of gluconeogenic substrates is not impaired in contrast to what was previously thought [160].

In conclusion, the only study in young children on gluconeogenesis in malaria reports a 73% contribution of gluconeogenesis to EGP after a short-term fast. In adults with malaria, this contribution varies from 75% to 100%.

4.4. Glycogenolysis in infectious disease

One single study reports on the response of plasma glucose concentration to a bolus glucagon in children with a chronic infection: normoglycemic, well-nourished, prepubertal HIV-infected children had a low response of plasma glucose concentration to glucagon (4%) in comparison with age-matched healthy controls (91%) after a 15-hour fast; but stable isotopes were not used in this study [161].

Despite the lack of direct measurements, the susceptibility to hypoglycemia in children with malaria is often ascribed to impaired glycogenolysis as a result of diminished glycogen stores [21]. This hypothesis seems to be supported by a study in adults with malaria who showed a subnormal response of plasma glucose concentration to glucagon [117]. However, this is contradicted by a study in adults with uncomplicated malaria who were fasted for 22 hours. In these patients, the decrease in the rate of decline of glycogenolysis was slower than that in healthy controls despite a much lower rate of glycogenolysis in the malaria patients, indicating that the regulation of glycogenolysis in malaria is not dictated by glycogen content, but is driven by the necessity to maintain euglycemia [162]. This means that impaired glycogenolysis is unlikely to be a causative factor in the occurrence of hypoglycemia in malaria in adults. It also suggests that malaria itself does not cause glycogen depletion, which is supported by the finding that hepatic glycogen is often still present in hypoglycemic adult malaria patients [117].

The mechanism by which hypoglycemia in children with malaria occurs remains uncertain. The limited available data suggest that in children glucose production is an important determinant of plasma glucose concentration. Although glucose production measured in children with malaria is not impaired during relatively short durations of fasting (up to 23 hours), longer periods of fasting may result in declining glucose production, thereby increasing the risk of hypoglycemia. Because gluconeogenesis does not seem to be impaired in malaria, the decline in glucose production in children may indeed be caused by decreased glycogenolysis due to diminishing liver glycogen content. This, and whether glycogen content is influenced by different infectious diseases during fasting, remains to be investigated.

In conclusion, the cause of hypoglycemia in young children with malaria remains uncertain. Impaired EGP as a result of decreased glycogenolysis due to diminished liver glycogen stores is presumed to be the reason, but studies in children are lacking.

5. Summary

Hypoglycemia in children is a common and serious condition that needs to be prevented because of the high risk of brain damage and mortality. Young age, prolonged fasting, and severe infectious disease are well-recognized risk factors for the occurrence of hypoglycemia in children. Young children are more at risk for developing hypoglycemia than older children and adults, especially in response to fasting. Endogenous glucose production decreases from infancy toward adulthood, and this decrease is related to the ratio of brain weight to body weight. The contribution of gluconeogenesis to EGP increases during short-term fasting and is comparable in adults and older children, whereas absolute gluconeogenesis is constant, indicating that the decline in EGP is caused by decreased glycogenolysis. Estimation of glycogen stores in young children can be done by combining measurements of the response of EGP to a bolus glucagon with stable isotope studies; however, data in children are scarce.

Young children with infectious diseases who develop hypoglycemia have a 4- to 6-fold risk of dying. This increased risk is recognized in several epidemiologic studies in children with various infectious diseases, of which malaria, pneumonia, and diarrhea are particularly common. Several assumptions are made in these studies as to the underlying cause of hypoglycemia, for example, impaired gluconeogenesis as a result of limited precursor supply or enhanced glycogenolysis resulting in rapid depletion of glycogen stores. However, very few studies with direct measurements of glucose kinetics in children are performed to support or refute these assumptions. The limited data in children with malaria suggest that EGP is a determinant of glucose concentration, indicating that hypoglycemia may occur as a result of impaired EGP. This is in contrast with adults because, in adults with malaria, EGP is increased but plasma glucose concentrations may be in the normoglycemic range, indicating that peripheral glucose uptake is facilitated. Studies in adults show that EGP increases in malaria and that gluconeogenesis is the main contributor to total EGP, making it unlikely that hypoglycemia in malaria is caused by impairment of gluconeogenesis. Such conclusion cannot readily be made for children because only 1 study reports on gluconeogenesis in young children with malaria. Whether hypoglycemia in young children with malaria is caused by impaired EGP as a result of decreased glycogenolysis due to diminished liver glycogen stores remains to be investigated.

To understand and thereby be able to anticipate the occurrence of hypoglycemia in young children, further research on glucose kinetics in these children is mandatory. In particular, studies in adults cannot be extrapolated to children because glucose metabolism during fasting and severe infections seems to be differently regulated between adults and children. These studies should focus on young children less than 5 years of age with infectious diseases during a period of prolonged fasting. Special reference should be given to measurements of glycogenolysis and liver glycogen content.

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