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IN PEDIATRIC NUTRITION

Infant Nutrition

Growing Up Milk for Toddlers

Cow's Milk Allergy

Functional Gastrointestinal Disorders

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Important Notice: Breastfeeding is best for infants and young children and Nutricia strongly recommends and supports breastfeeding. Nutricia supports the World Health Organization's global public health recommendation for exclusive breastfeeding for the first six months of life and continued for two years along with the introduction of safe and appropriate complementary foods after the first six months of life. For advice on breastfeeding and on decisions related to the health and nutrition of your baby, please consult your physician or other qualified healthcare providers. A well balanced diet, before, during and after delivery, will help sustain an adequate supply of breast-milk. Frequent feeding is the best way to establish and maintain a good milk supply. The introduction of partial bottle-feeding and/or other drinks and foods may have a negative effect on breastfeeding. It is very difficult to reverse a decision not to breast-feed.

CurrentViews
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EDITOR'S NOTE

The world of Medicine has made great advances since its early days. In recent years we have had the privilege of witnessing developments in understanding the pathogenesis of many of the diseases burdening humankind. It is frustrating, though, to realize that most of this up-to-date knowledge does not reach its natural recipients, who are specialists working in daily practice. Thus, we believe that the need for an informative journal is obvious and self-explanatory.

For this reason, CCM fills the gap in continuing medical education to benefit every day clinical practice, by publishing this innovative series of Current Views. In every issue, readers will find a review article and several summary articles. *Current Views in Pediatric Nutrition* was designed to solve the problem of information overload for specialist physicians. Each journal is compiled by the CCM editorial team based on an ongoing review of the international literature, and articles are selected for review and citation on the basis of their relevance to clinical practice.

Current Views in Pediatric Nutrition provides specialists with an attractive means of continuing medical education that demonstrates the best of critical thinking and is a source of, and a catalyst for, new ideas and learning. The editors and medical advisors at CCM have made every effort to search the international literature to present the most current, interesting and cutting edge articles, in order to make *Current Views in Pediatric Nutrition* a respected and useful tool for physicians with one aim: to provide a good service to their patients. For this issue, we have retrieved information from several well respected peer reviewed journals:

Am J Clin Nutr
Ann Nutr Metab
Br J Nutr
Foods
Front Neuroendocrinol
Front Pediatr
Gut Microbes
J Allergy Clin Immunol Pract
J Pediatr (Rio J)
J Pediatr Gastroenterol Nutr
J Pediatr
Neonatology
Neuroimage
Nutrients
Nutrition
Pediatrics
PLoS One
Prev Med
Trends Microbiol

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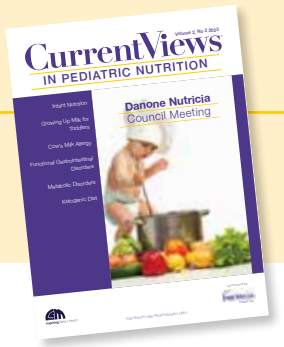

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A Note from the Regional Editors

Progress in Pediatric Nutrition has continued at a spectacular pace culminating in a rapid surge in the number of increasingly precise articles on the assessment of growth, the nutritional status assessment and feeding guidelines, biochemical evaluation of nutritional status, infant nutrition, enteral nutrition, parenteral nutrition, nutritional management in health as well as in disease for residents in Pediatrics, powered by research. The cumulative knowledge of the complexities of Pediatric Nutrition continues to be the foundation of new advances across the clinical care continuum.

Discoveries in the fields of metabolism, genomics and immunology have been particularly fruitful and have firmly established two new pillars of clinical care. These exciting fields of research also show immense promise for the future. Furthermore, Clinical Medical Societies have been updating their Guidelines for Pediatric Nutrition.

Current Views in Pediatric Nutrition was designed to solve the problem of information overload for specialist physicians. Each journal is compiled by the Regional Editors based on an ongoing review of the international literature, and articles are selected and then summarized for citation and review on the basis of their relevance to clinical practice.

Current Views in Pediatric Nutrition mainly caters to the needs of the professionals, researchers, clinical practitioners and medical practitioners in the field of Pediatrics. Our content covers topics that advance clinical practice, and tackle issues related to global Pediatrics. The Regional Editorial Board's aim is to include the most complete and reliable sources of information and discoveries ongoing in Pediatrics and Nutrition research and treatment. The Regional Editors work as a distinguished team of experts to ensure the highest standards of article selection. All relevant articles in the international literature are carefully considered and once selected, all materials are promptly processed and published.

The stringency of selecting and voting state-of-the-art articles was done by our respected Regional Editorial team members who are listed within the journal. Our fundamental purpose is to advance clinically-relevant knowledge of Pediatric Nutrition, and improve the outcome of prevention, diagnosis and treatment of pediatric disease.

In this second issue, due to the spectacular developments seen lately, original research articles, early reports and review articles covering key points, potential pitfalls, and management algorithms which allow for rapid-reference, and link with the latest evidence, related to the food fortification interventions, postbiotics in early life, the role of synbiotics in cow's milk allergy, iron supplementation, and ketogenic diet in epilepsy have been included.

We believe that the readers will find many topics of interest related to their everyday practice.

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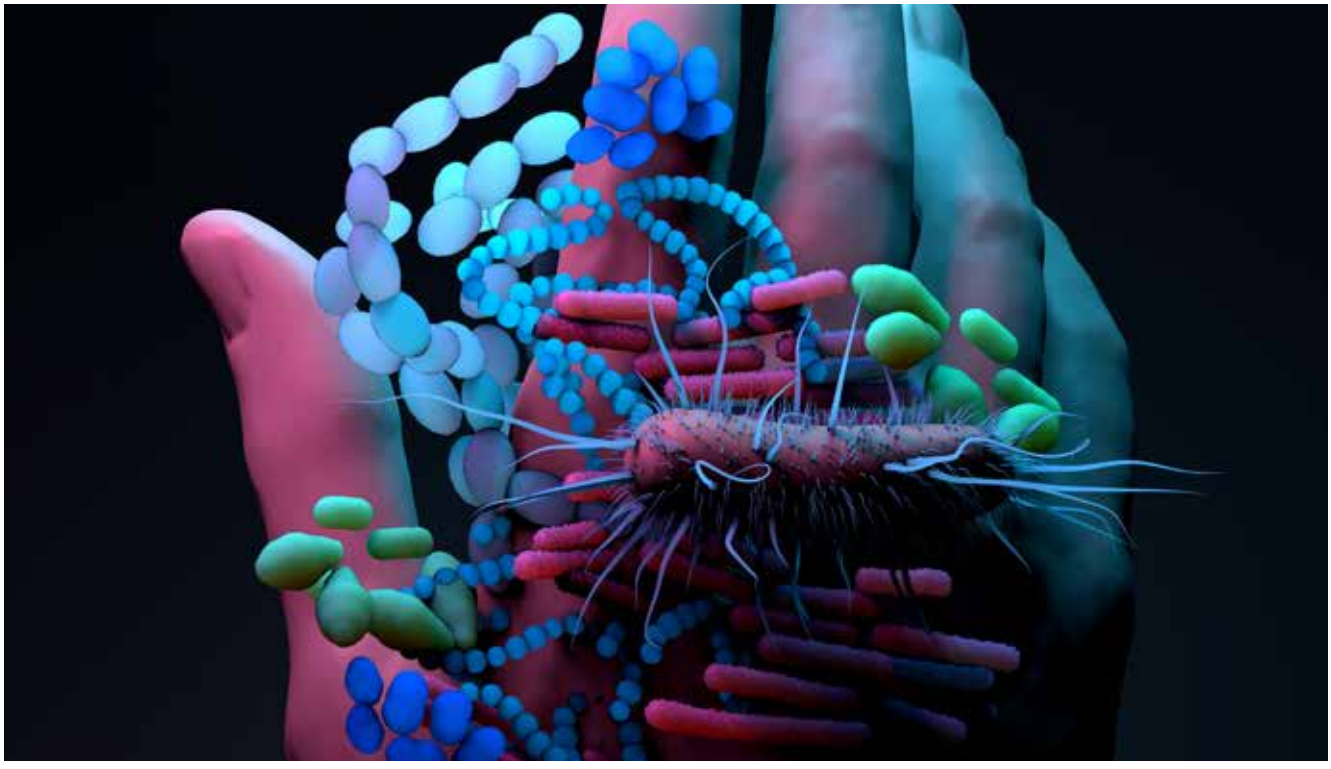
Infant Nutrition



Adaptation of the Infant Gut Microbiome during the Complementary Feeding Transition[1]

Source: *McKeen S, Roy NC, Mullaney JA, Eriksen H, Lovell A, Kussman M, Young W, Fraser K, Wall CR, McNabb WC. Adaptation of the infant gut microbiome during the complementary feeding transition. PLoS One. 2022 Jul 14;17(7):e0270213. doi: 10.1371/journal.pone.0270213.*

The infant gut microbiome progresses in composition and function during the introduction of solid foods throughout the first year of life. In this study the authors hypothesized that changes in the composition, rather than function, of the gut microbiome of infants, are more significant during the time-period when infants are introduced to solid foods (between 4 and 9 months of age), compared to approximately 3 months later (between 9 and 12 months of age) when the diet has continued to diversify.

The purpose of this study was to characterize changes in healthy infant gut microbiome composition, metagenomic functional capacity, and associated metabolites over the course of the complementary feeding period. Fecal samples were obtained at three 'snapshot' timepoints from infants participating in the 'Nourish to Flourish' pilot study: before the introduction of solid foods at approximately 4 months of age, after introducing solid foods at 9 months of age, and after continued diet diversification at 12 months of age. KEGG and taxonomy assignments were correlated with Liquid Chromatography-Mass Spectrometry (LC-MS) metabolomic profiles to identify patterns of co-abundance.

The composition of the microbiome diversified during the first year of life, while the functional capacity present in the gut microbiome remained stable. The introduction of solid foods between 4 and 9 months of age corresponded to a larger magnitude of change in relative abundance of sequences assigned to KEGG (Kyoto Encyclopedia of Genes and Genomes) pathways (sequences assigned to taxonomy and gene functions) and taxonomic assignments, as well as to stronger correlations with metabolites, compared to the magnitude of changes and number of correlations seen during continued diet diversification between 9 and 12 months of age. Changes in aqueous fecal metabolites were more strongly correlated with KEGG pathway assignments, while changes in lipid metabolites were associated with taxonomic assignments, particularly between 9 and 12 months of age.

This study investigated how the infant gut microbiome adapts to the addition and continuation of solid foods during the first year of life by characterizing shifts in species composition and functional capacity and identifying significant correlations with gut metabolites. Fecal samples were utilized as a proxy of the microbiome and metabolome in the lower gut. The novel aspect of this study was the identification of metabolites that associate with composition and predictive functional capacity of the microbiota before and after the introduction of solid foods. These highly correlated metabolites may be relevant compounds for further investigations into complementary feeding using targeted metabolomics.

The higher variance (beta diversity) of both taxonomy and KEGG pathway assignments at 4 months of age compared to 9 or 12 months of age suggests that the effects of early-life factors with known impacts on the infant gut microbiome that differed among infants in this cohort diminished with the addition of solid foods.

In brief, this study established trends in microbiome composition and functional capacity occurring during the complementary feeding period and identified potential metabolite targets for future investigations.

Partially Hydrolyzed Protein as a Protein Source for Infant Feeding: Do or Don't?[2]

Source: *Vandenplas Y, Ksiazyk J, Luna MS, Migacheva N, Picaud JC, Ramenghi LA, Singhal A, Wabitsch M. Partial Hydrolyzed Protein as a Protein Source for Infant Feeding: Do or Don't? Nutrients. 2022 Apr 21;14(9):1720. doi: 10.3390/nu14091720.*

Exclusive breastfeeding until the age of six months is the recommended feeding method for all infants. However, this is not possible for every infant. Therefore, a second choice of feeding, as close as possible to the gold standard, is needed. Hydrolyzed formulas for infants who are not breastfed can be of two types: partially or extensively hydrolyzed cow's-milk-protein based.

Partial hydrolysates have been available in many countries for more than 30 years. They have been marketed in Europe as "hypo-allergenic formulae". This terminology caused a lot of confusion, as the term "hypo-allergenic formula" is used in the US to describe a formula that is effective in the management of CMA in more than 90% of all infants, with a confidence interval of 95%. In Europe, the use of "hypo-allergenic" ("HA") was intended to indicate "reduced allergenicity", as it was hypothesized that hydrolyzed cow's milk protein would reduce its allergenicity.

This paper discusses if this second-choice feeding method should contain intact protein or partially hydrolyzed proteins. Partial hydrolysates are more easily digested than intact proteins. An accelerated transit time in preterm infants fed partially hydrolyzed formulas, compared to intact proteins,

was demonstrated. Numerous studies suggest a benefit of partially hydrolyzed formulas in managing infantile colic, regurgitation, and constipation. Unfortunately, the partial hydrolyzation of the protein is only one of several changes in formula composition in all these studies. Other changes include reduced lactose, change in lipid content, and the addition of a thickening agent, and, therefore, it is impossible to pinpoint the hydrolysate as the single influential factor.

The limited data available indicates that mother's milk is relatively rich in bioactive peptides. Whether partially hydrolyzed protein might be a protein source closer to human milk protein content than intact cow's milk needs further research. However, more research on protein and bioactive peptides in mother's milk should be a priority for future scientific development in this field. Results of such research will also provide an answer to the question of which option would be the best second choice for infant feeding if sufficient breast milk is not available.

In brief, the risks and benefits of choosing a partially hydrolyzed formula in non-exclusively breastfed infants should be discussed between the health care professional and the infant's caregivers. The current stage of knowledge leads more to a philosophical discussion than to an evidence-guided information. While there is a high degree of certainty that partially hydrolyzed formulas are safe, substantial proof of their benefit has not been demonstrated. Regarding allergy prevention, studies showed either no benefit or some benefit. Most studies show benefits regarding the management and prevention of functional gastrointestinal disorders, although the hydrolyzed protein was always only one of the multiple changes introduced to the formula.

The Role of Human Milk Lipids and Lipid Metabolites in Protecting the Infant against Non-communicable Disease[3]

Source: *George AD, Burugupalli S, Paul S, Mansell T, Burgner D, Meikle PJ. The Role of Human Milk Lipids and Lipid Metabolites in Protecting the Infant against Non-Communicable Disease. Int J Mol Sci. 2022 Jul 6;23(14):7490. doi: 10.3390/ijms23147490.*

The incidence of non-communicable diseases (NCD), including type 2 diabetes, cardiovascular disease and chronic obstructive pulmonary disease, is rapidly increasing and NCD are predicted to contribute to over 75% of deaths worldwide by 2030. The pathogenesis of most NCD begins in childhood, as early as the first 1000 days of life, and during this period of developmental and physiological plasticity, nutrition is a key determinant of long-term health outcomes.

Early life obesity tracks from childhood to adulthood, is associated with obesity, inflammation, and

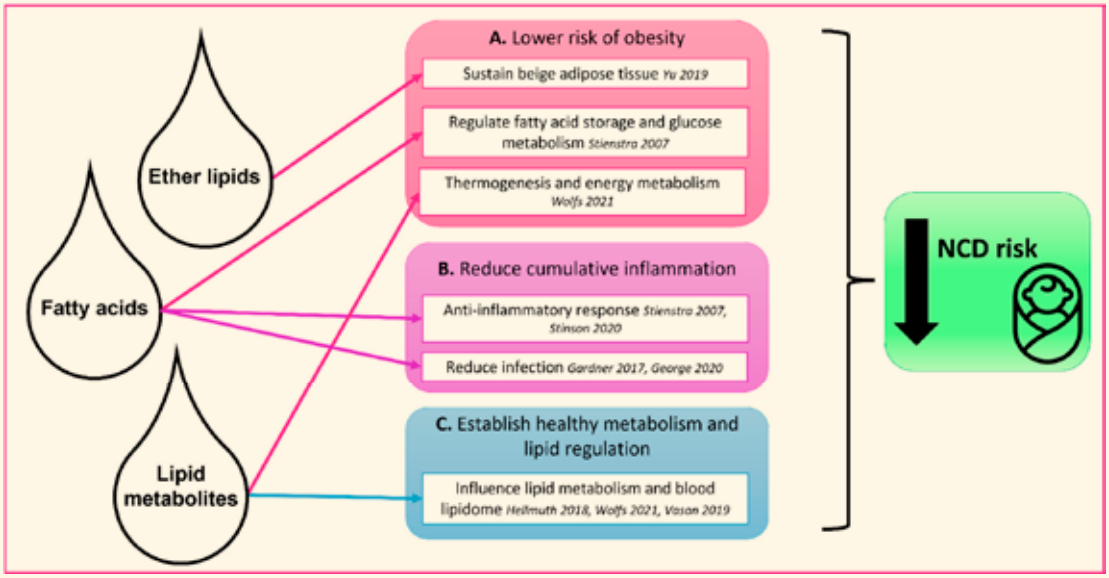


Figure 1. *Summary of the possible roles of bioactive human milk lipids and lipid metabolites in protecting the infant against non-communicable disease risk. Lipids and lipid metabolites are delivered to the infant early in life through human milk and contribute to (A) lower risk of obesity, (B) reduction in cumulative inflammation, and (C) establishment of healthy metabolism and lipid regulation. Arrows indicate identified associations between human milk components and infant protection, as per the literature. (George AD et al. Int J Mol Sci. 2022).*

metabolic dysfunction, and predicts non-communicable disease risk in later life. There is mounting evidence that these factors are more prevalent in infants who are formula-fed compared to those who are breastfed. Human milk provides the infant with a complex formulation of lipids, many of which are not present in infant formula, or are present in markedly different concentrations, and the plasma lipidome of breastfed infants differs significantly from that of formula-fed infants.

There is increasing evidence of the importance of lipids in human health and given the differences between human milk and infant formula lipid composition, as well as differences in the blood lipidome of breastfed and formula-fed infants, the lack of exposure to the human milk lipidome may contribute to metabolic dysfunction and the higher risk of NCD observed in formula-fed infants.

The lipid composition of human milk is a promising approach to understanding how breastfeeding protects against obesity, inflammation, and subsequent cardiovascular disease risk. Human milk lipids and lipid metabolites need to be recognized as bioactive, and new profiling strategies will be required to understand these lipids at an individual species level, and as a system of many different components in human cohorts.

In this study, the authors reviewed bioactive human milk lipids and lipid metabolites that may play a protective role against obesity and inflammation in later life and identified key knowledge gaps and highlight priorities for future research.

Enrichment of Infant Formula with Long-chain Polyunsaturated Fatty Acids and Risk of Infection and Allergy in the Nationwide ELFE Birth Cohort[4]

Source: *Adjibade M, Davisse-Paturet C, Bernard JY, Adel-Patient K, Divaret-Chauveau A, Lioret S, Charles MA, de Lauzon-Guillain B. Enrichment of infant formula with long-chain polyunsaturated fatty acids and risk of infection and allergy in the nationwide ELFE birth cohort. Allergy. 2022 May;77(5):1522-1533. doi: 10.1111/all.15137.*

With regard to early feeding, the protective effect of breastfeeding on infections is well-established, but its potential effect on allergic diseases is more controversial. Exclusive breastfeeding is recommended for the first 6 months of life or at least 4 months, but several studies have shown a high level of noncompliance with these recommendations. The new European regulations require the enrichment of formulas with docosahexaenoic acid (DHA) because of the positive effects of long-chain polyunsaturated fatty acids (LCPUFAs) on neurodevelopment and visual acuity.

The purpose of this observational study was to evaluate whether the consumption of LCPUFA-enriched formula was associated with the risk of infection and allergy in early childhood.

Analyses involved data from 8389 formula-fed infants from the ELFE birth cohort. Formula enrichment was identified from the list of ingredients of the formula consumed at 2 months. Infections (gastrointestinal, lower respiratory tract infections [LRTI], upper respiratory tract infections [URTI]) and allergies (wheezing, itchy rash, asthma medication, food allergy) from age 2 months to 5.5 years were reported by parents during follow-up surveys. Multivariable logistic regression models were used to assess associations between the consumption of LCPUFA-enriched formula and the risk of infection and allergy.

Among formula-fed infants at 2 months, 36% consumed formula enriched with DHA and arachidonic acid (ARA), and 11% consumed formula additionally enriched with eicosapentaenoic acid (EPA). Enriched formula consumption was not associated with infection or allergy, except for an association between consumption of DHA/ARA/EPA-enriched formula and lower use of asthma medications. Furthermore, as compared with non-DHA/ARA/EPA-enriched formula, consumption of formula with high EPA content (≥3.2 mg/100 kcal) was related to lower risk of LRTI and lower use of asthma medications.

In this observational study, one quarter of formula-fed infants consumed a formula enriched in DHA/ARA and just over one-tenth consumed a formula additionally enriched in EPA. In the full sample, consumption of infant formula with low DHA content (<10 mg/100 kcal) was associated with a higher risk of LRTI and wheezing up to age 5.5 years, whereas an opposite trend was observed for high DHA content. The consumption of formula with high EPA content (≥3.2 mg/100 kcal) was associated with a lower risk of LRTI and use of asthma medications up to age 5.5 years. No significant association was found between LCPUFA enrichment and occurrence of gastrointestinal infection, UTRI, itchy rash, or food allergy up to age 5.5 years. Among exclusively formula-fed infants, the consumption of formula with high EPA content was associated with a lower risk of URTI.

In conclusion, this study suggests that consumption of DHA/ARA/EPA-enriched formula (especially those with high EPA content) is associated with a lower risk of LRTI and lower use of asthma medications.

Presence and Levels of Galactosyllactoses and Other Oligosaccharides in Human Milk and their Variation during Lactation and according to Maternal Phenotype[5]

Source: *Eussen SRBM, Mank M, Kottler R, Hoffmann XK, Behne A, Rapp E, Stahl B, Mearin ML, Koletzko B. Presence and Levels of Galactosyllactoses and Other Oligosaccharides in Human Milk and Their Variation during Lactation and According to Maternal Phenotype. Nutrients. 2021 Jul 6;13(7):2324. doi: 10.3390/nu13072324.*

Human milk oligosaccharides (HMOS) are the third most abundant solid component in human milk (HM) after lactose and lipids, reaching between 5 and 20 g/L in mature HM. The concentrations of oligosaccharides in HM vary within and among women and are influenced by various factors, including the stage of lactation, parity, maternal diet, body mass index, ethnicity, socioeconomic status and genetic predisposition.

HMOS have been suggested to play an important role in healthy infants' development, ranging from reported effects on growth and early life immune function to effects on the gut microbiota and intestinal functions. HM is proposed to consist of more than 1000 individual and unique HMOS of which only approximately 200 are fully structurally characterized. Among the human milk oligosaccharides (HMOS); there has only been limited study of the galactosyllactoses (GLs).

The objective of this study was to describe the presence and relative levels of HMOS, including GLs, in human milk (HM) according to maternal Secretor and Lewis (SeLe) phenotype and lactation stage. Relative levels of 19 HMOS were measured in 715 HM samples collected in the first 4 months postpartum from 371 donors participating in the PreventCD study.

From a subset of 24 Dutch women (171 HM samples), samples were collected monthly up to 12 months postpartum and were additionally analyzed for relative and absolute levels of β6'-GL, β3'-GL and α3'-GL. Maternal SeLe phenotype or HM group was assigned based on the presence of specific fucosylated HMOS. Most HMOS, including β6'- and β3'-GL, were present in the vast majority (≥75%) of HM samples, whereas others (e.g., LNDFH II, 2'-F-LNH and α3'-GL) only occurred in a low number (<25%) of samples.

Clear differences were observed between the presence and relative levels of the HMOS according to the maternal phenotype and lactation stage. Absolute concentrations of β6'-GL and β3'-GL were higher in HM group IV samples compared to samples of the other three HM groups. β3'-GL was also higher in HM group II samples compared to

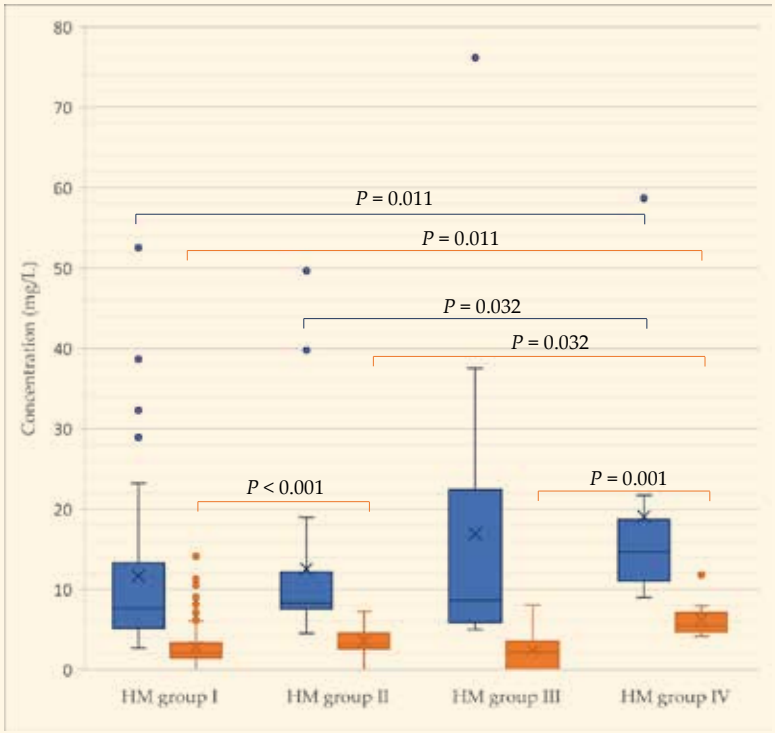


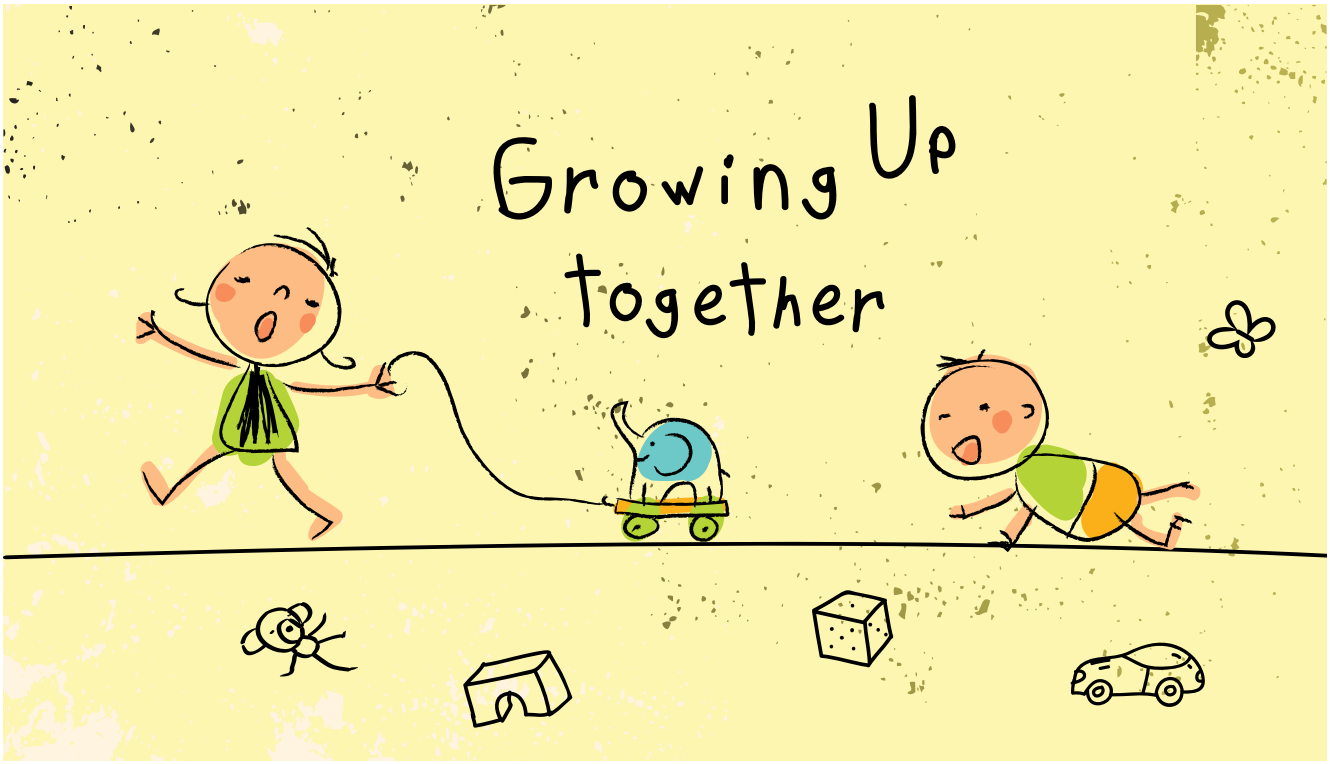
Figure 2. *Absolute concentrations of 1-6'-galactosyllactose (60-GL) and 1-3'-galactosyllactose (30-GL) in the human milk (HM) samples in the first year of lactation according to HM group. Significance values have been adjusted by the Bonferroni correction for multiple tests. A p-value < 0.05 was considered statistically significant. (Eussen SRBM, et al. Nutrients. 2021).*

HM group I samples. β3'-GL and β6'-GL were stable over lactation stages.

A total of 99.6% of the HM samples could be categorized into one of the four HM groups. Most HM samples were categorized as HM group I (66.4%), while 20.7% were assigned to HM group II, 8.7% to HM group III and 3.8% to HM group IV. This is nicely in line with the distribution of Se and Le polymorphisms as reported by Oriol et al. Three HM samples (0.4% of all samples) could not be grouped into one of the four HM groups. These HM samples had in common the absence or very low relative levels of 20-FL, DFL and LNFP I, whereas—in contrast to expectations—LNDFH I was abundantly present. LNDFH I is an 1-2-fucosylated HMOS and its presence indicates a functional FUT2 allele.

In conclusion, the presence and levels of HMOS vary according to HM group and lactation stage. Not all HMOS behave similarly: some HMOS depend strongly on maternal phenotype and/or lactation stage, whereas others do not. β3'-GL and β6'-GL were present in low concentrations in over 75% of the analyzed HM samples and showed differences between HM groups, but not between the lactation stages. Further research on the impact and correlation of the presence and levels of individual HMOS on the healthy development of infants is needed.

Growing Up Milk for Toddlers



Which Milk during the Second Year of Life: A Personalized Choice for a Healthy Future?[6]

Source: *Verduci E, Di Profio E, Corsello A, Scatigno L, Fiore G, Bosetti A, Zuccotti GV. Which Milk during the Second Year of Life: A Personalized Choice for a Healthy Future? Nutrients. 2021 Sep 27;13(10):3412. doi: 10.3390/nu13103412.*

Nutrition in early life is a crucial element to provide all essential substrates for growth. When reaching the age of 12 months, children are usually referred to as toddlers. During the first 1000 days of life, the time from conception to the child's second birthday, are considered a critical period for the healthy development of a newborn. According to the Dietary Reference Values (DRV) of European Food Safety Authority, the energy requirements between 1 and 3 years of life vary according to sex and percentile of physical activity levels (PAL).

Several studies have shown how the intake of micro and macronutrients in toddlers differs a lot from the recommendations of scientific societies. Protein intake often exceeds the recommended amount, while the intake of iron and zinc is frequently insufficient, as well as Vitamin D. Nutritional errors in the first years of life can negatively impact the health of the child in the long term.

To date, no clear evidence on which milk is suggested during the second year of life is yet to be established. In this study, we compare the nutrient profiles of cow's milk and specific formulas as well as nutritional risks in toddlers linked to growth and childhood obesity development. The purpose of this review was to resume the latest clinical studies on toddlers fed with cow's milk or young children formula (YCF), and the potential risks or benefits in the short and long term.

Fat intake should not be limited before 12 months of age, due to its importance in neurologic development. Between 1 and 3 years of age, fat recommended intakes are 35–40% of total daily energy intake (%En).

Long-chain PUFA, docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA) play an important role in brain development. It is known that the DHA status tends to decline during the complementary period, therefore toddlers' diet should guarantee 250 mg daily of EPA and DHA, and for toddlers 1–2 years old a 100 mg daily increase of DHA should be provided.

Carbohydrates should provide the largest percentage of macronutrients, 45% to 60% of %En, in children 1–3 years old. In toddlers there are some critical micronutrients, in which deficiencies have long-term consequences for growth and development as a child and may impact health as an adult. For example, data suggest that children aged 0–24 months may not be getting enough Vitamin D, iodine, or iron.

Italian guidelines for a healthy nutrition recommend daily consumption of 150 mL of cow's milk among children 1–2 years, while between 2 and 3 years the daily portion is 200 mL. Daily milk consumption provides digestible protein and calcium content essential for growth—however, milk has been placed at the bottom of the food pyramid defined by the Italian Society of Pediatrics, among the foods for which a daily consumption is suggested.

Young child formulae (YCF), also known as toddler's milk or growing-up milk (GUM), represent an alternative to cows' milk or breast milk for children 1–3 years of age. YCF are milk-based, or plant-protein-based, formulae intended to partially satisfy nutritional requirements of young children, thus fortified with nutrients that are commonly low during the transition to family-based food.

According to the European Food Safety Authority (EFSA), fortified cow's milk, fortified cereals, and cereal-based foods are efficient ways to increase intakes of these critical nutrients. However, in comparison with cow's milk, currently marketed YCF contain more ALA, DHA (if added), iron and Vitamin D but similar amounts of iodine.

Although the WHO recommends continuing breastfeeding in children up to 2 years of age, this event has been observed to be rarely fulfilled among the general population. Breastfeeding rates decrease rapidly with increasing age and only a few infants are breastfed until one year of life, and cow's milk is frequently introduced into the diet replacing breast milk. Cow's milk contains approximately 3 times as much protein as human milk.

Novel approaches in managing toddlers` nutrition should underline which type of milk is a better choice according to individual needs. When consuming a YCF alongside a balanced diet, nutritional requirements are more easily ensured, thanks to formulas specifically developed for toddlers. By contrast, dietary patterns including cow's milk should address daily consumption of fortified cereals and sunflower oil, together with olive oil to obtain an optimal macro- and micro-nutrient intake (Figure 3).

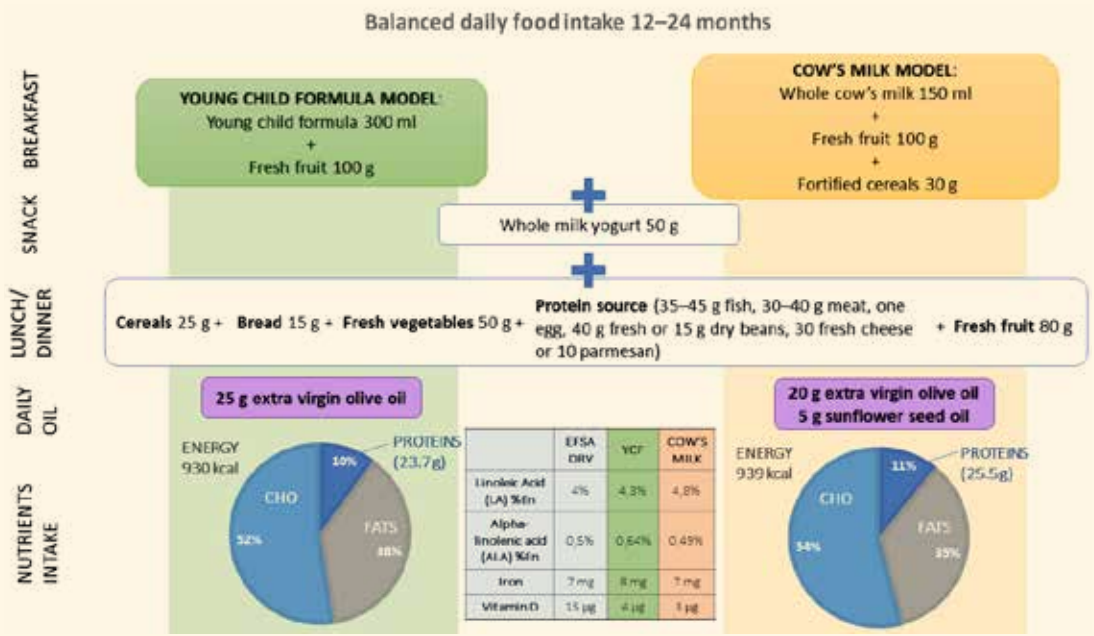


Figure 3. *Suggested daily food intake for 12–24-month-old children depending on the type of milk consumed (young child formula, cow's milk) to ensure a nutrients intake within the range of reference values. (Verduci E et al. Nutrients. 2021;13(10):3412).*

In conclusion, personalized dietary strategies could be favorable in promoting a healthy diet with an optimization of nutrients' intake. However, future studies are needed to better underline the role of YCF on growth and health of toddlers, and their possible effects in the long term.

Cow's Milk Allergy

The Clinical Burden of Cow's Milk Allergy in Early Childhood: A Retrospective Cohort Study[7]

Source: *Sorensen K, Meyer R, Grimshaw KE, Cawood AL, Acosta-Mena D, Stratton RJ. The clinical burden of cow's milk allergy in early childhood: A retrospective cohort study. Immun Inflamm Dis. 2022 Mar;10(3):e572. doi: 10.1002/iid3.572.*

Cow's milk allergy (CMA) is common in infants and children. Clinical presentations may vary, with a range of symptoms affecting the gastrointestinal (GI), skin and respiratory systems. Whilst the primary focus of research to date has been on the management of these symptoms, studies investigating the broader clinical burden of CMA are limited.

In this study, Sorensen et al performed a retrospective matched cohort study examining clinical data, including allergic symptoms and infections, extracted from case records within The Health Improvement Network database. A total of 6998 children (54% male) were included in the study, including 3499 with CMA (mean age at diagnosis 4.04 months) and 3499 matched controls without CMA, observed for a mean period of 4.2 years.

During the observation period, gastrointestinal (GI), skin and respiratory symptoms affected significantly more children with CMA ($p < .001$), which recurred more often ($p < .001$), compared with children without CMA. More children with CMA had symptoms affecting multiple systems ($p < .001$). CMA was associated with a greater probability of these symptoms requiring hypoallergenic formula (HAF) prescription persisting over time (log-rank test $p < .0001$, unadjusted hazard ratio [HR]: 0.81, 95% confidence interval [CI]: 0.76-0.85, $p < .001$), with a

longer median duration of symptoms and HAF prescription compared with the duration of symptoms in those without CMA (3.48 vs. 2.96 years).

GI, skin, respiratory and ear infections affected significantly more children with CMA than those without, increasing by 74% ($p < .001$), 20% ($p < .001$), 9% ($p < .001$), and 30% ($p < .001$) respectively. These infections also recurred more often among children with CMA, increasing by 62% for GI infections, 37% for skin and respiratory infections, and 44% for ear infections ($p < .001$).

This data, from nearly 7,000 children who were observed for more than 4 years on average, shows that children with CMA not only suffer from more symptoms, but also face a significantly greater infectious burden than children without CMA, providing valuable insights into the clinical experiences of children with CMA in the United Kingdom.

Whilst symptoms were common to both cohorts, those with CMA had significantly more symptoms compared with children without CMA. GI symptoms affected 55% more children with CMA, occurring 115% more often. The greatest increases in prevalence were seen in reflux and colic. Skin symptoms affected more children with CMA, with increases of 57% in eczema and 52% in urticaria and erythema, recurring 91% more often overall. Respiratory symptoms affected 96% more children with CMA, increasing by 108% for rhinitis and 89% for asthma, recurring 100% more frequently overall.

This real-world study provided evidence suggesting that CMA presents a significant clinical burden to children, which has implications for the healthcare system. Further research is warranted to understand the health economic impact of this, and the phenotypes, factors and management approaches which may affect clinical outcomes.

International Cross-Sectional Survey among Healthcare Professionals on the Management of Cow's Milk Protein Allergy and Lactose Intolerance in Infants and Children[8]

Source: *Madrazo JA, Alrefaee F, Chakrabarty A, de Leon JC, Geng L, Gong S, Heine RG, Järvi A, Ngamphaiboon J, Ong C, Rogacion JM. International Cross-Sectional Survey among Healthcare Professionals on the Management of Cow's Milk Protein Allergy and Lactose Intolerance in Infants and Children. Pediatr Gastroenterol Hepatol Nutr. 2022 May;25(3):263-275. doi: 10.5223/pghn.2022.25.3.263.*

The aim of this international survey among healthcare providers was to collect data on theoretical knowledge and clinical practices in the diagnosis and management of cow's milk protein allergy (CMPA) and lactose intolerance (LI) in infants. To this end, a global survey was conducted in several countries with diverse health care settings. The survey consisted of multiple-choice questions in 3 main domains: (1) understanding and clinical practices around CMPA and LI; (2) case scenarios; and (3) disease-specific knowledge and potential educational needs.

Responses were available from 1,663 participants. About 62% of respondents were general practitioners or general pediatricians, and the remainder were pediatric allergiologists/gastroenterologists (18%) or other health practitioners (20%). The survey identified knowledge gaps regarding the types of CMPA (IgE-mediated vs. non-IgE-mediated) and the clinical overlap with LI. The survey suggested diverse clinical practices regarding the use of hypoallergenic formulas, as well as misconceptions about the prebiotic benefits of lactose in extensively hydrolyzed formulas in non-breastfed infants with CMPA. Responses to the two case scenarios highlighted varying levels of awareness

of the relevant clinical practice guidelines. While respondents generally felt confident in managing infants with CMPA and LI, about 80% expressed an interest for further training in this area.

In general, healthcare professionals appeared to have a good understanding of the signs and symptoms of IgE-mediated CMPA. Consistent with its pathophysiology, most respondents chose the detection of cow's milk-specific serum IgE and skin prick testing as appropriate diagnostic tools. However, the role of diarrhea as a major clinical feature of IgE-mediated CMPA appeared to be overestimated. Some knowledge gaps also became apparent for the distinction between non-IgE-mediated CMPA and LI. These mainly related to signs and symptoms, with only a small proportion of respondents recognizing the spectrum of extra-intestinal manifestations in non-IgE-mediated CMPA, including atopic dermatitis.

In brief, this survey identified some knowledge gaps and regional differences in the management of infants with CMPA or LI. Local educational activities among general and pediatric healthcare providers may increase the awareness of clinical practice guidelines for the diagnosis and treatment of both conditions and help improve clinical outcomes.

The Association between Early Formula and Reduced Risk of Cow's Milk Allergy during the First Three Years of Life[9]

Source: *Ikari K, Tezuka J, Sanefuji M, Nakayama J, Nishima D, Sonoda Y, Ogawa M, Shimono M, Suga R, Honjo S, Kusuhara K, Ohga S; Japan Environment and Children's Study (JECS) Group. The association between early formula and reduced risk of cow's milk allergy during the first three year of life: a Japanese cohort study. Allergy Asthma Clin Immunol. 2022 Aug 7;18(1):71. doi: 10.1186/s13223-022-00712-z.*

Although breastfeeding has many benefits and is thus recommended for all infants, cow's milk (CM) formula can be used as a substitute for breastmilk. Observational studies have demonstrated that a reduced risk of CMA is associated with regular consumption of formula started by three months old whereas others have shown no definite association.

A recent observational study showed that regular consumption of cow's milk (CM) formula during early infancy (3-6 months old) was associated with a reduced risk of CM allergy (CMA) at 12 months old. However, the long-term association is unclear. The objective of this study, conducted by Ikari at al, was to examine how long this inverse association persists after 12 months old.

The authors used the dataset of an ongoing nationwide prospective cohort, the Japan Environment and Children's Study, in which participants were registered between January 2011 and March 2014. They analyzed 65,568 children followed-up until 36 months old. The exposure factors were the consumption statuses of formula milk from 0-3, 3-6, and 6-12 months old. The primary outcome was the prevalence of CMA at 6, 12, 18, 24 and 36 months old. CMA was defined as an allergic reaction and sensitization to CM protein in an individual with no or limited intake of this protein at the evaluation time, combined with physician-diagnosed food allergy. Multivariable regression models were used

to estimate the association between the periods of formula consumption and the prevalence of CMA.

It was found that the prevalence of CMA increased with a peak of 1.51% at 18 months old and then declined to 0.79% at 36 months old. Formula milk from 3-6 months old was associated with a reduced risk of CMA throughout the first 3 years of life, although the extent of the reduction was mitigated with age (adjusted relative risk: [95% confidence interval]: 0.19 [0.10-0.34] at 12 months old, 0.23 [0.16-0.33] at 18 months old, 0.41 [0.26-0.64] at 24 months old, and 0.47 [0.26-0.80] at 36 months old). The association between early formula and CMA were observed in both children with and without eczema, but more prominent and long-lasting in the former than the latter.

The authors previously reported that the risk of CMA at 12 months old was reduced when a child regularly consumed CM formula during early infancy (3–6 months old) rather than in the very-early period (0–3 months old). In this study, they demonstrated that this finding continued until 36 months old. The risk of CMA was consistently reduced in children fed formula early, although the extent of the reduced risk was mitigated with age. This association between early formula and CMA were observed in both children with and without eczema, but the effect sizes of the association were more prominent and long-lasting in the former than the latter.

These observations suggest that early formula would make an important contribution to CMA development persistently during early childhood.

Regular exposure to CM protein during infancy was associated with a reduced prevalence of CMA during early childhood. At present, however, this observational study does not necessarily encourage formula feeding, and randomized controlled trials are warranted to confirm the findings and their significance.

Functional Gastrointestinal Disorders

Intestinal Permeability in Children with Functional Gastrointestinal Disorders: The Effects of Diet[10]

Source: *Giorgio V, Margiotta G, Stella G, Di Cicco F, Leoni C, Proli F, Zampino G, Gasbarrini A, Onesimo R. Intestinal Permeability in Children with Functional Gastrointestinal Disorders: The Effects of Diet. Nutrients. 2022 Apr 11;14(8):1578. doi: 10.3390/nu14081578.*

Functional gastrointestinal disorders (FGIDs) are very common and life-impacting in children and young adults, covering 50% of pediatric gastroenterologist consultations. FGIDs are defined as a combination of clinical patterns characterized by chronic or recurrent gastrointestinal symptoms not explained by biochemical or structural alterations. FGIDs may be due to alterations in the gut-brain axis, dysbiosis and dysregulation of intestinal barrier, causing leaky gut. This may enhance increased antigen and bacterial passage through a damaged mucosa, worsening the impact of different medical conditions such as FGIDs.

Nutritional support is a primary therapy for some gastrointestinal diseases, i.e., Crohn's disease, as it allows the inflammatory activity to be controlled and may be an alternative to pharmacological treatment Little is known about the role of nutrients in modifying this "barrier disruption". The aim of this narrative review was to analyze the clinical evidence concerning diet and Intestinal Permeability (IP) in FGIDs in children.

Giorgio et al searched the PubMed/Medline library for articles published between January 2000 and November 2021 including children aged 0-18 years old, using keywords related to the topic. Since diet induces changes in the intestinal barrier and microbiota, the authors aimed at clarifying how it is possible to modify IP in FGIDs by diet modulation, and how this can impact on gastrointestinal symptoms.

Starting from the nutritional side, as shown in Figure 4, it has been demonstrated that a low-FODMAP (fermentable oligo-, di-, mono-saccharides, and polyols) diet, reducing carbohydrate fermentation and modulating microbiota, improves intestinal permeability, and so, intestinal discomfort in terms of bloating, bowel movements and number and peaks of abdominal pain episodes. There is still little clarity regarding the role played by dietary fibers, being able to bring benefits, or a symptom's worsening, but the major part of the studies currently available seem to demonstrate their benefit if administered in adequate quantities for age, and possibly from natural sources. These positive effects can be explained because dietary fibers are fermented by microbiota in short-chain fatty acids

(SCFAs) that mediate gut epithelial integrity and improve IP.

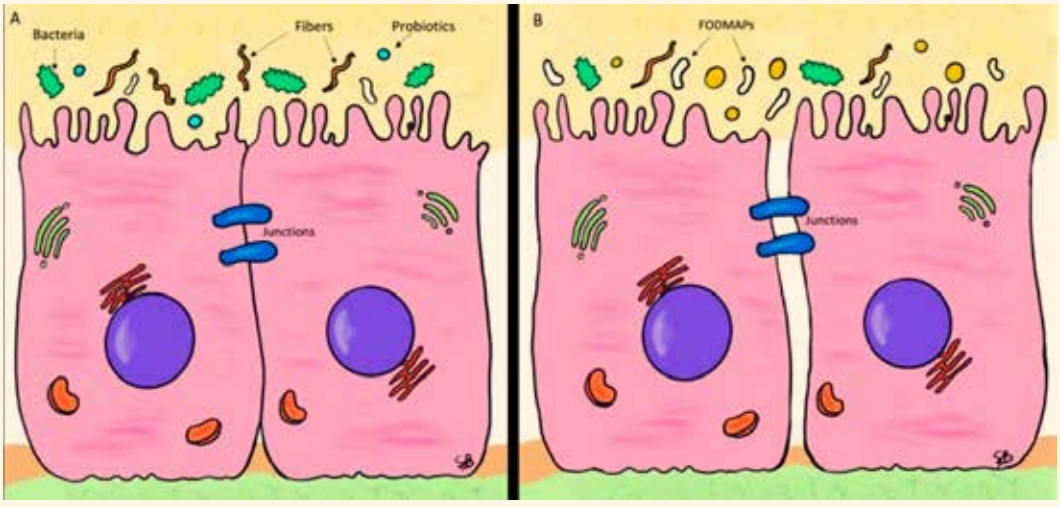


Figure 4. *Normal vs. leaky gut (A) Normal enterocytes characteristic of a healthy gut. Thanks to the barrier balance, due to microbiota, fibers and pre- and pro-biotics, the TJs are intact and IP is preserved; (B) Typical epithelium of a leaky gut. TJs are malfunctioning due to an excess of FODMAPs, dysbiosis and scarcity of fibers and pre- and pro biotics. (Giorgio Vet al. Nutrients. 2022).*

The authors found that that small changes in eating habits, such as a low-FODMAP diet, an adequate intake of fiber and intestinal microbiota modulation by prebiotics and probiotics, seem to lead to big improvements in quality of life.

The intestinal barrier plays a key role in improving or worsening symptoms in functional gastrointestinal disorders. Small changes in eating habits seem to lead to big improvements in quality of life. Many nutritional aspects - such as low FODMAPs, adequate intake of fiber, and intestinal microbiota modulated by prebiotics and probiotics - have an important positive effect on intestinal permeability. The knowledge about the complex communication mechanism of the gut–microbiota–brain axis is still scarce, and further studies are needed to better define these aspects.

Gut Microbiota in Various Childhood Disorders: Implication and Indications[11]

Source: *Saeed NK, Al-Beltagi M, Bediwy AS, El-Sawaf Y, Toema O. Gut microbiota in various childhood disorders: Implication and indications. World J Gastroenterol. 2022 May 14;28(18):1875-1901. doi: 10.3748/wjg.v28.i18.1875.*

Gut microbiota has a significant role in gut development, maturation, and immune system differentiation. It exerts considerable effects on the child's physical and mental development. The gut microbiota composition and structure depend on many host and microbial factors. The host factors include age, genetic pool, general health, dietary factors, medication use, the intestine's pH, peristalsis, and transit time, mucus secretions, mucous immunoglobulin, and tissue oxidation-reduction potentials.

The microbial factors include nutrient availability, bacterial cooperation or antagonism, and bacterial adhesion. Each part of the gut has its microbiota due to its specific characteristics. The gut microbiota interacts with different body parts, affecting the pathogenesis of many local and systemic diseases.

Over the first year of life, the gut microbiota in infants born by caesarean section appears less stable with a predominance of pathogenic bacteria such as Klebsiella and Enterococcus and delayed acquisition of the beneficial Bifidobacterium. Breast or bottle feeding also significantly impacts the gut microbiota. Exclusively breastfed infants have lower microbial diversity with a predominance of infant-type Bifidobacteria than formula-fed babies whose gut microbiota is more diverse and like older children. The predominance of infant-type Bifidobacteria significantly impacts the immune system's maturation and development, which may help decrease the incidence of childhood infections.

Dysbiosis is a common finding in many childhood disorders such as autism, failure to thrive, nutritional disorders, coeliac disease, Necrotizing Enterocolitis, helicobacter pylori infection, functional gastrointestinal disorders of childhood, inflammatory bowel diseases, and many other gastrointestinal disorders. Dysbiosis is also observed in allergic conditions like atopic dermatitis, allergic rhinitis, and asthma. Dysbiosis can also impact the development and the progression of immune disorders and cardiac disorders, including heart failure. Probiotic supplements could provide some help in managing these disorders.

Early modification and restoration of gut microbiota may be an encouraging tool to counteract the increasing childhood metabolic disorders, including overweight and obesity, providing the specific anti-obesity microbiota.

In this narrative review, the authors shed some light on the role of microbiota in the development and management of common childhood disorders.

In brief, there is an intimate relationship between the human and his body microbes. The gut is the primary residence for the microbiota, as it provides the bacteria with a convenient environment for thriving. The microbiota plays a significant role in gut development, maturation, and immune system differentiation. It exerts a considerable effect on the child's physical and mental development. Gut dysbiosis is also a potential pathogenic factor for developing various childhood disorders inside and outside the gastrointestinal tract. Probiotics may have a role in managing these disorders with variable degrees. Even though probiotics could help address these disorders, we need more studies to prove the efficacy, select the proper probiotic for each disease, the appropriate dose, and ensure its safety.

Saudi Experts Consensus on Diagnosis and Management of Pediatric Functional Constipation[12]

Source: *Alshehri DB, Sindi HH, AlMusalami IM, Rozi IH, Shagrani M, Kamal NM, Alahmadi NS, Alfuraikh SS, Vandenplas Y. Saudi Experts Consensus on Diagnosis and Management of Pediatric Functional Constipation. Pediatr Gastroenterol Hepatol Nutr. 2022 May;25(3):163-179. doi: 10.5223/pghn.2022.25.3.163.*

Pediatric gastrointestinal (GI) disorders, including diarrhea, constipation, colic, and regurgitation, are highly prevalent and nonspecific, especially in the Gulf and Middle-Eastern countries. Although functional gastrointestinal disorders (FGIDs) are very common in pediatric patients, there is a scarcity of published epidemiologic data, knowledge of the characteristcs, and management patterns from Saudi Arabia, which is the 2nd largest Arabic country in terms of area and the 6th largest Arabic country in terms of population, with 10% of its population aged <5 years.

Functional constipation (FC) is an FGID that has shown a rising prevalence among Saudi infants and children in the last few years, which urges us to update our clinical practices. Nine pediatric consultants attended two advisory board meetings to discuss and address current challenges, provide solutions, and reach a Saudi national consensus for the management of pediatric constipation. The pediatric consultants agreed that pediatricians should pay attention to any alarming signs (red flags) found during history taking or physical examinations. They also agreed that the Rome IV criteria are the gold standard for the diagnosis of pediatric FC.

Different therapeutic options are available for pediatric patients with FC. Dietary treatment is recommended for infants with constipation up to six months of age. When non-pharmacological interventions fail to improve FC symptoms, pharmacological treatment with laxatives is indicated. First, the treatment is aimed at disimpaction to remove fecal masses. This is achieved by administering a high dose of oral polyethylene glycol (PEG) or lactulose for a few days. Subsequently, maintenance therapy with PEG should be initiated to prevent the re-accumulation of feces.

In addition to PEG, several other options may be used, such as Mg-rich formulas or stimulant laxatives. However, rectal enemas and suppositories are usually reserved for cases that require acute pain relief. In contrast, infant formulas that contain prebiotics or probiotics have not been shown to be effective in infant constipation, while the value of partially hydrolyzed formula is inconclusive.

Treatment recommendations included initial therapy, maintenance therapy, and follow-up visits. The goal of maintenance therapy is to maintain soft bowel movements one or two times per day. Ensuring stool regularity is an essential part of the treatment plan because rectal impaction can recur and restart the constipation cycle. These clinical practice recommendations are intended to be adopted by pediatricians and primary care physicians across Saudi Arabia.

Metabolic Disorders

Usefulness of the Waist-to-height Ratio for Predicting Cardiometabolic Risk in Children and its Suggested Boundary Values[13]

Source: *Muñoz-Hernando J, Escribano J, Ferré N, Closa-Monasterolo R, Grote V, Koletzko B, Gruszfeld D, ReDionigi A, Verduci E, Xhonneux A, Luque V. Usefulness of the waist-to-height ratio for predicting cardiometabolic risk in children and its suggested boundary values. Clin Nutr. 2022 Feb;41(2):508-516. doi: 10.1016/j.clnu.2021.12.008.*

Body mass index (BMI) does not differentiate between fat and lean mass or consider the distribution of fat mass. In contrast, waist circumference (WC) is a low-cost, simple and valid measurement that has the strength of being a better indicator of abdominal fat mass, which has been related to cardiovascular risk parameters in both adults and children. There is limited information available on the usefulness of the waist-to-height ratio (WHtR) as an abdominal obesity marker in children. The objective of this study was to compare the ability of a WHtR >90th percentile, a WHtR ≥0.50, a WHtR ≥0.55 and a BMI z-score ≥2 SD to predict cardiometabolic risk in children followed-up at different ages.

To this end, Muñoz-Hernando et al evaluated data from 660 children at 5, 8 and 11 years of age who participated in the Childhood Obesity Project trial in 5 European countries. The authors classified children with or without cardiometabolic (CMet) risk (yes vs. no) according to the presence of ≥2 parameters (blood pressure, homeostasis model assessment of insulin resistance (HOMA-IR), triglyceride levels and high-density lipoprotein (HDL) cholesterol levels) ≥90th percentile.

It was found that the odds ratio for CMet risk in children at all followed-up ages was statistically significant for all measures. The odds ratio (OR) for the WHtR ≥0.55 cut-off was 29.1 (5.6, 151.7) at 5 years of age, 11.8 (4.1, 33.8) at 8 year of age and 3.6 (1.7, 7.7) at 11 years of age, compared to the WHtR <0.55 cut-off. The WHtR ≥0.55 cut-off showed a higher OR at younger ages than the BMI z-score ≥2SD, WHtR ≥90th percentile and WHtR ≥0.50 cut-offs and a higher positive predictive value (82% at 5 years of age compared to 55%, 36% and 41%, respectively).

Among the different obesity markers that were evaluated, the WHtR >0.55 cut-off had the best discrimination power. The use of a WHtR ≥0.5 cut-off as an abdominal obesity criterion associated with cardiovascular (CV) disease risk was first proposed in adults. In several studies, a WHtR ≥0.5 cut-off was strongly related to CV risk and metabolic syndrome and was a significantly better predictor for CV outcomes, such as diabetes or hypertension, than BMI or WC. A systematic review and a meta-analysis proposed using a cut-off of 0.5 for the WHtR in children and adolescents, the same as in adults, to detect children with increased cardiometabolic risk.

It was concluded that a WHtR ≥0.55 is a suitable cut-off for screening children at high cardiometabolic risk in the general young European population.

Breastfeeding May Benefit Cardiometabolic Health of Children Exposed to Increased Gestational Glycemia in Utero[14]

Source: *Ong YY, Pang WW, Huang JY, Aris IM, Sadananthan SA, Tint MT, Yuan WL, Chen LW, Chan YH, Karnani N, Velan SS, Fortier MV, Choo J, Ling LH, Shek L, Tan KH, Gluckman PD, Yap F, Chong YS, Godfrey KM, Chong MF, Chan SY, Eriksson JG, Wlodek ME, Lee YS, Michael N. Breastfeeding may benefit cardiometabolic health of children exposed to increased gestational glycemia in utero. Eur J Nutr. 2022 Aug;61(5):2383-2395. doi: 10.1007/s00394-022-02800-7.*

There is altered breastmilk composition among mothers with gestational diabetes and conflicting evidence on whether breastfeeding is beneficial or detrimental to their offspring's cardiometabolic health. Ong et al aimed to investigate associations between breastfeeding and offspring's cardiometabolic health across the range of gestational glycemia.

The authors included 827 naturally conceived, term singletons from a prospective mother-child cohort. We measured gestational (26-28 weeks) fasting plasma glucose (FPG) and 2-h plasma glucose (2 hPG) after an oral glucose tolerance test as continuous variables. Participants were classified into 2 breastfeeding categories (high/intermediate vs. low) according to their breastfeeding duration and exclusivity. Main outcome measures included magnetic resonance imaging (MRI)-measured abdominal fat, intramyocellular lipids (IMCL), and liver fat, quantitative magnetic resonance (QMR)-measured body fat mass, blood pressure, blood lipids, and insulin resistance at 6 years old (all continuous variables). The authors evaluated whether gestational glycemia (FPG and 2 hPG) modified the as-

sociation of breastfeeding with offspring outcomes after adjusting for confounders using a multiple linear regression model that included a 'gestational glycemia × breastfeeding' interaction term.

It was shown that with increasing gestational FPG, high/intermediate (vs. low) breastfeeding was associated with lower levels of IMCL (p-interaction = 0.047), liver fat (p-interaction = 0.033), and triglycerides (p-interaction = 0.007), after adjusting for confounders. Specifically, at 2 standard deviations above the mean gestational FPG level, high/intermediate (vs. low) breastfeeding was linked to lower adjusted mean IMCL [0.39% of water signal (0.29, 0.50) vs. 0.54% of water signal (0.46, 0.62)], liver fat [0.39% by weight (0.20, 0.58) vs. 0.72% by weight (0.59, 0.85)], and triglycerides [0.62 mmol/L (0.51, 0.72) vs. 0.86 mmol/L (0.75, 0.97)]. hPG did not significantly modify the association between breastfeeding and childhood cardiometabolic risk.

Despite emerging evidence linking increased gestational glycemia with altered breastmilk composition, the authors did not find breastfeeding to be significantly associated with any adverse cardiometabolic risk biomarkers among children born to mothers with elevated gestational glycemia (FPG or 2 hPG) across the numerous cardiometabolic biomarkers investigated and sensitivity analyses performed in this study; on the contrary, breastfeeding was found to be associated with a protective effect.

These findings suggest breastfeeding may confer protection against adverse fat partitioning and higher triglyceride concentration among children exposed to increased glycemia in utero.

Distinct Causal Effects of Body Fat Distribution on Cardiometabolic Traits among Children: Findings from the BCAMS Study[15]

Source: *Fu L, Cheng H, Zhao X, Hou D, Xie X, Mi J. Distinct causal effects of body fat distribution on cardiometabolic traits among children: Findings from the BCAMS study. Nutr Metab Cardiovasc Dis. 2022 Jul;32(7):1753-1765. doi: 10.1016/j.numecd.2022.03.030.*

Observational studies reveal that different body fat measures are associated with cardiometabolic disease with different effects. However, causality is not reflected by such observations. In this study, Fu et al aimed to explore and compare the causal relationships of general obesity (measured by body mass index (BMI)), adipose obesity (measured by fat mass percentage (FMP)) and central obesity (measured by waist-to-height ratio (WHtR)) with cardiometabolic traits among children.

To this end, the authors conducted one sample Mendelian randomization (MR) analysis in 3266 children from Beijing Children and Adolescents Metabolic Syndrome Study. Genetic instruments based on 28 SNPs were performed to explore and compare the causal associations of genetically determined BMI, FMP and WHtR with cardiometabolic traits.

The genetic instruments were robustly correlated with observed BMI, FMP and WHtR. Each genetically 1-SD increment in BMI, FMP and WHtR were causally associated with increment in systolic blood pressure (SBP), diastolic blood pressure (DBP), log-transformed fasting plasma glucose (FPG), log-transformed homeostasis model assessment of pancreatic beta cell function (HOMA-β), and decrease in log-transformed high-density lipoprotein cholesterol (HDL), respectively (all $p < 0.05$ after Bonferroni correction).

The receiver operating characteristic curve indicated that BMI and FMP showed stronger effects on SBP, DBP, HOMA-β and HDL than WHtR (all $p < 0.05$). We also observed causal associations of BMI and FMP with log-transformed fasting insulin and HOMA-IR.

In summary, this study demonstrated that the genetic predisposition to elevated childhood BMI, FMP and WHtR had significant associations with cardiometabolic traits during the period of childhood, giving the supportive evidence for the causal relationships of childhood general obesity, adipose obesity and central obesity with childhood cardiometabolic disorders in an Asian population. Compared with central obesity, general and adipose obesity are supposed to have a stronger influence on blood lipids and glycemic phenotypes in children. For avoiding adverse cardiometabolic disorders at later life, the authors appealed for more efforts to prevent obesity at an early age, especially general and adipose obesity.

Meal-related Asprosin Serum Levels Are Affected by Insulin Resistance and Impaired Fasting Glucose in Children with Obesity[16]

Source: *Corica D, Pepe G, Aversa T, Currò M, Curatola S, Li Pomi A, Alibrandi A, Ientile R, Wasniewska M. Meal-Related Asprosin Serum Levels Are Affected by Insulin Resistance and Impaired Fasting Glucose in Children With Obesity. Front Endocrinol (Lausanne). 2022 Jan 6;12:805700. doi: 10.3389/fendo.2021.805700.*

Asprosin physiologically increases in fasting conditions and decreases with refeeding and has been implicated in glucose homeostasis. An alteration of meal-related circadian oscillation of asprosin has been suggested in adults affected by type 2 diabetes mellitus.

In this study, the authors tested the hypothesis of an alteration in the meal-related variation of asprosin levels in non-diabetic children and adolescents with obesity and assessed which metabolic vari-

ables condition this variation in non-diabetic children and adolescents with obesity. This was a cross-sectional study which included 79 children and adolescents with obesity. Children underwent clinical and biochemical assessments, including oral glucose tolerance test (OGTT), and liver ultrasound evaluation. Asprosin serum levels were measured by an enzyme-linked immunosorbent assay in a fasting state and at the 120-minute OGTT timepoint (2h-postprandial asprosin).

Fasting and 2h-postprandial asprosin serum levels did not significantly differ in the entire study population (374.28 ± 77.23 vs 375.27 ± 81.26; p=0.837). 55.7% of patients had a significant increase in 2h-postprandial asprosin compared with fasting levels. The asprosin level increase condition was significantly associated with HOMA-IR (homeostasis model assessment of insulin resistance) (OR,1.41; 95%CI,1.005-1.977; p= 0.047), fasting glycaemia (OR,1.073; 95%CI,1.009-1.141; p=0.024) and HOMA-B (homeostasis model assessment for β-cell function) (OR,0.99; 95%CI,0.984-0.999; p=0.035).

Moreover, the impaired fasting glucose (IFG) condition was associated with the increase in asprosin levels (OR, 3.040; 95%CI, 1.095-8.436; p=0.033), even after adjustment for HOMA-IR, body mass index standard deviation score (BMI SDS), sex and pubertal stage.

This study found that asprosin levels did not significantly decrease at 2h-postprandial assessment in obese non-diabetic children and that this trend was significantly influenced by the presence of insulin resistance (IR) and impaired fasting glucose (IFG). The authors speculated that in obese children and adolescents with IR and IFG there may be an altered production of asprosin which in turn may promote IR worsening by stimulating hepatic glucose secretion and subsequent hyperinsulinemia. The asprosin increase condition and, in particular, alteration of its circadian secretion, might be an early biomarker of impaired glucose regulation (IGR) in obese children with IR.

In conclusion, IR and IFG influenced meal-related changes of asprosin serum levels in this study population of obese, non-diabetic, children. Alteration of asprosin circadian secretion might be an early biomarker of impaired glucose regulation in obese children with insulin resistance.

Ketogenic Diet

Updates on the ketogenic Diet Therapy for Pediatric Epilepsy[17]

Source: *Ko A, Kwon HE, Kim HD. Updates on the ketogenic diet therapy for pediatric epilepsy. Biomed J. 2022 Feb;45(1):19-26. doi: 10.1016/j.bj.2021.11.003.*

The ketogenic diet (KD) is a high-fat, low-carbohydrate diet, in which fat, instead of glucose, acts as a major energy source through the production of ketone bodies. The KD was formally introduced in 1921 to mimic the biochemical changes associated with fasting and gained recognition as a potent treatment for pediatric epilepsy in the mid-1990s.

Recent clinical and scientific knowledge supports the use of the KD in drug-resistant epilepsy patients for its anti-seizure efficacy, safety, and tolerability. The KD is also receiving growing attention as a potential treatment option for other neurological disorders.

This article reviewed the recent updates on the KD, focusing on its mechanisms of action, its alternatives, expansion on its use in terms of age groups and different regions in the world, and future issues.

Depending on the individual situation and extent of disease, KDs can be a good option for patients with drug-resistant epilepsy. Numerous mechanisms of action of these diets have been proposed, which has led to exploration of their use for various other neurologic disorders. In the future, it is hoped that the effectiveness of ketogenic therapies will be demonstrated in more disease groups and that KDs will become more widely used on a global basis.

The Efficacy of Non-fasting Ketogenic Diet Protocol in the Management of Intractable Epilepsy in Pediatric Patients: A Single Center Study from Saudi Arabia[18]

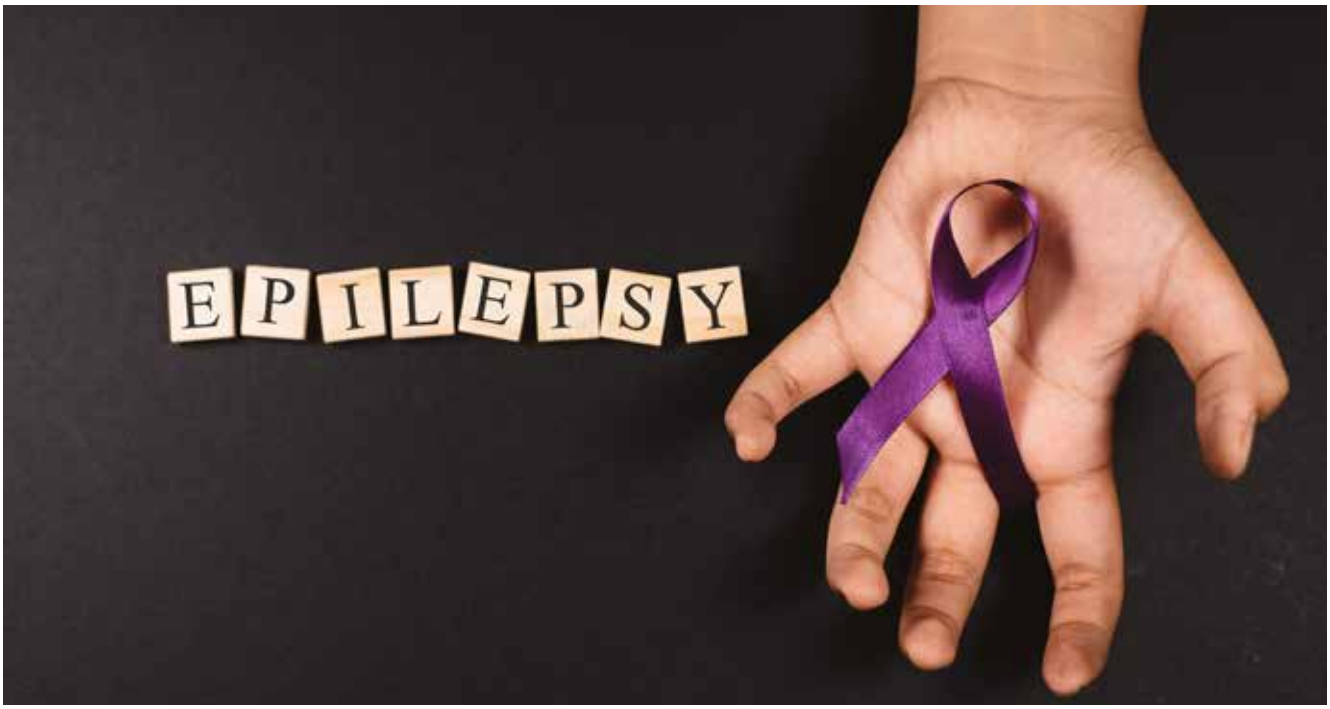
Source: *Alameen Ali H, Muthaffar O, AlKarim N, Kayyali H, Elmardenly A, Tamim A, Alansari H. The efficacy of non-fasting ketogenic diet protocol in the management of intractable epilepsy in pediatric patients: a single center study from Saudi Arabia. J Int Med Res. 2022 Mar;50(3):3000605221081714. doi: 10.1177/03000605221081714.*

The objective of this study was to review the characteristics and outcomes of pediatric patients on a ketogenic diet (KD), an established treatment option for individuals with intractable epilepsy, in a tertiary epilepsy center.

This retrospective study included pediatric patients diagnosed with intractable epilepsy who had experienced no benefits from at least two appropriately chosen antiseizure medications. All patients were hospitalized, started a KD without fasting, and were observed for complications and tolerance. The etiology of epilepsy, side effects, and KD efficacy on seizure outcomes were also examined. Of 16 children included in the study, nine (56%) experienced significant seizure improvement, with three becoming seizure-free during the KD. Ten patients were fed orally, and six were fed through gastrostomy feeding tubes. Most were on a 3:1 fatto-protein and carbohydrate ratio, and nine reached ketosis within the first three days of KD initiation. Initial recurrent hypoglycemia was documented in four patients, and four experienced vomiting and acidosis. Most families complied with the diet, and all of the children gained weight during the study period.

Overall, the KD demonstrated strong efficacy, with three patients (19%) showing more than 50% improvement, and six (37%) showing more than 90% improvement.

In conclusion, ketogenic diets are an established and effective treatment for childhood epilepsy, with reversible mild adverse effects. A non-fasting KD protocol is a safe and effective option for children with intractable epilepsy.



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