

High-sugar feeding and increasing cholesterol levels in infants

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Hypercholesterolaemia is an important risk factor for cardiovascular disease. Both total and LDL cholesterol levels are three-fold higher at the end of the first year of life and about four-fold higher in adulthood compared with the neonatal period. In the USA, only 25% of infants are exclusively breastfed and simple carbohydrate-rich formulas are preferentially consumed. Spikes in fasting glucose and insulin have been reported in formula-fed infants and are associated with higher levels of proprotein convertase subtilisin/kexin type 9, suggesting a potential link between high simple sugar intake and consequent increase in LDL cholesterol in early childhood.

Keywords

Low-density lipoprotein • Lipid metabolism • Proprotein convertase subtilisin/kexin type 9 • Carbohydrates • Cardiovascular disease prevention

Neonates are born with low levels of both total and LDL cholesterol. The average total cholesterol in a new-born is 70 mg/dL (1.8 mmol/L), and LDL cholesterol is reported as 23.8 ± 10.62 mg/dL (0.62 ± 0.27 mmol/L) in male and 25.5 ± 9.29 mg/dL (0.65 ± 0.24 mmol/L) in female neonates.¹ During the first year of life, LDL increases substantially to 63 ± 24.92 mg/dL (1.63 ± 0.65 mmol/L) and 58.1 ± 24.27 mg/dL (1.5 ± 0.63 mmol/L) in males and female infants, respectively (Figure 1).¹ The average levels of total cholesterol in adults are 193 ± 42 mg/dL (4.99 ± 1.08 mmol/L), and LDL cholesterol, 115 ± 35 mg/dL (3.0 ± 0.91 mmol/L).

Nutrition during infancy is composed of breast milk, cow's milk, and other formula substitutes, or a combination thereof, with a slow transition to solid food from 6 to 12 months of age. As the nutritional composition of formula is different from breast milk, preference for one type over the other could potentially influence carbohydrate metabolism and cholesterol homeostasis. According to Centres for Disease Control (CDC) and Prevention—Healthy People 2020, the majority of infants in the USA are either exclusively formula-fed or formula is added to breastfeeding; only 25% of babies born are exclusively breastfed for the first 6 months.² Breastfeeding rates vary widely in Europe. For instance, 90% of infants were breastfed in Bavaria where formula-feeding was

associated with preterm infants, lower educational levels, and negative attitudes of the partners towards breastfeeding.³ On the other hand, the UK showed one of the lowest breastfeeding rates in Europe. Whereas 73.1% of mothers start with breastfeeding in England⁴ only 43.2% continue for 6–8 weeks.⁵ In Scotland, 49.3% of women were reported to be breastfeeding soon after birth, but only 38.9% at 6–8 weeks.⁶

An inverse association between breastfeeding and total and LDL cholesterol levels later in life has been reported. Mean total cholesterol levels in adulthood were lower in breastfed infants compared with formula-fed infants,⁷ and the difference was even more pronounced in seven studies that compared exclusively breastfed and formula-fed infants (-0.15 mmol/L; 95% confidence interval CI -0.23 , -0.06 mmol/L).⁸ Exclusive breastfeeding is defined by WHO as no additional food or liquid for the first 4 months of life (www.who.int/features/factfiles/breastfeeding/en). The results were inconsistent in another systematic review of infant milk-feeding practice and cardiovascular disease (CVD) outcomes¹⁰ likely due to variable inclusion criteria; no definitive conclusions were made, and some based on individual studies, such as increased total cholesterol levels only in 5–11-year-old formula-fed boys. Mechanisms underlying the association between breastfeeding and lower cholesterol levels in adulthood

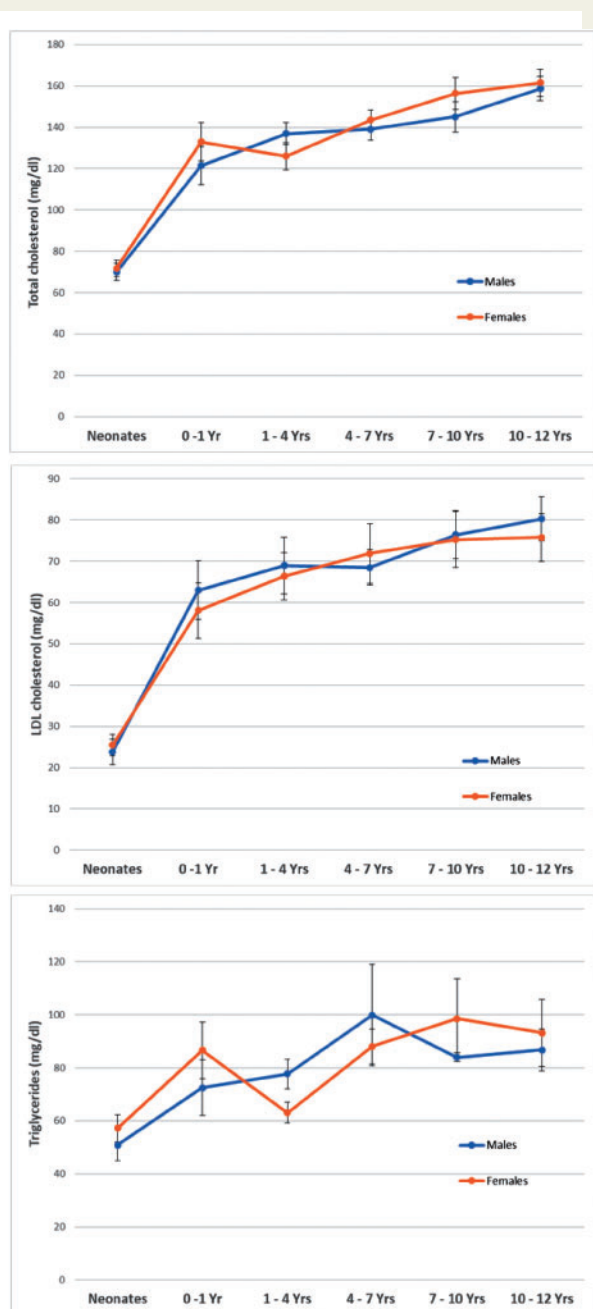


Figure 1 Evolution of lipid profile from infancy to adolescence. Lipid profile, including total cholesterol (top), LDL cholesterol (middle), and triglycerides (bottom), in normal healthy children up to 12 years of life is drawn from the data reported in reference 1. There is substantial increase in cholesterol and LDL cholesterol level within the 1–4 years of life; triglycerides remain almost unchanged.

could potentially be explained by differences in formula and breast milk composition.

- Human breast milk has higher cholesterol content than formula, which, in turn, is high in plant-based oils, such as palm and soybean oil. It has been proposed that the high cholesterol in breast milk

induces nutritional programming wherein early exposure to exogenous cholesterol suppresses endogenous synthesis of cholesterol through downregulation of hepatic hydroxymethyl glutaryl coenzyme A (HMG CoA) reductase.⁹

- The main carbohydrate in breast milk is lactose. However, the majority of commonly sold formulas contain corn syrup, corn syrup solids, corn maltodextrin, glucose syrup, brown rice syrup, and sucrose (table sugar), which are sweeter to the taste and easy to digest; only some formulas use lactose as the main source of carbohydrate.

Hypothesis

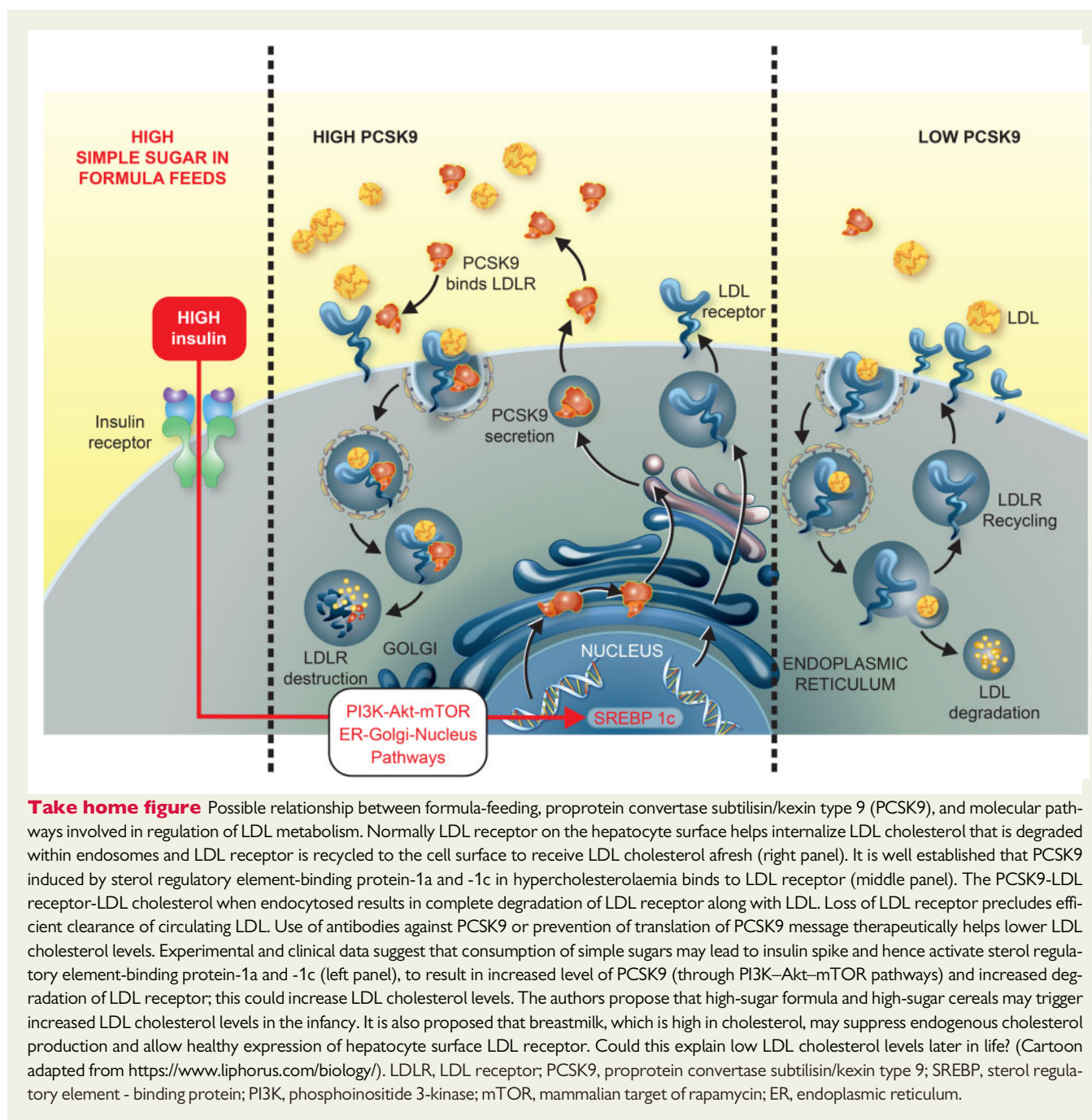
The actions of proprotein convertase subtilisin/kexin type 9 (PCSK9), a well-characterized regulator of LDL homeostasis, explain at least in part the association between high-sugar consumption in infancy (and hence high-insulin state) and dyslipidaemia later in life. As the majority of babies born in the USA are formula-fed, simple carbohydrates from formula might contribute to increases in serum glucose and insulin with subsequent induction of PCSK9, leading to increases in LDL cholesterol levels.¹

Proposed mechanism

PCSK9 is synthesized in the liver and binds to an extracellular domain of the LDL receptor (LDLR) (*Take home figure*). Normally, circulating LDL is sequestered by LDLR and internalized into clathrin-coated vesicles where the LDLR is recycled back to the cell membrane. When coupled to PCSK9, LDLR is degraded in endosomes precluding LDLR recycling. Consequently, there is reduced LDLR availability and clearance of circulating LDL contributing to higher cholesterol levels. Pharmacological inhibition of PCSK9 restores LDLR recycling and reduces circulating LDL levels.

Observational studies have shown that plasma PCSK9 concentration is directly related to circulating levels of glucose and insulin. A study of >1700 children revealed a positive correlation of fasting glucose and hyperinsulinemia to increased levels of PCSK9.¹⁰ Moreover, compared with breastfed children, higher 120-minute glucose (+10.1%), fasting insulin (+15.8%) and higher LDL cholesterol (+0.22 mmol/L) in adulthood were reported in bottle-fed babies.¹¹ In a randomized double-blinded intervention study of breastfed and formula-fed 3-month-old infants, plasma metabolites and insulin were measured at baseline, and up to 120 min after feeding; formula-fed infants revealed higher plasma amino acids and insulin.¹²

Five out of eight top selling formula brands in the USA use corn syrup solids and brown rice syrup as the main source of carbohydrate. Whereas various forms of corn syrup have a high glycaemic index (GI) up to 100, lactose has a 50% lower GI. The amount of carbohydrates that 3-month-old infants consume in 24 h is up to 60 g and could increase to as high as 80 g at 6 months. Cereal is usually added as a first solid meal around the age of 6 months. Each 15 g of cereal (minimum amount served as a first solid meal) contains up to 15 g of carbohydrates. Infants could consume up to ½ cup (30 g) of cereal mixed with milk in 1–2 meals by the age of 1 year, which will contribute up to 20 g of simple sugar, in addition to 5–8 oz of milk.



Expression of LDLR and PCSK9 is regulated by sterol regulatory element-binding protein (SREBP)-1a, -1c, and -2. The predominant stimuli for SREBP activation are low intracellular sterol levels and insulin. SREBP-1a and -1c are responsible for the regulation of carbohydrate and fatty acid metabolism by activating genes encoding fatty acid synthetase, acetyl-CoA carboxylase, and glucokinase. PCSK9 mRNA levels are significantly increased in mouse hepatocytes in the presence of insulin and high glucose concentration; glucose-driven increases are not observed in the absence of insulin.¹³ Hepatocytes

over-expressing active SREBP-1c manifest 4.4-fold higher glucokinase and 2.3-fold higher levels of PCSK9 mRNA when exposed to insulin compared to controls.¹³ Fasting for 24 h decreases PCSK9 mRNA, and high carbohydrate refeeding restores PCSK9 expression through increases in nuclear SREBP-1c. Although LDLR mRNA levels are also increased in the presence of insulin,¹³ it was subsequently clarified that the effect of insulin on LDLR protein expression is biphasic;¹⁴ LDLR protein expression initially increases in parallel with LDLR mRNA but decreases below baseline after 24 h. This relationship is

observed *in vivo* in liver-specific insulin receptor knockout (LIRKO) mice, a model marked by decreased levels of PCSK9 mRNA and protein; LDLR mRNA levels are lower but LDLR protein remains normal, suggesting that insulin may increase both LDLR synthesis (by activating SREBP-1) and LDLR degradation (by increasing PCSK9).

Insulin may not be the only regulator of PCSK9 and LDLR expression, because even in the absence of insulin receptors (LIRKO), mice still respond to fasting with 80% reduction in PCSK9. Interestingly, decreases in PCSK9 during fasting are not accompanied by decreases in active (nuclear) SREBP-1c, suggesting that SREBP-1c influences PCSK9 expression when stimulated through glucose-insulin and not under baseline conditions, such as fasting. Another possibility might be an increase in Sirtuin1 expression during fasting; indeed, sirtuin1 deacetylates PCSK9 at specific residues and in turn prevents the secretion of the protein from hepatocytes.¹⁵

Summary

Both total and LDL cholesterol levels are low in new-born babies and rise significantly within the first year of life. Early diet might contribute to this increase. In the USA, most infants are formula-fed, either solely or in combination with breast milk. The carbohydrates in most formulas are simple sugars, such as corn syrup solids, which can alter endogenous cholesterol programming. One potential mechanism underlying this relationship is glucose- and insulin-mediated increases in PCSK9 and consequent targeting of LDLR protein, setting the stage for a cycle of increasing LDL. In addition, breast milk could potentially prevent endogenous cholesterol production through suppression of HMG CoA reductase. It is noteworthy that for the first time in history, the 2020 Dietary Guidelines Advisory Committee Report to the US Secretary of Agriculture and Secretary of Human and Health Services has recommended to avoid foods and beverages with added sugars during the first 2 years of life.¹⁶ Breastfeeding is the preferred form of nutrition during the first 6–12 months of life and could help initiate CVD prevention at birth. More research, however, is needed to compare breastfeeding and formula-feeding in terms of PCSK9 induction and LDL levels in infancy.

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