



Carbohydrate as nutrient in the infant and child: range of acceptable intake

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Carbohydrates are the major source of energy for humans. Following their digestion, almost all ingested carbohydrates are converted to glucose. Glucose is the primary oxidative fuel for the brain. Although few studies have been done in infants and children to define the upper and lower limits of carbohydrate intake, such information may be derived from the published data on glucose metabolism *in vivo*. The upper and lower limits are determined by the need to provide for total energy expenditure, need for other essential nutrients such as protein and fats, requirements of the glucose dependent tissues such as the brain, and the need to minimize the protein cost of gluconeogenesis and thus irreversible loss of nitrogen. With these considerations, the upper and lower boundaries of carbohydrate intake in relation to age are described.

Introduction

Glucose is the most abundant endogenous carbohydrate in humans. It is a major source of energy for the brain and other vital organs. In addition, it is an important carbon source for the *de novo* synthesis of fatty acids and a number of amino acids. The majority of exogenously administered carbohydrates are metabolized following their conversion to glucose. Limited information is available regarding the changes in whole body metabolism at the upper and lower limits of carbohydrate intake in infants and children, therefore such data can only be inferred from the available information on glucose metabolism *in vivo*.

Defining the upper and lower limits of carbohydrate intake in infants and children is difficult due to the paucity of such information. The majority of scientific data on glucose and energy metabolism have been obtained in the newborn period—a critical transitional phase of metabolic adaptations and focus of inquiry for a long time. Very few studies have been performed in children between one year and puberty. Data for this period cannot be extrapolated, neither from the newborn nor from the adolescent or adult, because of the impact of growth, in particular the impact of differences in growth of various organs at different periods during this time (Falkner & Tanner, 1986). Finally, few studies have reported the impact of the type of carbohydrates such as lactose, sucrose or glucose polymer, on whole body metabolism in infants and children. Although lactose has been shown to enhance calcium absorption, and glucose polymers can impact gastric emptying, the effect of these carbohydrates on physiological processes such as fatty acid synthesis and nitrogen accretion have not been determined (Ziegler & Fomon, 1983; Stathos *et al*, 1996; Wirth *et al*, 1990; DeCurtis *et al*, 1986; Southgate, 1995). In this context, it is significant to note that lactose is a

primary carbohydrate source for the human neonate and child, and the biological advantage of one of its constituent hexoses, galactose, remains to be defined. Recognizing these limitations, in the following review an attempt is made to define the acceptable intake of carbohydrates based upon available scientific data. Only those studies that have been performed in clearly defined circumstances have been used to make such comparisons, and therefore the review is not all-inclusive.

Basis for calculation of acceptable intakes

The boundaries of acceptable intake of carbohydrate may be inferred from the following:

1. Rate of endogenous production and utilization of glucose
2. Response to administration of glucose
3. Glucose utilization by the brain
4. Relation between glucose/carbohydrate intake and nitrogen sparing
5. Basal and total energy expenditure
6. Effect of the type of carbohydrate such as sucrose, lactose, etc., on metabolism

Rates of production and utilization of glucose

Quantitative estimates of rates of production and utilization of glucose in infants and children have been performed using stable isotopic tracers. The majority of these investigations are limited to the immediate newborn period with a few studies in older children and adolescents. In addition, more recent data are, for the most part, confined to premature low birth weight infants. Estimates of the rate of appearance of glucose (Ra) can be influenced by the tracer isotope used (Kalhan, 1996) and by the particular population studied. The data displayed in Table 1 are taken from multiple sources (Bier *et al*, 1977; Denne & Kalhan, 1986; Patel & Kalhan, 1992; Kalhan *et al*, 1986; King *et al*,

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1982; Cowett *et al*, 1983; Sunehag *et al*, 1993; Kalhan, 1994; Arslanian & Kalhan, 1992, 1994; Austin *et al*, 1994; Amiel *et al*, 1991; Tserng & Kalhan, 1983). The rates of glucose turnover in the preterm infants are approximated from published reports because of the scarcity of true basal data in this population. The rates of appearance of glucose shown in Table 1 represent estimates made during the basal state. The rates of oxidation of glucose are calculated from the measurements of respiratory quotient (RQ). The endogenous rate of production of glucose expressed per kg body weight is highest in the immediate neonatal period and gradually decreases with age. During puberty the rate of production of glucose is significantly higher than that in adults (Arslanian & Kalhan, 1992, 1994; Austin *et al*, 1994; Amiel *et al*, 1991; Tserng & Kalhan, 1983). Based on respiratory exchange data, it can be inferred that 65–75% of glucose produced (Ra) is oxidized to carbon dioxide. Such a rate of oxidation will meet only ~50% of the energy need at any age. We chose to calculate oxidation of glucose from respiratory quotient data rather than tracer isotope data because respiratory calorimetry data include all sources of glucose oxidized including intracellular glycogen (Glamour *et al*, 1995).

Response to administration of glucose

The relation between exogenously administered glucose and the contribution of carbohydrate to total energy was systematically evaluated in normal healthy adults by Glamour *et al* (1995). Fourteen healthy non-diabetic adults were studied either during fasting or during intravenous glucose infusion at constant rate. As anticipated, there was suppression of endogenous glucose production in response

Table 1 Basal rates of appearance (Ra) and oxidation of glucose in children

	Glucose Ra ^a		Glucose Oxidation ^b	
	(mg/kg·min)	(g/kg·d)	(% Ra)	(g/kg·d)
Preterm infant	~8.0	11.5	?	?
Term infant	5.0	7.2	65	4.7
Child	~4.0	5.8	?	?
Adolescent	3.0	4.3	75	3.2
Adult	2.0	2.9	73	2.2

^aAverage from several studies (detail in text).

^bCalculated from respiratory gas exchange.

? Data not available.

to glucose infusion with complete suppression at high rates of infusion. Figure 1 shows a linear correlation between the total rate of appearance of glucose in circulation, as measured by isotopic tracer dilution, and the non-protein respiratory quotient (RQ), so that at glucose Ra of 30 μmol/kg·min (5.4 mg/kg·min or 7.8 g/kg·d), the non-protein RQ became equal to 1.0, suggesting that the entire non-protein energy needs were met by carbohydrate oxidation. A carbohydrate intake of 7.8 g/kg·d will correspond to ~30 kcal/kg·d or 2100 kcal for a 70 kg adult. When the contribution of glucose to CO₂ was measured by tracer C, a constant fraction 50–60% of glucose C appeared in CO₂. The biological significance of this observation is unclear and may represent the relation between pyruvate cycling and the cycling of carbon in the TCA cycle (Glamour *et al*, 1995). Nonetheless these data are important as they point to the problems of tracer-determined oxidation of glucose. Based upon respiratory calorimetry studies, all the daily energy expenditure can be met when carbohydrates alone are administered as nutrient source. In human adults, this will correspond to 7.8 g/kg·d.

The rates of oxidation of glucose and its contribution to energy consumption have been examined in preterm and term newborn infants in response to glucose alone or with amino acid and fat administration. The majority of these studies have utilized ¹³C labeled tracers and quantified the appearance of ¹³C in expired CO₂. Sauer *et al* (1986) studied 16 infants born at 36.3 ± 0.9 weeks gestation at ~14 days after birth. All infants were recovering from gastrointestinal illness or surgery and were receiving exogenous glucose infusion. The rate of glucose infusion varied from 10 to 24 g/kg·d (Figure 2). Glucose kinetics were measured using [U-¹³C]glucose tracer. The rate of oxidation of glucose was quantified both from respiratory gas exchange (termed glucose utilization) and from the appearance of ¹³C in CO₂ (termed glucose oxidation). Their data show that newborn infants can utilize increasing amounts of glucose in order to meet energy demands. In addition, the use of isotopic tracers, as in adults, results in underestimation of the contribution of glucose to CO₂ when compared with data obtained from respiratory calorimetry measurements. In fact, at any rate of appearance of glucose (Ra), the fractional contribution of glucose C to breath CO₂ as measured by ¹³C tracer was approximately 50%. Other investigators have also observed similar results when glucose oxidation was estimated using ¹³C labeled glucose

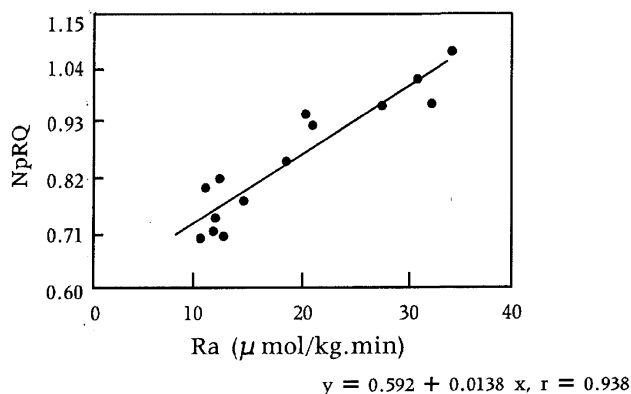


Figure 1 Correlation between rate of appearance of glucose measured by isotopic tracer dilution and non-protein respiratory quotient (NpRQ) in normal healthy adults (Reproduced with permission, Glamour *et al*, 1995).

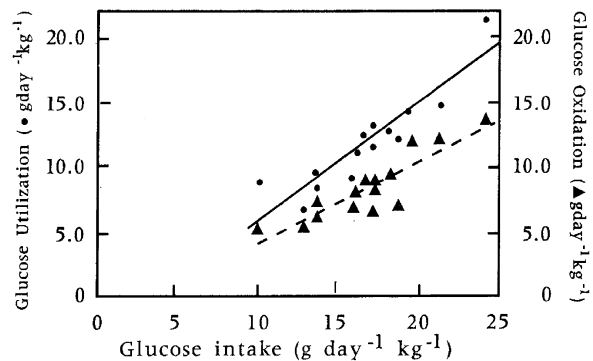


Figure 2 Relation between glucose intake and glucose utilization (measured by respiratory calorimetry) and oxidation (measured by ¹³C appearance in CO₂) during infusion of [U-¹³C]glucose in newborn infants (Reproduced with permission, Sauer *et al*, 1986).

Table 2 Glucose Ra and oxidation in newborn infants

Study	Subjects	Nutrients	NPRQ	Total Glucose Ra ^a (mg/kg·min)	Ro/Ra ^a (%)
[1]	Term	G/AA	—	16.8	50
[2]	Preterm				
	AGA	G	—	6.0	50
	SGA	G	—	5.3	50
[3]	Preterm	G/AA	1.04	12.6	53
		G/AA/F	0.96	9.9	45
[4]	Preterm				
	AGA	G/AA	0.97	7.9	56
	SGA	G/AA	0.93	8.1	66

[1] Sauer *et al.*, 1986; [2] Van Goudoever *et al.*, 1993; [3] Van Aerde *et al.*, 1989; [4] Lafeber *et al.*, 1990.

^aTotal glucose Ra was measured by tracer dilution during [U-¹³C]glucose infusion and glucose oxidation (Ro) by the appearance of ¹³C in CO₂.

during the administration of different nutrient combinations, that is, with and without amino acids and fat (Table 2) (VanGoudoever *et al.*, 1993; Van Aerde *et al.*, 1989; Lafeber *et al.*, 1990). All of these data together suggest that exogenous glucose can be used to provide for all the energy needs of infants. Similar studies have not been reported in older children and adolescents.

Glucose utilization by the brain

The brain, along with the renal medulla, and red and white blood cells, is the primary consumer of glucose in the body. Of these, the brain appears to be quantitatively the major organ utilizing glucose *in vivo*. Detailed studies of oxygen and glucose consumption by the brain under optimal basal conditions in normal infants and children have not been reported. This is in part the consequence of lack of easy accessibility of this organ for such studies. Previous studies have quantified oxygen and glucose consumption by the brain in anesthetized or unanesthetized children using Fick's principle (Settergren *et al.*, 1976, 1980; Mehta *et al.*, 1977; Kennedy & Sokoloff, 1957; Kennedy, 1956; Sokoloff *et al.*, 1977). Arterio-venous gradients of glucose, oxygen, lactate, pyruvate and ketones were measured across the brain. Cerebral blood flow was estimated by the nitrous oxide uptake method (Kennedy & Sokoloff, 1957; Kennedy, 1956). Although the concentrations of the various substrates in the arterial and venous blood could be measured with minimal errors, the variance in the estimated cerebral blood flow was relatively large, leading to a wide range in the estimates of glucose and oxygen consumption. Recently, a number of investigators have reported regional rates of glucose consumption by the brain using ¹⁸F-2-fluoro-2-deoxyglucose and positron emission tomography (PET) (Hatazawa *et al.*, 1987; Chugani, 1993; Chugani & Phelps, 1986; Chugani *et al.*, 1987; Kinnala *et al.*, 1996; Suhonen-Polvi *et al.*, 1993). These studies are also confounded by the lack of true normative data. For example, several of such studies were performed on infants who had suffered perinatal asphyxia. Although these infants recovered completely neurologically, the PET data obtained in the immediate neonatal period, that is, soon after perinatal trauma, could not be considered to represent a normal state since (perinatal) asphyxia itself with or without edema has been suggested to decrease cerebral metabolic rate (Suhonen-Polvi *et al.*, 1993). In the following, we have extracted as much as possible the 'most' normative data on glucose and oxygen consumption by the brain from the published

studies. In order to examine the impact of age and growth, we have first presented changes in brain size with increasing age before quantifying the rates of glucose consumption and oxidation.

Changes in brain weight with age. Quantitative measurements of brain weight from autopsy data have been reported by Dobbing and Sands (1973) and by Dekaban and Sadowsky (1978). As shown in Figure 3, a linear correlation between brain weight and body weight was observed up to 10 kg body weight (corresponding to approximately 1 year) followed by a decreased rate of brain growth until the adult size was achieved. The data were expressed as (brain weight/body weight ratio) × 100 = 13.6435 - 0.3673 × body weight. The second report (Dekaban & Sadowsky, 1978) plots the relation between body weight and brain weight from over 5000 autopsy studies (Figure 4). As shown, there is a rapid increase in brain weight in both sexes until the body weight reaches about 18 kg (4–5 y of age); thereafter the increase in brain weight is much slower so that by 7–8 y (~25 kg body weight), the brain has almost reached the adult size. Thus the brain's metabolic/nutritional requirements in a 7- to 8-year-old child should almost correspond to that of an adult, while those of a 4- to 5-year-old will be slightly less.

Cerebral uptake of oxygen and glucose. The rate of glucose consumption by the brain can be calculated from published O₂ consumption data and changes in brain mass in relation to age. Several studies in the literature have quantified oxygen uptake by the brain by measuring the rate of cerebral blood flow and arteriovenous oxygen gradient. These data are summarized in Table 3. The average rate of oxygen consumption in children was 235 μmol/100 g·min. Two studies (Settergren *et al.*, 1976, 1980) recorded lower rates of oxygen consumption, 104 and 135 μmol/100 g·min. These measurements were done while the children were under general anesthesia in preparation for surgery. In adults, the average rate of oxygen consumption was 160 mol/100 g·min (Kennedy & Sokoloff, 1957; Kennedy, 1956; Sokoloff *et al.*, 1977). Since each mole of glucose consumes 6 moles of oxygen, and assuming all the oxidative energy of the brain is derived from glucose, these oxygen consumption data can be transformed into glucose

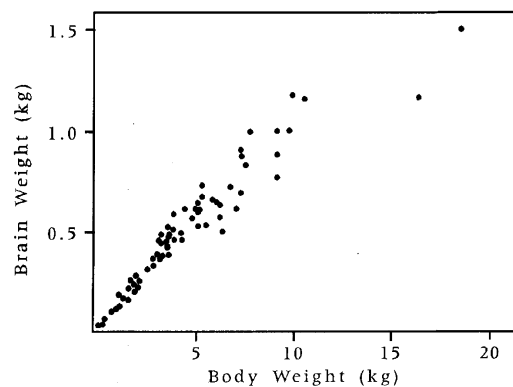


Figure 3 Relation between body weight and brain weight in children (Reproduced with permission, Dobbing & Sands, 1973).

Table 3 Cerebral uptake of oxygen and glucose

Study	Age (range, n)	O ₂ Consumption ($\mu\text{mol}/100\text{ g}\cdot\text{min}$)	Glucose Equivalent (O ₂ Consumption/6) ($\mu\text{mol}/100\text{ g}\cdot\text{min}$)	Glucose Consumption (measured) ($\mu\text{mol}/100\text{ g}\cdot\text{min}$)
[1]	5 months (11 days–12 months, n = 12) ^a	104.4 ± 8.0	17.4	27.2 ± 6.2
[2]	11 months ± 2 (n = 10)	258.7 ± 15.8	43.1	65.6 ± 2.9
[3]	11 days–15 years (n = 70) ^a	134.8 ± 5.6	22.4	24.8 ± 2.2
[4]	6.1 years ± 0.9 (3–11 years, n = 9)	230.8 ± 10.2	38.4	
[5]	6.2 years (n = 6)	227.6 ± 14.2	37.9	
[6]	Children	232.1	38.6	
[7]	21.8 years (n = 12)	149.1 ± 10.2	24.8	
[8]	24.5 years ± 0.8 (n = 12)	186.6 ± 20.9	31.1	
[9]	Adult	156.25	26.0	30.5

[1] Settergren *et al*, 1976; [2] Mehta *et al*, 1977; [3] Settergren *et al*, 1980; [4 & 8] Kennedy & Sokoloff, 1957; [5 & 7] Kennedy, 1956; [6 & 9] Sokoloff *et al*, 1977.

^aStudies were performed under general anesthesia.

Average cerebral oxygen consumption for children = 235 $\mu\text{mol}/100\text{ g}\cdot\text{brain wt}\cdot\text{min}^{-1}$ (average of [2], [4], [5], [6]), and for adults 160 $\mu\text{mol}/100\text{ g}\cdot\text{brain wt}\cdot\text{min}^{-1}$ (average of [7], [8], [9]).

equivalent of 39 $\mu\text{mol}/100\text{ g}\cdot\text{min}$ in children and 26 $\mu\text{mol}/100\text{ g}\cdot\text{min}$ in adults. The calculations are lower than actual measurements in children (65.9 ± 2.9 , study 2, Table 3), and similar to the one actually reported in adults (30.5 $\mu\text{mol}/100\text{ g}\cdot\text{min}$, study 9). These average data of oxygen consumption by the brain are used to calculate the cerebral glucose consumption per kg body weight and are displayed in Table 4. In order to meet the cerebral glucose requirement, glucose or carbohydrate intake should correspond to 37 g/day in neonates and progressively increase, in proportion to the increase in cerebral mass, reaching a maximum of 135 g/d in adolescents. In adults the estimates are lower, corresponding to 98–100 g/d. It should be underscored that such computation assumes that oxidation is the only fate of cerebral glucose uptake, and that glucose is the only oxidative fuel being utilized by the brain. The last two assumptions are appropriate, considering that the contribution of ketones, except in prolonged fasting in adults, is small and that non-oxidative disposal of glucose, that is, release of lactate and pyruvate by the brain, is also small (Settergren *et al* 1976, 1980; Mehta *et al*, 1977).

Recently, cerebral metabolic rate of glucose has been quantified in children and adults using positron emission tomography (PET). The limitation and potential errors of this method have been discussed (Hatazawa *et al*, 1987). The absolute values of Local Cerebral Metabolic Rate of glucose (LCMRglc) reported by Chugani in 29 normally developing infants and children and corresponding adult values are displayed in Figure 5 (Chugani, 1993). LCMRglc data are lower than those obtained from A-V gradients in infants and children < 3 y of age and higher in children between 3–8 y of age. In children > 8 years of age and in adults, LCMRglc measured by PET are similar to those reported previously. The difference in these measurements in children < 8 y are not easily explained except that most children studied by PET have either had a perinatal neurological trauma or at older age had residual neurological deficits. Similar lower rates of glucose metabolism by brain in the newborn infant have been reported by other investigators (Kinnala *et al*, 1996; Suhonen-Polvi *et al*, 1993).

Relation between carbohydrate intake and protein/nitrogen sparing

We could not find any data which have systematically evaluated the relation between carbohydrate intake and

nitrogen loss in children. Studies in completely starving adults by Gamble (1946) over fifty years ago showed that 'the maximal protein sparing effect of glucose is approximately gained by providing a daily intake of 100 g'. Further increase in carbohydrate intake did not result in a further reduction in protein oxidation or irreversible nitrogen loss. These rates of glucose intake (100 g/d for adults) correspond to the cerebral metabolic rate of glucose in adults (Table 4), and approximate 20% of total energy

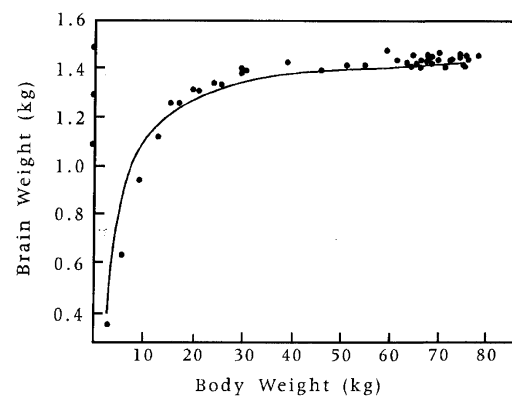
Table 4 Estimates of glucose consumption by the brain

	Body weight	Brain weight ^a	Glucose consumption		
	(kg)	(g)	(mg/kg-min) ^b	(g/kg-d) ^b	(g/d)
Newborn	3.2	399	8.0	11.5	37
1 year	10	997	7.0	10.1	101
5 years	19	1266	4.7	6.8	129
Adolescent	50	1360	1.9	2.7	135
Adult	70	1400	1.0	1.4	98

^aBrain weight—data from figures 3 and 4.

^bkg = kg body weight.

Average cerebral oxygen consumption: for children = 235 $\mu\text{mol}/100\text{ g}\cdot\text{brain wt}\cdot\text{min}$, and for adults 160 $\mu\text{mol}/100\text{ g}\cdot\text{brain wt}\cdot\text{min}$ from Table 3. Cerebral glucose consumption ($\mu\text{mol}/\text{min}$) = cerebral oxygen consumption ($\mu\text{mol}/\text{min}$)/6 (see text for details).

**Figure 4** Relation between body weight and brain weight in children and adults (Reproduced with permission, Dekaban & Sadowsky, 1978).

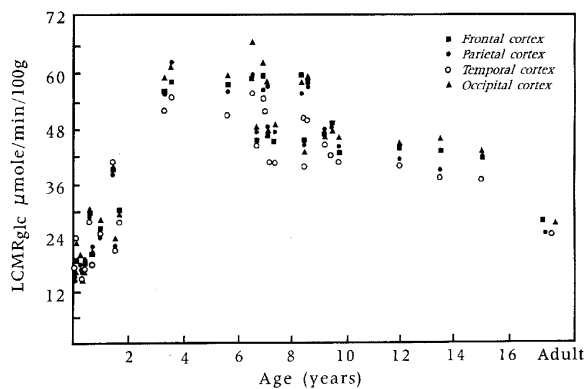


Figure 5 Change in local cerebral metabolic rate of glucose (LCMRglc) in cerebral cortex with age (Reproduced with permission, Chugani, 1993).

consumption (~ 1800 kcal/d). Similar systematic evaluations of nitrogen/protein sparing by carbohydrate intake have not been done in other studies in adults or children. Whether one can extrapolate the observation in adults to children is subject to conjecture.

Energy expenditure in infants and children

Quantitative measurements of total energy expenditure (TEE) in infants and children were reviewed in detail by the International Dietary Energy Consultative Group (Torun *et al*, 1996). In all age groups measurements of TEE by the doubly labeled water method were lower than energy intakes recommended by WHO. The average data for TEE in various age groups are displayed in Table 5. The data have also been averaged for boys and girls. The carbohydrate equivalents for the daily energy expenditure are calculated. As shown, there is an increase in TEE per kg body weight during the first year, reaching a peak between 1–3y of age, followed by a continuous decline until adult levels are reached.

Type of carbohydrate

The impact of type of carbohydrate, such as lactose, sucrose or glucose polymer, starches, etc., on metabolic advantages in children have not been examined in detail. Although lactose is the most abundant carbohydrate in the infant diet, its biological significance remains unclear except that it has been suggested to promote absorption of calcium and other minerals (Ziegler & Fomon, 1983). However, more recent studies using calcium isotopic

Table 5 Upper limit^a of carbohydrate for infants and children

Age	Total Energy Expenditure ^b (kcal/kg-d)	Carbohydrate Equivalent ^c (g/kg-d)
Newborn	70	19
1–3 y	85	22
4–6 y	68	18
12–13 y	55	14
18–19 y	44	12
Adult	35	9

^aUpper limit should be determined by the minimal need for protein and fat obtained. Therefore the described upper limits here are theoretical maximal in order to meet all the energy needs.

^bFrom reference (Torun *et al*). Average of data for boys and girls. Estimate based upon double labeled water method.

^cCarbohydrate equivalent = TEE/3.8, assuming each gram of carbohydrate yields 3.8 kcal.

tracers have not confirmed these observations. Southgate has reviewed the digestion and metabolism of dietary sugars (Southgate, 1995). Although the source of sugar in foods does not by itself affect the rate of absorption or metabolism of the sugars, the form in which the sugars are ingested and the physical and chemical properties of the food matrices, however, do impact the rates of absorption. These factors may influence gastric emptying and the rate of transport of sugar across the small intestine. After absorption, all ingested sugars converge toward glucose and the original dietary source has only minimal effects on metabolism. Recent data from animal studies suggest that a prolonged high sucrose diet can induce insulin resistance (Pagliassotti *et al*, 1994, 1996) and impact triglyceride metabolism.

Other considerations include changes in the gut transit time, particularly due to lactose intolerance in very young infants and in certain ethnic populations. An increase in transit time will result in increased delivery of carbohydrates to the large bowel and consequently greater bacterial fermentation (Kien *et al*, 1987, 1989, 1992, 1996). The quantitative contribution of the bacterial fermentation products, that is short chain fatty acids, to whole body energy metabolism, remains inconclusive (Kien *et al*, 1989). Short chain fatty acids produced by bacterial fermentation have been shown to affect whole body glucose metabolism (Thorburn *et al*, 1993).

Upper and lower limits of carbohydrate intake

Based upon the data discussed above, one can define the acceptable upper and lower limits of carbohydrate intake. It should be recognized that these limits remain theoretical since careful experimental studies examining the impact of these boundaries of carbohydrate intake on whole body metabolism, growth, etc., have not been possible in children for ethical reasons.

Upper limit

The upper limit of carbohydrate intake is constrained by the need for other macronutrients, that is, protein and fat. Although the total energy needs of an individual can be met entirely by carbohydrates in the short term, there is an obligatory need for proteins and fat in order to provide for growth and for essential nutrients. Thus the upper limits of carbohydrate intake should be calculated after subtracting the minimal needs for protein and fats. Table 5 presents the estimated total energy expenditure and the corresponding glucose equivalents. Theoretically, the calculated carbohydrate equivalents could be administered to meet the entire energy needs of the organism. High carbohydrate could potentially cause increased lipogenesis and predispose to obesity.

Lower limit

In contrast to the goals for upper limits, the goals for estimating the lower limit of carbohydrate intake can be more clearly defined and are as follows:

1. Meet the energy needs of the brain and other glucose dependent organs;
2. Minimize protein cost of gluconeogenesis and irreversible protein and nitrogen loss;
3. Prevent ketosis and associated risk.

Table 6 Minimum carbohydrate requirement in infants and children

	Ra glucose (g/kg-d)	Ro glucose (g/kg-d)	Brain glucose utilization (g/kg-d)	Nitrogen sparing (g/kg-d)
Preterm	11.5	?	?	?
Term newborn	7.2	4.7	11.5	?
Children	5.8	?	6.8	?
Adolescent	4.3	3.2	2.7	?
Adult	2.9	2.2	1.4	1.4

Ra glucose = rate of appearance of glucose.

Ro glucose = rate of oxidation of glucose.

? = not determined.

In order to meet these goals, the carbohydrate intake can be calculated based upon (i) the endogenous rate of glucose production, or (ii) the rate of oxidation of glucose, or (iii) an estimate of glucose uptake by the brain, or (iv) the carbohydrate required to minimize irreversible protein loss. These estimates are presented in Table 6 for different age groups. The measured rate of glucose utilization by the brain per kg body weight matches closely the rate of glucose production in infants and children, starts to decrease in adolescents and is lowest in adults. It is important to note that in adults, where actual experimental data have been obtained (Sokoloff *et al.*, 1977; Gamble, 1946), the glucose uptake by the brain was similar to that resulting in minimal wasting of nitrogen in fasting adults. The data in Table 6 suggest that administration of carbohydrate in order to meet the glucose requirement of the brain may be sufficient to minimize nitrogen loss and therefore may also define the lower limit of carbohydrate intake. Since lipolysis and ketogenesis are highly sensitive to carbohydrate administration, such an intake should be sufficient to prevent ketosis.

Limitation of the estimate of boundaries of carbohydrate intake

The proposed limits of carbohydrate intake in children and adolescents are primarily based upon very limited information obtained in controlled circumstances and are indirect. Therefore, they may not necessarily directly apply to free living state. The following limitations should be recognized:

1. The glucose kinetic data are based upon short measurements and do not reflect changes throughout the day. The impact of change in activity and the effect of growth have not been considered. In addition, nutrient intake is usually discontinuous (bolus). How the data of continuous or constant rate of glucose turnover should be translated into data for bolus feeds remains unknown.
2. All the data presented are based upon glucose as the surrogate carbohydrate, so they cannot be directly converted and applied to other carbohydrate sources such as lactose, sucrose, fiber, etc., because of differences in rates of digestion and absorption. In addition, since galactose constitutes 50% of the carbohydrate in breast milk, and since the role of galactose in human metabolism is not fully understood, administration of glucose alone or estimates based upon glucose alone may not truly reflect the actual requirement.
3. The proposed lower limit assumes that glucose is the only source of energy for the brain. This probably is not true (Denne & Kalhan, 1986; Settergren *et al.*, 1976).

Quantitative estimates of oxidation of endogenously released glucose, at least in the fasting human newborn, could not provide all the energy for the oxidative metabolism of the brain (Denne & Kalhan, 1986). Thus the brain may have other, although quantitatively small, obligatory energy sources.

4. The interaction between carbohydrate and proteins has not been considered.

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References

- Amiel SA, Caprio S, Sherwin RS, Plewe G, Haymond MW & Tamborlane WV (1991): Insulin resistance of puberty: a defect restricted to peripheral glucose metabolism. *J. Clin. Endocrinol. Metab.* **72**, 277–282.
- Arslanian SA & Kalhan SC (1992): Effects of growth hormone releasing hormone on insulin action and insulin secretion in a hypopituitary patient evaluated by the clamp technique. *Acta. Endocrinol.* **127**, 93–96.
- Arslanian S & Kalhan S (1994): Correlations between fatty acid and glucose metabolism. Potential explanation of insulin resistance of puberty. *Diabetes* **43**, 908–914.
- Austin A, Kalhan S, Orenstein D & Arslanian S (1994): Roles of insulin resistance and -cell dysfunction in the pathogenesis of glucose intolerance in cystic fibrosis. *J. Clin. Endocrinol. Metab.* **79**, 80–85.
- Bier DM, Leake RD, Haymond MW, Arnold KJ, Gruenke LD, Sperling MA & Kipnis DM (1977): Measurement of "true" glucose production rates in infancy and childhood with 6,6-dideuteroglucose. *Diabetes* **26**, 1016–1023.
- Chugani HT & Phelps ME (1986): Maturation changes in cerebral function in infants determined by ¹⁸F-DG positron emission tomography. *Science* **231**, 840–843.
- Chugani HT, Phelps ME & Mazziotta JC (1987): Positron emission tomography study of human brain functional development. *Ann. Neurol.* **22**, 487–497.
- Chugani HT (1993): Positron emission tomography scanning: applications in newborns. *Clin. Perinatol.* **20**, 395–409.
- Cowett RM, Susa JB, Giletti B, Oh W & Schwartz R (1983): Glucose kinetics in infants of diabetic mothers. *Am. J. Obstet. Gynecol.* **146**, 781–786.
- DeCurtis M, Senterre J, Rigo J & Putet G (1986): Carbohydrate derived energy and gross energy absorption in preterm infants fed human milk or formula. *Arch. Dis. Child.* **61**, 867–870.
- Dekaban AS & Sadowsky D (1978): Changes in brain weights during the span of human life: relation of brain weights to body heights and body weights. *Ann. Neurol.* **4**, 345–356.
- Denne SC & Kalhan SC (1986): Glucose carbon recycling and oxidation in human newborns. *Am. J. Physiol.* **251**, E71–E77.
- Dobbing J & Sands J (1973): Quantitative growth and development of human brain. *Arch. Dis. Child.* **48**, 757–767.
- Falkner F & Tanner JM (eds) (1986): *Human Growth, A Comprehensive Treatise. Volume 2, Postnatal Growth Neurobiology*. New York: Plenum Press.
- Gamble JL (1946): Physiological information gained from studies on the life raft ration. *Harvey Lectures* **42**, 247–273.
- Glamour TS, McCullough AJ, Sauer PJJ & Kalhan SC (1995): Quantification of carbohydrate oxidation by respiratory gas exchange and isotopic tracers. *Am. J. Physiol.* **268**, E789–E796.
- Hatazawa J, Brooks RA, DiChiro G & Bacharach SL (1987): Glucose utilization rate versus brain size in humans. *Neurology* **37**, 583–588.
- Kalhan SC, Oliven A, King KC & Lucero C (1986): Role of glucose in the regulation of endogenous glucose production in the human newborn. *Pediatr. Res.* **20**, 49–52.
- Kalhan SC (1994): Metabolism of glucose in very low birth weight infants. In *Year Book of Neonatal and Perinatal Medicine*, ed. AA Fanaroff, M Klaus, pp. xix–xxx. Chicago: Mosby Year Book, Inc.
- Kalhan SC (1996): Stable isotopic tracers for studies of glucose metabolism. *J. Nutr.* **126**, 362S–367S.
- Kennedy C (1956): The cerebral metabolic rate in children. In *Neurochemistry*, ed. SR Korey & I Numberger, pp 230–238. New York: Hoeber-Harper.

- Kennedy C & Sokoloff L (1957): An adaptation of the nitrous oxide method to the study of the cerebral circulation in children; normal values for cerebral blood flow and cerebral metabolic rate in childhood. *J. Clin. Invest.* **36**, 1130–1137.
- Kien CL, Liechty EA, Myerberg DZ & Mullett MD (1987): Dietary carbohydrate assimilation in the premature infant: evidence for a nutritionally significant bacterial ecosystem in the colon. *Am. J. Clin. Nutr.* **46**, 456–460.
- Kien CL, Heitlinger LA, Li BU & Murray RD (1989): Digestion, absorption, and fermentation of carbohydrates. *Sem. Perinatol.* **13**, 78–87.
- Kien CL, Kepner J, Grotjohn KA, Gilbert MM & McClead RE (1992): Efficient assimilation of lactose carbon in premature infants. *J. Pediatr. Gastroent. Nutr.* **15**, 253–259.
- Kien CL, McClead RE & Cordero L Jr (1996): In vivo lactose digestion in preterm infants. *Am. J. Clin. Nutr.* **64**, 700–705.
- King KC, Tserng K & Kalhan SC (1982): Regulation of glucose production in newborn infants of diabetic mothers. *Pediatr. Res.* **16**, 608–612.
- Kinnala A, Suhonen-Polvi H, Aarimaa T, Kero P, Korvenranta H, Ruotsalainen U, Bergman J, Haaparanta M, Solin O, Nuutila P & Wegelius U (1996): Cerebral metabolic rate for glucose during the first six months of life: an FDG positron emission tomography study. *Arch. Dis. Child.* **74**, F153–F157.
- Lafeber HN, Sulkers EJ, Chapman TE & Sauer PJJ (1990): Glucose production and oxidation in preterm infants during total parenteral nutrition. *Pediatr. Res.* **28**, 153–157.
- Mehta S, Kalsi HK, Nain K & Menkes JH (1977): Energy metabolism of brain in human protein-calorie malnutrition. *Pediatr. Res.* **11**, 290–293.
- Pagliassotti MJ, Shahrokhi KA & Moscarello M (1994): Involvement of liver and skeletal muscle in sucrose-induced insulin resistance: dose-response studies. *Am. J. Physiol.* **266**, R1637–R1644.
- Pagliassotti MJ, Prach PA, Koppenhafer TA & Pan DA (1996): Changes in insulin action, triglycerides, and lipid composition during sucrose feeding in rats. *Am. J. Physiol.* **271**, R1319–R1326.
- Patel D & Kalhan S (1992): Glycerol metabolism and triglyceride-fatty acid cycling in the human newborn: effect of maternal diabetes and intrauterine growth retardation. *Pediatr. Res.* **31**, 52–58.
- Sauer PJJ, Van Aerde JEE, Pencharz PB, Smith JM & Swyer PR (1986): Glucose oxidation rates in newborn infants measured with indirect calorimetry and [^{13}C]glucose. *Clin. Sci.* **70**, 587–593.
- Settergren G, Lindblad BS & Persson B (1976): Cerebral blood flow and exchange of oxygen, glucose, ketone bodies, lactate, pyruvate and amino acids in infants. *Acta. Paediatr. Scand.* **65**, 343–353.
- Settergren G, Lindblad BS & Persson B (1980): Cerebral blood flow and exchange of oxygen, glucose ketone bodies, lactate, pyruvate and amino acids in anesthetized children. *Acta. Paediatr. Scand.* **69**, 457–465.
- Sokoloff L, Fitzgerald GG & Kaufman EE (1977): Cerebral nutrition and energy metabolism. In *Nutrition and the Brain*, eds. RJ Wurtman & JJ Wurtman, Vol. 1, pp 88–139. New York: Raven Press.
- Southgate DAT (1995): Digestion and metabolism of sugars. *Am. J. Clin. Nutr.* **62**, 203S–211S.
- Stathos TH, Shulman RJ, Schanler RJ & Abrams SA (1996): Effect of carbohydrates on calcium absorption in premature infants. *Pediatr. Res.* **39**, 666–670.
- Suhonen-Polvi H, Kero PN, Korvenranta H, Ruotsalainen U, Haaparanta M, Bergman J, Simell O & Wegelius U (1993): Repeated fluorodeoxyglucose positron emission tomography of the brain in infants with suspected hypoxic-ischaemic brain injury. *Eur. J. Nucl. Med.* **20**, 759–765.
- Sunehag A, Ewald U, Larsson A & Gustafsson J (1993): Glucose production rate in extremely immature neonates (<28 weeks) studied by use of deuterated glucose. *Pediatr. Res.* **33**, 97–100.
- Thorburn A, Muir J & Proietto J (1993): Carbohydrate fermentation decreases hepatic glucose output in healthy subjects. *Metabolism* **42**, 780–785.
- Torun B, Davies PSW, Livingstone MBE, Paolisso M, Sackett R & Spurr GB (1996): Energy requirements and dietary energy recommendations for children and adolescents 1 to 18 years old. *Eur. J. Clin. Nutr.* **50**, Suppl 1, S37–S81.
- Tserng K & Kalhan SC (1983): Estimation of glucose carbon recycling and glucose turnover with [^{13}C]glucose. *Am. J. Physiol.* **245**, E476–E482.
- Van Aerde JEE, Sauer PJJ, Pencharz PB, Smith JM & Swyer PR (1989): Effect of replacing glucose with lipid on the energy metabolism of newborn infants. *Clin. Sci.* **76**, 581–588.
- VanGoudoever JB, Sulkers EJ, Chapman TE, Carnielli VP, Efstatiopoulos T, Degenhart HJ & Sauer PJJ (1993): Glucose kinetics and glucoregulatory hormone levels in ventilated preterm infants on the first day of life. *Pediatr. Res.* **33**, 583–589.
- Wirth FH Jr, Numerof B, Pleban P & Neylan MJ (1990): Effect of lactose on mineral absorption in preterm infants. *J. Pediatr.* **117**, 283–297.
- Ziegler EE & Fomon SJ (1983): Lactose enhances mineral absorption in infancy. *J. Pediatr. Gastroent. Nutr.* **2**, 288–294.