Essential Fatty Acid Requirements for Term and Preterm Infants

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The essential fatty acids (EFAs) are a group of naturally occurring unsaturated fatty acids with a chain length of 18, 20, or 22 carbon atoms and containing between two and six methylene-interrupted double bonds in cis-configuration. These fatty acids are essential to the diet of humans and all higher animals, as they cannot be synthesized de novo from other lipids or from carbohydrates and amino acids. There are two fundamental EFAs, linoleic and α-linolenic acid, from which all others are derived metabolically (1-3). The essentiality of the polyunsaturated fatty acids (PUFAs) is related to their capability to incorporate into lipids and to act as a precursor in the formation of prostaglandins.

PLACENTAL TRANSFER AND CORD BLOOD POLYUNSATURATED FATTY ACIDS

Normal growth of infants is dependent upon an adequate supply of EFAs (4). The human fetus, like the adult, is unable to synthesize the EFAs, which must therefore be derived from the maternal circulation and pass through the placenta. We confirmed the observations that maternal plasma lipids are elevated during pregnancy and that these levels are significantly higher than in the neonate (5). However, we showed no change in cord plasma phospholipids, cholesterol esters, triglycerides, and free fatty acid concentration throughout gestation.

No differences in the fatty acid composition of the phospholipids, cholesterol esters, triglycerides, and free fatty acids were found in cord venous and arterial plasma obtained from 32 caucasian infants at birth. The fatty acid composition of cord plasma phospholipids at different gestational ages is shown in Fig. 1. Gestational age varied from 24 to 44 weeks; all were normally grown infants. The concentration of linoleic acid in cord plasma phospholipids was less than 40% that of the maternal value. The lowest levels of this fatty acid were noted before 34 weeks gestation. However, venous and arterial cord plasma contained higher concentrations of the more unsaturated fatty acid—arachidonate—than did maternal plasma (5,6). The concentration of docosahexaenoic acid, which is a homologue of the α-linolenic acid series, was noted to be higher in cord blood plasma at term as com-
pared with maternal levels (5,6). The combined percentages of fatty acid concentrations of the linoleic and linolenic acid series in cord plasma phospholipid showed a steady rise in values from 25.5 at 24 to 33 weeks to 33.7 at 34 to 37 weeks and 36.0 at term as compared with maternal levels of 39.9. The increased combined total of the linoleic acid series in plasma phospholipid correlated well with the tissue levels of these fatty acids (5). Bruce et al. (7) reported a continuous rise in the relative concentration of fatty acids of the linoleic series in skeletal muscle phosphoglycerides, from 10% at the beginning of the second trimester of gestation to almost 50% at the age of 1 year. Factors that may be responsible for these findings are (a) the increased concentration of the polyenoic fatty acids—derivatives of linoleic acid—may result from increased activity of the fetomaternal unit by preferential transfer of these fatty acids in later gestation, or (b) enzymatic activity in the placenta or the fetus may be responsible for the desaturation and elongation of these essential fatty acids (8).

Fatty acid composition of adipose tissue triglycerides in the newborn infant also differs from that of the mother (9) in the same manner as that of plasma lipids. These data are consistent with the presence of a placental transfer mechanism for certain fatty acids, including the EFAs. Because of the low concentration of linoleic acid in fetal adipose tissue, its contribution to fetal plasma free fatty acid composition during lipolysis is small.
The concentration of the fatty acid \( \Delta 5,8,11 \)-eicosatrienoic acid was found to be higher in cord plasma of all infants than in maternal plasma, and the level appears to increase with advanced gestation (Fig. 1). Although this abnormal fatty acid is elevated in EFA deficiency, such a diagnosis is not certain at the time of birth since the polyenoic acids of the linoleic acid series may be higher in the newborn infant than in the mother, yet the possibility is not eliminated that the infant may have a relative lack of EFAs. Furthermore, increased \( \Delta 5,8,11 \)-eicosatrienoic acid level may reflect a generalized increase in desaturation and/or elongation of fatty acid chains in the developing fetus.

**TISSUE POLYUNSATURATED FATTY ACID COMPOSITION**

Body stores of EFAs are low in low birth weight infants (10). The concentration of linoleic acid in fetal tissue is less than that seen in adults, and the proportion of linoleic acid in muscle phospholipids is found to increase with advancing gestational age (7).

We have analyzed various tissue samples from 25 human fetuses and newborns for the relative concentration of the fatty acids in phospholipids, cholesterol esters, triglycerides, and free fatty acids. Their gestational ages ranged from 16 to 44 weeks. Representative tissue from kidney medulla and cortex is shown in Fig. 2. No differences are observed between the levels of the individual EFAs, linoleate and arachidonate, in the different tissues beyond 16 weeks of gestation. However, the level of arachidonate in the various tissue phospholipids is markedly elevated as compared with the level of linoleic acid. These studies demonstrate that fetal tissues are rich in the EFA arachidonate, the prostaglandin precursor. Linoleate and arachidonate cord plasma values are a reflection of their tissue levels (9). Both show a reduced linoleate level compared with the maternal level; however, the level of higher homolog, arachidonate, is higher than the maternal value. The low plasma concentration of linoleate reflects the reduced tissue level of this fatty acid. This situation increases the maternal–fetal gradient for linoleic acid, which may facilitate its transfer across the placenta. The relatively high concentration of the higher PUFA arachidonate in fetal tissue could result from increased activity of the fetoplacental unit by preferential transfer of these fatty acids or by enzymatic activity in the placenta or the fetus that is responsible for desaturation and elongation of these EFAs. Tissue enrichment in arachidonic acid may play an important role by maintaining the normal function of biological membranes and serving as a substrate for prostaglandin biosynthesis. These functions may influence fetal physiology during intrauterine development.

Following birth, the diet affects the fatty acid composition of adipose tissue. In the period of rapid weight gain, during early infancy, changes in adipose tissue composition can occur in a relatively short time (11,12). Widdowson et al. (13) demonstrated a profound difference in the fatty acid composition of adipose tissue between British and Dutch infants between birth and 1 year. The differences were influenced directly by the nature of the fat in the diet.
FIG. 2. Percent fatty acid composition of renal phospholipids in neonates at various gestational ages. No changes are seen between the levels of linoleate and arachidonate in the renal tissue beyond 16 weeks of gestation. Closed circles, arachidonic acid medulla; open circles, arachidonic acid cortex; closed squares, linoleic acid medulla; open squares, linoleic acid cortex.

ESSENTIAL FATTY ACID DEFICIENCY SYNDROME

Associated with Oral Diets

Work with experimental animals showed that the very young are more susceptible to develop EFA deficiency due to lack of fat in the diet than are adults (14). Similarly, body stores of EFAs are low in low birth weight infants, which results in the deficiency state becoming evident more rapidly and the administration of the deficient nutrient inducing a more rapid response than in an adult. Most of the earlier studies that have been performed on humans included infants. These studies, which started as early as 1919 by Von Gröer (15), show the effects of diets low in fat on growth or weight loss, susceptibility to infection (15,16), and skin eruption (16). The observation that skin lesions in rats fed low-fat diet were cured by the addition of fats rich in PUFAs stimulated clinical studies in infants and children with chronic eczema (17). Moreover, these results were encouraging enough to warrant further studies in order to evaluate the role of unsaturated fatty acids in human nutrition.

Combes et al. (18) did not observe skin changes uniformly in premature infants
who were fed milk mixtures low in linoleic acid for periods of 18 to 37 days. However, histologic features of the skin showed evidences of linoleic acid deficiency and serum di-, tri-, and tetra-anoic acid levels were significantly different from infants fed 4% of the calories as linoleate. Hansen et al. (4) fed 42% healthy infants one of five proprietary milk mixtures adequate in protein, minerals, and vitamins but varying in linoleic acid content from less than 0.1% to 7.3% of the calories. Two of the milk mixtures were found to contain inadequate amounts of linoleic acid for the infant's requirement. One was low in fat (1.0% of calories), and one contained fat low in linoleic acid. A high proportion of babies who were fed the latter two milk mixtures before 6 weeks of age and who remained on the diets for 3 months developed dry, thick desquamated skin and retarded growth. The clinical manifestations disappeared after the administration of diets that provided 1% or more of calories as linoleic acid.

Further studies (19) demonstrated that infants do not usually show overt signs of fat deficiency until they have been on cow's milk formula for about 2 months. The clinical syndrome of linoleic acid deficiency appears as inefficient somatic growth with poor weight gain in spite of adequate caloric intake and skin lesions. These manifestations showed a dramatic response to a diet containing linoleic acid.

In infants fed diets low in linoleic acid, increased caloric consumption was reported by Adam (20). In spite of the differences of 20% to 40% in caloric intake between infants fed diets low in linoleic acids and infants fed linoleic acid supplemented diets, weight curves were similar for the majority of infants. Hansen et al. (4) found no significant difference in caloric efficiency for infants between milk mixtures containing 2.8% or 7.3% of calories as linoleic acid.

Associated with Parenteral Nutrition

The provision of optimal nutrition for low birth weight infants and for infants with congenital anomalies of the gastrointestinal tract and with inflammatory bowel disease remains a significant problem. Recently, total parenteral nutrition (TPN) has been established as a form of therapy for these conditions (21,22). Studies on infants who were maintained on long-term fat-free parenteral nutrition demonstrated the development of clinical signs together with biochemical evidence of EFA deficiency (23,24). The administration of diets containing linoleic acid converted these clinical and biochemical manifestations to normal.

We studied (21) five sick newborns who were maintained on fat-free intravenous alimentation and developed very rapid biochemical changes in the plasma that were compatible with the diagnosis of EFA deficiency during the first week of life and were reversible with oral feedings containing EFAs. The youngest and smallest infants exhibited these changes as early as the second and third days of life.

The body of a premature infant of 1,000 g contains approximately 0.5% glyco- gen, 1% fat, and 8.5% protein (10). In such an infant, the total caloric reserve is
450 kcal/kg and the nonprotein caloric reserve is only 110 kcal/kg. The minimal metabolic requirement of an infant this size is about 30 to 40 kcal/kg/24 hr on the first day of life and rises to 45 to 50 kcal/kg/24 hr thereafter. With increments for activity, stress of hypo- or hyperthermia, asphyxia, infection etc, the total caloric expenditure is probably in the order of 50 to 75 kcal/kg/24 hr. Because of the limited nonprotein caloric reserve, these infants must mobilize fatty acids early for caloric needs when faced with deficient dietary intake. Thus, the borderline stores of EFAs characteristic of the premature and the high caloric expenditure in these infants may contribute to the early onset of EFA deficiency, which we observed among prematures on fat-free parenteral feedings. Furthermore, during parenteral hyperalimentation the outflow of linoleic acid from adipose tissue is blocked, at least in part, by the high insulin levels accompanying glucose administration. During prolonged fat-free intravenous hyperalimentation, there is a correlation between low EFA levels in plasma and in tissues (24). Similar correlation has been demonstrated by us (unpublished data) in cases with rapid onset of EFA deficiency.

**Effect on Red Blood Cells**

Fatty acid composition of red blood cells changes in relation to dietary linoleate as it does in plasma, but the changes become evident more slowly (25). No changes in red blood cell osmotic fragility in neonates with rapid onset of EFA deficiency were demonstrated in our study.

**Effect on Platelets**

The importance of arachidonic acid biotransformation in platelets has been elucidated (26). In addition, hemorrhagic problems of unknown etiology are common in sick low birth weight infants (27). Many premature infants are being treated with TPN, and EFA deficiency is a frequent occurrence. Hence, we examined the rapid onset of EFA deficiency in premature infants and its possible effect on platelet function and found that the deficient infants had impaired platelet aggregation when compared with controls (28). In addition, the platelets from EFA-deficient infants demonstrated clearly evidence of disaggregation. On recovery from their deficient state, the low birth weight infants had platelet functions similar to those of apparently healthy premature infants. The relationship between the platelet dysfunction and EFA deficiency is speculated on the possible connection between arachidonic acid depletion (i.e., EFA deficiency) and decreased thromboxane, a key mediator of human platelet aggregation. Decreased arachidonic acid content in platelet phospholipids was documented in our laboratory in a newborn infant who rapidly developed EFA deficiency in the neonatal period (29).
Effect on Prostaglandins

We measured the excretion of the major urinary metabolite of prostaglandins E₁ and E₂, 7α-hydroxy-5, 11-diketotetrano-prostane-1, 16-dioic acid (PGE-M) in three infants during EFA deficiency, upon recovery from the deficiency state and in nine thriving control neonates (30). A significant difference between the PGE-M excretion in the group of infants with EFA deficiency before and after treatment was found (p < 0.05) (Fig. 3). Significant differences in PGE-M excretion were also found between the control group and the EFA-deficient infants. The biochemical evidences of EFA deficiency and the decreased levels of PGE-M excretion are rapidly corrected when patients resume a diet containing EFA.

Effect on Pulmonary Surfactant

We studied a low birth weight infant who developed biochemical evidence of EFA deficiency in the plasma after suffering from chronic bronchopulmonary dys-

![Graph showing urinary excretion of PGE-M](image)

**FIG. 3.** Comparison of the urinary excretion of PGE-M expressed as nanograms/mg urinary creatinine (CR) between three groups of infants: (a) Infants pre- and posttreatment with Intralipid; (b) thriving neonates (controls); and (c) infants with EFA deficiency and upon recovery. Note that PGE-M excretion following the administration of Intralipid is similar to the levels obtained from infants with essential fatty acid deficiency. (From ref. 30.)
plasia and recurrent episodes of necrotizing enterocolitis (31). A lower than normal level of palmitic acid and an increased level of palmitoleic and oleic acids were seen in pulmonary surfactant phospholipid components. Upon treatment and recovery from EFA deficiency, the fatty acid pattern both in plasma and surfactant phospholipids returned to normal along with clinical improvements in the respiratory illness. The impairment of surfactant phospholipids may diminish lung function and so contribute to the pathophysiology of hyaline membrane disease, chronic bronchopulmonary dysplasia, cystic fibrosis (32), and other respiratory diseases associated with inadequate nutrition inviting an EFA deficiency.

Effect on the Central Nervous System

The availability of long-chain PUFAs seems to be related to the degree of brain and central nervous system development. Linoleic and α-linolenic acids represent a small proportion of the fatty acyl components of the phosphoglycerides of fetal brain (8). In contrast, arachidonic and docosahexaenoic acids, more unsaturated EFAs, are readily incorporated into the structural lipids of the developing brain (8, 33). In humans, the brain undergoes an accelerated growth phase during the last trimester of pregnancy and the first 18 months of postnatal life. During this vulnerable period, EFAs are required for structural expansion of the brain.

Since brain phospholipids contain high levels of PUFAs of both the linoleic and α-linolenic acid series, it has been shown that changes in their ratio in the diet modify the relative proportion of PUFAs derived from these essential precursors, in tissues including brain and brain subcellular structures (34).

White et al. (35) studied the brain lipids of three premature infants who were maintained on fat-free parenteral nutrition and succumbed. They demonstrated fatty acid alterations indicative of essential fatty acid deficiency in the two major component phospholipids of brain, ethanolamine and choline phosphoglycerides, in the cerebrum and less so in the cerebellum. There was also a tendency toward reduction of brain phospholipid concentrations in these infants.

Crawford et al. (33) demonstrated in the human a stepwise progression in the degree of polyunsaturation and chain length from maternal diet to maternal liver, placenta, fetal liver, and fetal brain. Thus, it is attractive to postulate that prolonged intra- and extrauterine malnutrition may produce a low birth weight infant and that this individual may suffer significant, perhaps irreparable, developmental damage to the central nervous system.

REQUIREMENTS FOR POLYUNSATURATED FATTY ACIDS

Estimates of quantitative requirements of linoleic acid were based upon the rate of growth or the development of dermatitis, phenomena to which many factors contribute, some of which are unrecognized and uncontrolled.

The earliest estimate of the infant's requirements for linoleic acid as approxi-
mately 1% of the calories was based on clinical observations, caloric intake and serum levels of the di-, tri-, and tetraenoic acids (20). When the means of assessing linoleate requirement from a curve relating triene–tetraene ratio to intake of linoleate was developed (1), it became apparent that the requirements of infants could be deduced from this biochemical parameter as well. Extensive data relating PUFAs of human serum to intake of linoleate are presented in the classical study of Hansen et al. (4). From that study it appears that 1% of calories is a minimum requirement and that 4% of calories is an optimal intake. The plot of triene–tetraene ratio of serum fatty acids versus linoleate intake in infants reveals that the low ratio indicative of normal EFA metabolism was reached by about 1% of calories as linoleic acid (36). The effect of dose responsive dietary intake of linoleic acid upon the total dienes, trienes, and tetraenes of serum revealed that 1% to 2% of calories as linoleate satisfies the requirements for all the biochemical conversions of PUFA, as well as permitting normal growth and preventing dermatitis (37).

The potency of arachidonic acid as EFA has been shown to be greater than that of linoleic or ω-linolenic acids, but all are effective in the treatment of EFA deficiency and promote normal growth. Although the ω-linolenic (ω3) series has been considered to be essential, it cannot fulfill all the functions of the 6 series and so has been questioned as possessing true essentiality (38). Although tissues, the central nervous system in particular, contain relatively high proportion of the metabolic products of 7-linolenic acids, we must await demonstration of their particular function.

SUPPLEMENTATION OF POLYUNSATURATED FATTY ACIDS

Traditionally, linoleic acid is considered the dietary essential fatty acid for it is the commonest fatty acid that will provide sufficiently all the requirements known for PUFAs in human and animals and can function alone in the diet to meet the EFA requirements.

Diet

*Human Breast Milk*

The fatty acid composition of human milk has been studied in detail. The patterns of fatty acids from the two breasts were found to be similar after the same nursing, but fasting and time of day both influenced total fat and fatty acid composition of the milk (39). Fatty acid composition of breast milk changes with the nature of the dietary fat (40). With the trend in the fatty acid content of the United States diet toward a higher proportion of unsaturated fatty acids including linoleate, there is an increase in breast milk content that can vary from 1.0% to 43.0% fat, but an average content range from 8% to 10%. Since fat provides about 50%
of the calories in human milk, it contains more than an adequate amount of the EFA linoleate.

**Infant Formulas**

The American Academy of Pediatrics has recommended (41) that infant formulas should contain a minimum of 3.3 g of fat/100 kcal (30% of calories) and 300 mg of linoleic acid/100 kcal (approximately 1.7% of total calories) to provide a fat to carbohydrate ratio within a range that is customary in infant diets. The academy was concerned that excess linoleic acid would produce peroxidation and increase the vitamin E requirements but did not set an upper limit on the linoleate content of the diet, noting that in some human milks the linoleic acid content is 8% to 10% of the fat.

Several of the most widely used formulas are based on cow’s milk protein with lactose. All contain vegetable oils of one type or another. All the formulas contain considerably more linoleic acid than human milk lipids (42). The long-term effects of these dietary regimens are unknown.

**Parenteral Fat Emulsion**

In order to achieve complete parenteral nutrition in infants, it is necessary to administer adequate amounts of calories and nutrients in a restricted volume. In the newborn infant, it is difficult to provide an optimal caloric intake in the form of amino acids and carbohydrates, because excessive fluid volumes are needed when isotonic solutions are used and the glucose load of hypertonic solutions is frequently not tolerated. Therefore, fat emulsions, which have a high density and low osmolality, have been used increasingly to provide additional calories and essential fatty acids (43,44). These emulsions, like most vegetable oils, are rich in the essential fatty acid linoleate. Studies (30,44) documented the efficacy of the administration of fat emulsions in alleviating clinical and biochemical manifestations of EFA deficiency and that its administration would result in an increase of the linoleic acid level in the plasma and tissue lipids.

**Inunction of Oil**

Inunction of sunflower seed oil to forearms of patients with EFA deficiency lowered the rate of water loss, cured scaly lesions and corrected abnormal skin lipids (45), and restored their abnormal plasma fatty acids, indicating that penetration of the linoleic acid through the skin had occurred (46). We studied two sick newborn infants who received fat-free parenteral nutrition and developed biochemical and clinical evidence of EFA deficiency (25). Following the inunction of sunflower seed oil these manifestations disappeared. However, it seems impossible from our studies to predict the exact amount of linoleic acid absorbed following inunction.
Even the cutaneous application of relatively large quantities used in our patients failed to replenish tissues deficient in EFA. We demonstrated the ability to correct platelet dysfunction and to increase prostaglandin E biosynthesis and turnover by the inunction of sunflower seed oil in newborn infants with EFA deficiency (47).

EXCESSIVE INTAKE OF POLYUNSATURATED FATTY ACIDS

Since Burr and Burr demonstrated the importance of certain fats necessary for normal growth (48), research on EFAs has been mainly concerned with the symptoms of EFA deficiency and the administration of the minimal EFA requirement to prevent or treat the deficiency state. However, little is known about the toxicity or adverse effects of high levels of these substances in the diet.

Toxic Effect of Polyunsaturated Fatty Acids

The release by the United States Food and Drug Administration of artificial fat emulsions has made available for parenteral feeding a preparation of high caloric density that is rich in essential fatty acids, especially linoleic. However, several hazardous effects have been reported in the newborn infant: a reduced clearance rate in small-for-date infants, as well as among premature infants born before 32 weeks of gestation and during an acute illness (49), displacement of bilirubin from albumin binding sites and an increased risk of kernicterus in jaundiced newborns (50), the deposition of lipid material in macrophages that may alter immunity (44,51), immunosuppressive effect (52), altered pulmonary gas exchange (53), and the potential risk for substitution of phytosterols for cholesterol in the developing central nervous system, which could lead to changes in myelin configuration and function (49).

Effect on Tissue Fatty Acid Composition and Prostaglandin Biosynthesis

We have measured tissue lipid composition and the excretion of the major urinary metabolite of prostaglandins E₁ and E₂, PGE-M, in three infants who received total parenteral nutrition including Intralipid for several weeks and compared these values with control infants (30). Linoleic acid is incorporated into the major lipid classes of the plasma, red blood cells, and tissues in infants receiving Intralipid. Concomitantly with the increase in the relative concentration of linoleate, a decrease in the higher PUFA homolog, arachidonate, is apparent (Fig. 4). This may indicate a competition between these EFAs for esterification and storage in tissue lipids, a balanced content of the intake of the linoleic and linolenic acids, a rapid turnover of the long chain PUFAs, or a combination of these factors. However, the sum of the two EFAs, linoleate and arachidonate, is similar in red blood cell and tissue phospholipids of control infants and in infants who received Intralipid.

A significant difference between the PGE-M excretion in the group of infants
before and after the administration of Intralipid was found in this study (Fig. 3). Differences in the urinary excretion were seen between the control group and the infants receiving Intralipid. PGE-M excretion following the administration of Intralipid was similar to that obtained from infants with EFA deficiency. The decrease in PGE-M excretion in patients receiving high amounts of linoleic acid is most likely related to a decrease in the precursor EFA, arachidonate, although an inhibiting effect of linoleic acid on prostaglandin synthesis is possible (54).

**Effect on Platelet Function**

Chronic administration of a diet rich in linoleate reduced platelet aggregation in humans (55). Prolonged administration of Intralipid to sick newborn infants resulted in changes of the fatty acid composition of their platelets' phospholipids and those platelets showed reduced aggregation in response to different agents known to induce platelet aggregation (Z. Friedman, unpublished data).

**REFERENCES**


