Optimizing growth and development: a nutritional biochemical approach to pediatric health

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Thesis mentor: Assoc. Prof. Lara Batičić, PhD

The graduation thesis was graded on 26.02.2024 in Rijeka, before the Committee composed of the following members:

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3. Full Prof. Vlatka Sotošek, MD, PhD

The graduation thesis contains 40 pages, 4 figures, 1 table, 41references.

Preface

This diploma thesis is lovingly and gratefully dedicated to my cherished family and dear partner, whose support, endless encouragement, and unwavering belief in my potential have been pivotal throughout my medical studies.

To my family, for your unwavering confidence in me, for every encouraging word during those late-night study sessions, for sharing in each of my achievements, and for your unwavering support through every hurdle. Your belief in me has fueled my determination and resilience.

To my partner, for your endless patience, deep understanding, and constant encouragement. You have been my rock, providing the strength I needed to pursue the demanding path of medical education. This thesis represents not just my academic journey but also the shared strength and commitment that have defined our journey together.

I am profoundly grateful to you all for being by my side during this challenging yet fulfilling journey. Your support has been invaluable, making this achievement as much yours as it is mine.

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1. List of abbreviations and acronyms

$(CH_2O)n$	basic chemical formula of carbohydrates
AA	arachidonic acid
AAP	American Academy of Pediatrics
AA	amino acid
ACOG	American College of Obstetricians and Gynecologists
ATP	adenosine triphosphate
CD	Crohn’s disease
CNS	central nervous system
DHA	docosahexaenoic acid
EGF	epidermal growth factor
ENCCs	enteric neural crest-derived cells
ENS	enteric nervous system
EPA	eicosapentaenoic acid
FDA	food and drug administration
GI-tract	gastrointestinal tract
HMOs	human milk oligosaccharides
IBD	inflammatory bowel disease
IDA	iron deficiency anemia
IGF-I	insulin-like growth factor
IUGR	intrauterine growth restriction
LCPUFA	long-chain polyunsaturated fatty acids
LDL	low-density lipoprotein
Lf	lactoferrin
NCCs	neural crest cells
NEC	necrotizing enterocolitis
NOVA classification	Portuguese nova classificação, “new classification”
OH	hydroxyl group
RA	retinoic acid
RCTs	randomized controlled trials
RET	receptor tyrosine kinase
TCA	tricarboxylic acid
UC	ulcerative colitis

UK	United Kingdom
UPF	ultra-processed food
US	United States
WHO	World Health Organization

2. Introduction

The thesis on "Optimizing Growth and Development: A Nutritional Biochemical Approach to Pediatric Health" undertakes a comprehensive exploration of the intricate relationship between pediatric nutrition, biochemistry, and overall health. The foundational section provides an overview of essential biochemical compounds of vital nutrients and biomolecules.

This exploration then delves into the embryological development of the gastrointestinal tract, offering insights into the early stages that lay the groundwork for understanding how nutritional inputs shape physiological foundations.

Subsequently, the thesis examines the intricate processes of digestion and absorption of various biochemical compounds, elucidating the mechanisms through which the body extracts essential nutrients from ingested foods (1).

This dialogue lays the groundwork for a thorough examination of how feeding practices influence growth, particularly emphasizing breastfeeding and formula feeding. The comparison carefully studies how it affects health.

The next section involves an investigation into nutritional deficiencies that may arise in the absence of specific compounds in a child's diet. This part aims to unravel the consequences of deficiencies and their potential impact on optimal growth and development.

The thesis concludes by looking ahead to future possibilities and challenges in the area of pediatric nutrition. This encompasses factors like climate change, making sure there's enough food, dealing with obesity, considering processed foods, addressing nutritional differences, and understanding the impact of global connections and cultural influences.

3. Aims and objectives

This research centered around "Optimizing Growth and Development: A Nutritional Biochemical Approach to Pediatric Health," aims to delve into the intricate interplay between nutritional biochemistry and the well-being of children. The overarching objectives of this thesis encompasses several key aspects.

Firstly, it seeks to provide a comprehensive understanding of the intricate relationship between nutritional biochemistry and pediatric health. In doing so, the research aims to shed light on the nuanced factors that contribute to optimal growth and development in children. Another pivotal aim involves the investigation and elucidation of foundational biochemical compounds. This exploration intends to provide a detailed overview of these essential compounds, unraveling their specific roles in various physiological processes crucial to pediatric growth. The embryological development of the gastrointestinal (GI) tract represents another crucial facet of this research. By delving into the early stages of GI tract development, the goal is to uncover insights that form the foundation for understanding how nutrition significantly shapes the trajectory of growth in children. Additionally, the research focuses on investigating the impact of different feeding practices, with a specific emphasis on breastfeeding and formula feeding. This comparative analysis aims to deepen our understanding of how these practices influence the growth and development of children. Furthermore, the research aims to shine a light on potential nutritional deficiencies that may arise in the absence of specific compounds. By doing so, it seeks to comprehend the consequences of these deficiencies on optimal growth and development in the pediatric population.

Anticipating the future, this thesis projects ahead to analyze upcoming trends and challenges in the realm of pediatric nutrition. It aspires to address global challenges such as climate change, food security, and nutritional inequalities. Additionally, it seeks to project strategies for preventing and managing pediatric obesity, considering the roles of nutritional interventions and lifestyle adjustments.

By aligning these multifaceted aims and projections, the research endeavors to contribute valuable insights to the field of pediatric nutrition. Through fostering a holistic understanding, it aspires to inform not only current practices, but also future strategies aimed at optimizing the growth and development of children.

4. Literature review

4.1 Introduction to nutritional Biochemistry

The chemical composition of food can vary widely because there are different types, different ingredients and how the food is prepared. But in general, all different types of food consist of a combination of basic chemical components. Our daily intake is consistent of 2 major groups of nutrients. There are different macronutrients and micronutrients. The macronutrient group includes carbohydrates, proteins, and lipids (fats). And the other part are micronutrients that include minerals and also vitamins (2). Understanding the chemical structure of these components is essential in understanding how they contribute to food's properties and our health. These components will be further discussed in this paragraph.

4.1.1 Carbohydrates

This group constitutes a fundamental energy source within the dietary intake. Carbohydrates are one of the primary sources of energy in the diet. The full breakdown of the primary digestible carbohydrates in our diet, which include starch, sucrose, and lactose, results in the formation of monosaccharides such as glucose, fructose, and galactose. The daily consumption of carbohydrates is around 5-20g (3).

Carbohydrates are organic compounds, which are made up of the following atoms – carbon, oxygen, and hydrogen. The basic chemical formula is $(CH_2O)n$ – "n" represents the number of repeating units (4).

Carbohydrates are compounds derived from polyhydric alcohols and can exist as ketones or aldehydes. They are classified as Monosaccharides, Disaccharides, Oligosaccharides, Polysaccharides.

Monosaccharides are classified according to the number of carbon atoms (ranging from 3 to 7) and the presence of either having the aldehyde or ketone functional group attached, resulting in categorizations such as trioses, tetroses, pentoses, hexoses, or heptoses (5).

All cells possess the capability to generate energy, in particular adenosine triphosphate (ATP), through the metabolic processes of glycolysis. This can occur through the conversion of glucose into 3-carbon compounds or via the integrated processes of glycolysis and the tricarboxylic acid (TCA) cycle, leading to generating carbon dioxide and water (3).

While animals have the ability to produce carbohydrates from amino acids, the majority of carbohydrates in their diet are ultimately sourced from plants. Glucose stands out as the most critical carbohydrate in this context. Most dietary carbohydrates are absorbed into the bloodstream in the form of glucose. It is generated through the breakdown of dietary starch and disaccharides by hydrolysis. Furthermore, the liver plays a role in converting various other sugars into glucose (1).

Glucose plays a central role as the primary metabolic fuel for the majority of mammals and serves as a vital source of energy for growing fetuses. Moreover, glucose serves as the essential building material for carbohydrate formation. This includes glycogen, used as energy storage; ribose and deoxyribose, which are vital components of nucleic acids; and galactose, a critical element in the synthesizing of lactose found in milk, glycolipids, as well as its role in conjunction with proteins to form glycoproteins. Conditions associated with carbohydrate metabolism include diseases like galactosemia, lactose intolerance, diabetes mellitus, and glycogen storage disorders (1).

4.1.2 Proteins

Proteins belong to a fundamental category of compounds that compose living organisms. They serve as a vital function in the body acting as essential "construction materials" for the development of numerous cellular and extracellular structures. Their remarkable adaptability and versatility are attributed to their unique structure, as proteins are comprised of lengthy, unbranched, and often intricately folded chains of amino acids.

Amino acids are vital organic substances consisting of a carbon atom linked to a hydrogen atom, a carboxyl group, additionally an amino group and a side chain which is known as the R-group (6).

Within the scope of human proteins, a standard set of twenty amino acids (AAs) is typically present. Within this group, there are indispensable AAs (e.g. leucine, lysine, phenylalanine, histidine, etc.). They earn their "essential" designation because the body lacks the capability to produce their carbon structures internally and they need to be taken up through dietary (3).

In contrast, another group of AAs which consists of specifically glycine, alanine, serine, cysteine, tyrosine, glutamine, glutamic acid, asparagine, and aspartic acid is generally regarded as nonessential in most situations. This categorization stems from their ability to be manufactured from internal precursors or from the essential AAs, in the body (3).

Several factors influence an individual's protein needs (Table 1.), including the quantity of non-protein calories supplied, overall energy demands, the quality of the protein consumed, and the individual's nutritional condition. When calorie intake falls short of energy requirements, protein requirements tend to rise.
The magnitude of this increase is directly connected to the deficiency in energy supply. Consequently, nitrogen equilibrium serves as an indicator of both protein intake and energy equilibrium. In some cases, rectifying a negative nitrogen balance can be accomplished by simply increasing calorie intake when the overall calorie intake has been insufficient (3).

Table 1. Daily protein requirement, in different clinical conditions (3)

Clinical condition	Daily protein requirement (g/kg IBW)
Normal	0.80
Metabolic stress	1.0-1.6
Hemodialysis	1.2-1.4
Peritoneal dialysis	1.3-1.5

4.1.3 Lipids

Lipids are organic compounds characterized by their hydrophobic (water-repellent) nature, encompassing a diverse group of fatty, waxy, or oily molecules that serve various structural, energy storage, and signaling roles in living organisms. These substances dissolve in organic solvents but resist dissolving in polar solvents such as water. Lipids comprise a wide array of compounds, which consist of phospholipids, steroids, triglycerides (fats and oils), and waxes (7). Collectively, these lipid molecules are essential components of various physiological functions in the human body.
A lipid or fat molecule is composed of two distinct parts. In triglycerides, the first part is the glycerol core and the second part are three tails with a fatty acid attached.
Another organic molecule is Glycerol characterized by three hydroxyl (OH) groups, while a fatty acid is defined by an elongated hydrocarbon chain connected to a carboxyl group. The fatty acids typically consist of 12 to 18 carbon atoms, although variations can range from as few as 4 to as many as 36 (8).
A fat molecule is created through a chemical process called dehydration synthesis. In this reaction, the hydroxyl groups of glycerol form bonds with the carboxyl groups of fatty acids.

Through this process, a fat molecule is produced, featuring three fatty acid tails firmly linked to the glycerol's core by means of ester connections.
These ester bonds are marked by the proximity of an oxygen atom next to a carbonyl (C=O) unit. Triglycerides, a prevalent form of fat, may consist of three identical fatty acid tails or a blend of three diverse fatty acid tails, exhibiting variations in both length and the presence of double bonds (8).
There are several fatty acids naturally occurring in the human body. In one category are the saturated fatty acids – Stearic, Lauric, Palmitic, Myristic, and Arachidic fatty acids. The other group consists of Palmitoleic, Oleic, Linoleic, Linolenic, Arachidonic fatty acids, this group is the so called unsaturated fatty acid group (1).

4.1.4 Vitamins

Vitamins are crucial for numerous biochemical functions in the human body, and they are indispensable for promoting and sustaining overall health. These essential nutrients can be categorized into two primary groups: the ones soluble in fat (Vitamin A, D, E, K), which are stored efficiently in body fat after absorption, and water-soluble, which are easily flushed out of the body and not readily stored (3). Fat-soluble vitamins have various important functions. For instance, vitamin A is crucial for vision and cell differentiation. Another one which is important is vitamin D, which plays a vital function in calcium and phosphate metabolism, and it also contributes to differentiation of cells. The antioxidant is vitamin E. Vitamin K is pivotal in the process of blood clotting. Besides dietary insufficiency, deficiency syndromes of fat-soluble vitamins can result from conditions impacting digesting and also absorbing of all these vitamins. These conditions encompass disorders of the biliary system, steatorrhea, and they may lead to deficiency symptoms like xerophthalmia, in children rickets disease, night blindness but also osteomalacia in adults. There are more outcomes like hemolytic anemia, hemorrhagic disease, and neurologic disorders of newborns. Overconsumption of vitamins A and D can lead to toxic effects. Vitamin E is acknowledged for its antioxidant properties, with the potential to contribute preventing atherosclerosis and cancer. Similarly, vitamin A and its precursors, carotenes, are also associated with these health benefits. Nonetheless, in excessive doses, they can also serve as detrimental pro-oxidative agents (1).
The B complex vitamins (including riboflavin, thiamine, cobalamin, pantothenic acid, folate, biotin, and niacin) and Vitamin C are classified as water-soluble vitamins. These vitamins are typically present in an array of foods, especially fruits and vegetables being among the most

important sources. Additionally, they can be found in peas, eggs, cereals, meat, fortified grains, and legumes. These soluble-in-water vitamins are readily expelled from the body and must be ingested at regular intervals to sustain good health (9).

4.1.5 Minerals

Minerals are also an essential compound that is widely distributed in our daily nutrition. People that are usually eating a mixed diet, should have an adequate intake of them (1).

Minerals serve various crucial functions within the body, each category contributing distinctly to physiological processes. Structural functions are executed by magnesium, phosphate, and calcium, playing pivotal roles in maintaining the integrity of biological structures. Meanwhile, sodium and potassium take on the responsibility of membrane function, influencing the delicate balance required for cell communication. Specific minerals, such as cobalt, selenium, iron, copper, molybdenum, and zinc, serve as prosthetic groups for enzymes, playing a crucial role in the catalytic functions of vital enzymes. Additionally, minerals such as calcium, sodium, potassium, iodine, chromium, manganese, and magnesium assume a regulatory role and play a part in hormone action within the body. Vanadium, tin, nickel, and silicon are deemed essential, though their specific functions remain unknown. On the other hand, lithium fluoride, while essential, lacks a clearly established function. Certain minerals have recognized effects on the body, yet their essentiality remains undetermined. These include cadmium, silver, strontium, mercury, boron, arsenic, bromine, lead, aluminum, germanium, and cesium. These minerals may be present in foods but are known to be toxic in excess, underscoring the importance of maintaining a delicate balance in their intake (1).

4.2 Development of the gastrointestinal tract

The gastrointestinal tract (GI-tract) undergoes an intricate and complex developmental process during embryonic stages (Figure 1.), subsequently assuming the crucial roles of digesting and absorbing nutrients, as well as eliminating waste products from the body.

In the first three weeks of embryonic development the implantation of the blastocyst is happening. At the same time, it is also the starting point for the development of the GI-tract. In the third week of embryonic development, a significant milestone unfolds as the digestive tube initiates its intricate differentiation process, coinciding with the occurrence of gastrulation. At the outset, the primary gut tube emerges as a sophisticated, hollow cylinder comprising endodermal cells encased by surrounding mesodermal layers. The endodermal sheet undergoes a dynamic elongation and ventral folding at both the anterior and posterior ends, culminating in a convergence near the yolk sac to meticulously shape and finalize the formation of a closed tube (10).

Entering the fourth week of embryonic development, a pivotal event transpires as the buccopharyngeal membrane undergoes resorption. This critical process leads to the closure of the cranial end of the developing digestive tube, marking a significant step in the intricate orchestration of embryogenesis (10).

Between weeks six and ten of embryonic development, a notable occurrence takes place as the midgut protrudes the ring of umbilicus, projecting extensively beyond the peritoneal cavity. Subsequently, in week ten, a rotation process ensues, returning the midgut to its proper position. Simultaneously, during week seven, a crucial developmental step involves the closure obliteration of the vitelline duct, which previously linked the yolk sac and the lumen of the midgut (10).

As embryonic progression unfolds, the nineth week witnesses the initiation of the cloacal distal membrane, commences while the initiation of formation of villus. By week eleven, the intestines display distinctive longitudinal and circular muscle layers, underscoring the maturation of structural components. Week twelve marks the commencement of crypt development, contributing to the overall complexity of the intestinal structure.

Advancing further, week 14 sees the development of the muscularis mucosae, an integral layer in the architecture of the gastrointestinal tract. By week 24, fetal intestinal absorption function undergoes notable advancements, setting the stage for increased functionality. The culmination of this developmental journey occurs around week 32 when fetal intestinal absorption reaches a level comparable to that of adults, emphasizing the attainment of a mature and functional digestive system (10).

4.2.1 Development of the Stomach

The intricate process of embryonic stomach development unfolds across multiple stages during embryogenesis, encompassing the intricate formation of this vital organ. Initiated in the 5th week, the development commences with a fusiform expansion of the foregut. The dorsal side's accelerated growth surpasses that of the ventral side, resulting in the creation of a large convex curvature directed backward and a smaller convex curvature at the anterior end.

A pivotal event in this developmental narrative is the subsequent 90° clockwise rotation of the stomach, a maneuver that also induces a shift in the positions of the two Vagus nerves. Following this rotation, the stomach undergoes tilting, revolving around a sagittal axis. Consequently, the large curvature now points downward, a phenomenon akin to a second gastric torsion. This intricate sequence of morphological changes underscores the complexity and precision involved in the embryonic development of the stomach (11).

4.2.2 Development of the liver

Embryonic liver originates from the distal, a process initiated around day 22. This developmental advancement occurs alongside the transverse septum, situated at the top of the emerging abdominal cavity. Hepatocytes, the primary constituents of the liver, along with biliary epithelial cells, arise from the endoderm, forming crucial components of the "early" gut. Critical morphogenesis of liver is the intricate interplay with neighboring mesodermal structures, which contribute vasculature to support the organ's formation. The colonization by cells derived from the mesoderm brings about a hematopoietic population in the liver. This group serves as the primary source of blood cells for the growing fetus from the second to the seventh month of gestation.

In fetal development, the liver plays a vital role as the first organ to receive oxygen-rich blood from the left umbilical vein coming from the placenta. A portion of this blood is diverted to the fetal systemic circulation through a bypass facilitated by the ductus venosum.

In extrauterine life, it is significant that the umbilical vein and ductus venosum both become obliterated, signifying a shift in circulatory dynamics (12).

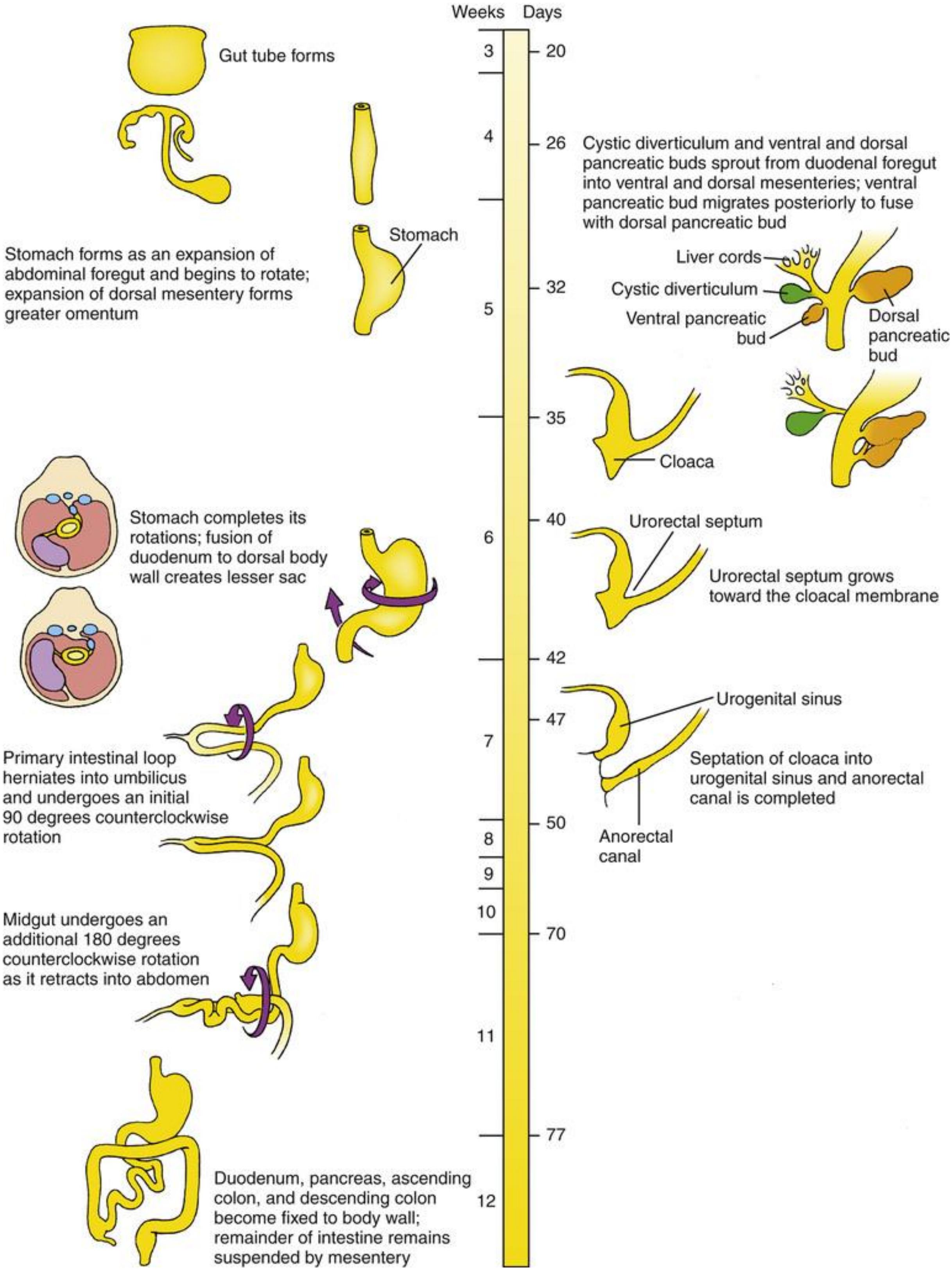

Figure 1. Timeline of GI-development (13)

4.2.3 The enteric nervous system

This system, responsible for regulating gastrointestinal functions, originates from neural crest cells (NCCs). The development of the enteric nervous system (ENS) critically depends on the balanced migration, proliferation, and differentiation of enteric neural crest-derived cells (ENCCs). Disorders like Hirschsprung disease highlight the importance of these processes.

The ENS, referred to as the "second brain," autonomously regulates gastrointestinal functions with over 100 million neurons and 18 subtypes. Abnormal ENS development leads to severe disorders, such as Hirschsprung disease, providing insights into related conditions and potential therapies.

ENS development involves NCC migration from specific axial levels of the neural tube. Vagal NCCs, particularly from the postotic hindbrain, contribute significantly. Sacral NCCs also play a role in colorectal development.

Retinoic acid (RA) within the somitic environment activates receptor tyrosine kinase (RET) expression in migrating NCCs. After entering the foregut mesenchyme as ENCCs, cells colonize the entire gut tube.

Vagal- and sacral-derived ENCCs differ intrinsically, with vagal cells being more invasive. Recent mouse studies suggest alternative migration pathways, emphasizing the complexity of ENS development. Understanding these intricacies is crucial for advancing therapeutic approaches for neurointestinal diseases (14).

4.2.4 Postnatal development of GI-tract

Significant development, structural changes, and functional maturation take place in the gastrointestinal (GI) tract when the fetus is born. The esophagus notably undergoes rapid cell proliferation in its epithelium and experiences a heightened production and buildup of mucus in its glands. Simultaneously, the stomach undergoes changes characterized by swift tissue expansion and a marked increase in its ability to secrete acid. Enhanced tissue growth accompanied by marked epithelial modifications occurs in the intestine. These modifications involve the small intestine's epithelial cells losing their ability to absorb macromolecules and the large intestine's epithelial cells losing their capacity to synthesize digestive enzymes, AAs, and glucose absorption (15).

These noted transformations become evident to be closely tied to the initiation of colostrum ingestion, as newborns deprived of colostrum or fed only water showed minimal alterations in the GI tract. Elevated levels of numerous hormones and growth-stimulating peptides, such as insulin, cortisol, epidermal growth factor (EGF), and insulin-like growth factor I (IGF-I), are present in maternal colostrum. According to current evidence, EGF and IGF-I found in colostrum are crucial for the postnatal development of the GI tract in newborns (15).

4.3 Process of digestion

The process of digestion is a complex sequence of events that breaks down food into its constituent nutrients, which the body can then absorb and use. This process begins in the mouth and concludes in the small intestine, with each stage specifically tailored to handle different types of nutrients: carbohydrates, lipids (fats), proteins, vitamins, and minerals.

4.3.1 Digestion and absorption of carbohydrates

Carbohydrates undergo breakdown through hydrolysis, resulting in the liberation of oligosaccharides, mono- and disaccharides. The glycemic index, which measures the rise in blood glucose level following carbohydrate consumption, designates glucose, galactose, lactose, maltose, isomaltose, and trehalose with an index of 1 (100%). Conversely, fructose, sugar alcohols, and sucrose exhibit a lower glycemic index. Starch's glycemic index fluctuates, while nonstarch polysaccharides maintain a constant 0 index. Due to their minimal impact on insulin levels, foods possessing a low glycemic index are deemed beneficial. Within the large intestine, bacterial fermentation utilizes resistant starch and nonstarch polysaccharides as substrates, producing essential short-chain fatty acids like butyrate. Notably, butyrate exhibits potential antiproliferative properties, offering a safeguard against colorectal cancer (1).

Crucially, amylases break down starch through the hydrolysis of a $\alpha(1 \rightarrow 4)$ glycosidic bond hydrolysis, yielding dextrin, glucose, maltose, and maltotriose. On the brush border membrane of intestinal epithelial cells, disaccharidases such as maltase, sucrase-isomaltose, lactase, and trehalase are positioned to aid the absorption of the ensuing monosaccharides. Deficiency in lactase may lead to lactose intolerance, while sucrase-isomaltase deficiency can cause sucrose intolerance. Lactase activity typically decreases after weaning in most mammals, resulting in lactose intolerance. However, certain populations, such as North Europeans and nomadic tribes in Africa and Arabia, retain lactase into adulthood. Two distinct mechanisms govern monosaccharide absorption in the small intestine: a sodium-dependent process for glucose and galactose, and carrier-mediated diffusion for fructose and sugar alcohols. (Figure 2.) Osmotic diarrhea may result from an excess intake of fructose and sugar alcohols. Marine mammals, producing carbohydrate-free high-fat milk, do not have lactase in their pups (1).

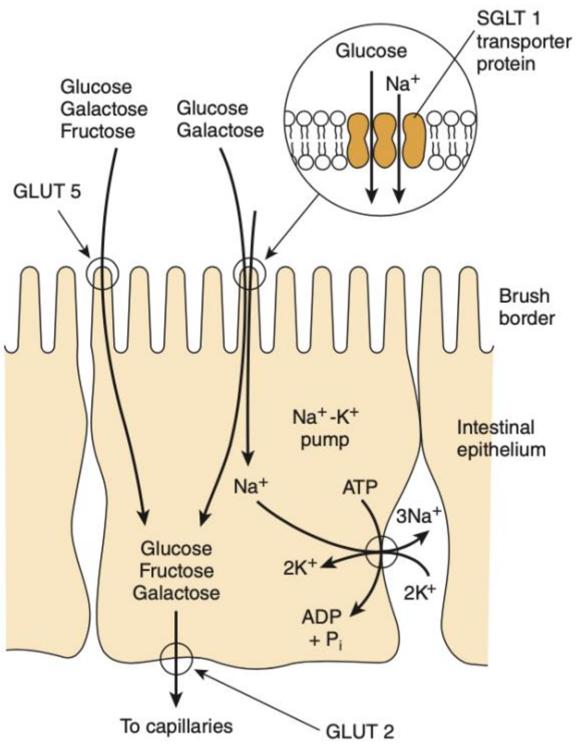

Figure 2. The intestinal epithelium facilitates the transport of fructose, glucose, and galactose (1).

4.3.2 Digestion and absorption of lipids

Triacylglycerols, along with phospholipids to a lesser extent, constitute the primary dietary lipids. Before absorption, these hydrophobic molecules, primarily triacylglycerols and phospholipids, must undergo hydrolysis and emulsification into small droplets, also called micelles. The absorption of fat-soluble vitamins (A, D, E, and K), cholesterol, carotenes, and various other lipids, which are incorporated into lipid micelles, is crucial for this process. (Figure 3.) On a diet extremely low in fat, the uptake of carotenes and fat-soluble vitamins becomes impaired.

The breakdown of the sn-3 ester bond by lingual and gastric lipases initiates the hydrolysis of triacylglycerols, resulting in the formation of 1,2-diacylglycerols and free fatty acids. Subsequent digestion in the small intestine by pancreatic lipase leads to the production of 2-

monoacylglycerols and free fatty acids. Bile salts assist in emulsification, forming micelles that convey the products of digestion to the brush border of mucosal cells for uptake (1).

1-monoacylglycerols hydrolysis to fatty acids and glycerol occurs within the intestinal epithelium. Simultaneously, 2-monoacylglycerols are converted back into triacylglycerols via the monoacylglycerol pathway. Long-chain fatty acids are esterified into triacylglycerol by mucosal cells and then released as chylomicrons into the lymphatic system, subsequently entering the bloodstream. Cholesterol, upon absorption in lipid micelles, is esterified within the intestinal mucosa prior to incorporation into chylomicrons. Stanols and plant sterols compete with cholesterol for the process of esterification, inhibiting cholesterol absorption and reducing plasma cholesterol levels (1).

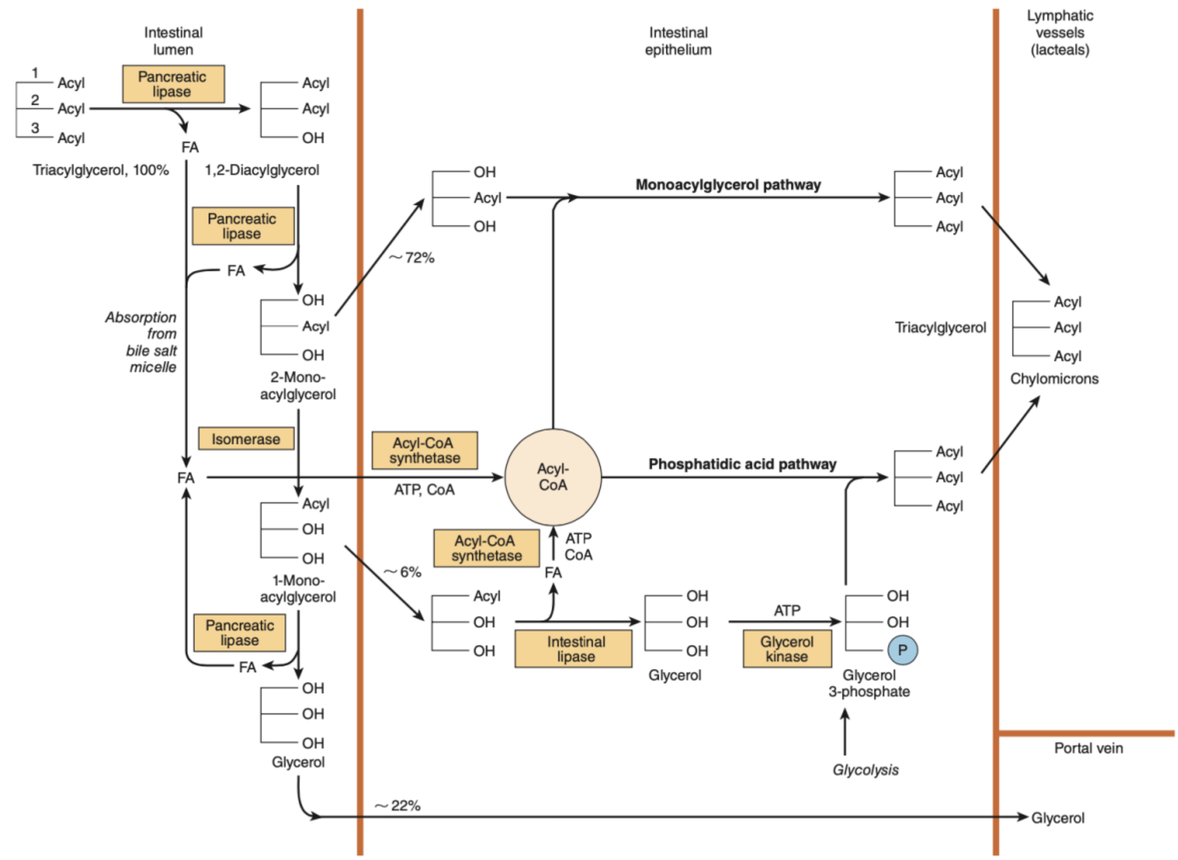

Figure 3. Digestion and absorption of triglycerols (1)

4.3.3 Digestion and absorption of proteins

Proteins in their natural state resist digestion due to the limited accessibility of their peptide bonds to proteolytic enzymes. The process of proteolytic digestion involves two primary classes of enzymes: endopeptidases, which hydrolyze bonds throughout the protein molecule, and exopeptidases, which hydrolyze bonds from the ends of peptides.

Found in gastric juice, pepsin initiates hydrolysis of bonds near amino acids with bulky sidechains. In the small intestine, the pancreas releases trypsin, chymotrypsin, and elastase, further contribute to protein breakdown. Aminopeptidases release amino acids from the amino terminals, while carboxypeptidases, a type of exopeptidase, release them from the carboxyl ends. Located in the brush border of intestinal mucosal cells, dipeptidases and tripeptidases hydrolyze di- and tripeptides.

Secreted initially as inactive zymogens, proteases are activated by removing a masking peptide chain. Through the intestinal mucosa, the digestive products, such as free amino acids, tri- and dipeptides, and oligopeptides, are then absorbed. In the absorption of free amino acids, specific amino acid transporters facilitate the process through active transport mechanisms. Hydrolysis of tripeptides and dipeptides occurs within intestinal mucosal cells prior to their transportation into the hepatic portal vein. Absorption of larger peptides may occur through alternately transcellular or paracellular pathways, potentially leading to allergic reactions to certain foods (1).

4.3.4 Digestion and absorption of vitamins and minerals

Throughout the process of digestion, the release of vitamins and minerals from food varies in degree. The presence of chelating compounds, especially for minerals, significantly influences the availability of these nutrients, and this dependence varies with the type of food. In the process of fat digestion, lipid micelles facilitate the absorption of fat-soluble vitamins, whereas in the small intestine, water-soluble vitamins and most mineral salts are absorbed via methods like active transport or carrier-mediated diffusion. The absorption of calcium relies on the presence of vitamin D, which prompts the synthesis of calbindin, an essential calcium-binding protein crucial for absorption. Compounds like phytic acid in cereals can bind to calcium, hindering its absorption, and minerals such as zinc may also be chelated by phytate. Iron absorption is a highly regulated process to prevent iron overload. Inorganic iron is gathered by mucosal cells via a transporter for divalent metal ions that is linked to protons, and this iron is then stored through attachment to ferritin. Exiting mucosal cells, iron utilizes ferroportin, a transport protein, contingent on the availability of free transferrin in the plasma. (Figure 4.)

Various factors influence iron absorption. The process is notably boosted by Vitamin C, particularly when treating iron deficiency anemia with iron salts. Increased iron absorption is also contributed to by alcohol and fructose. The process of absorbing heme iron from meat is different and significantly more efficient than the absorption of inorganic iron. Nevertheless, the uptake of both inorganic and heme iron is impeded by calcium, leading to a substantial decrease in iron availability when a glass of milk is consumed with a meal.

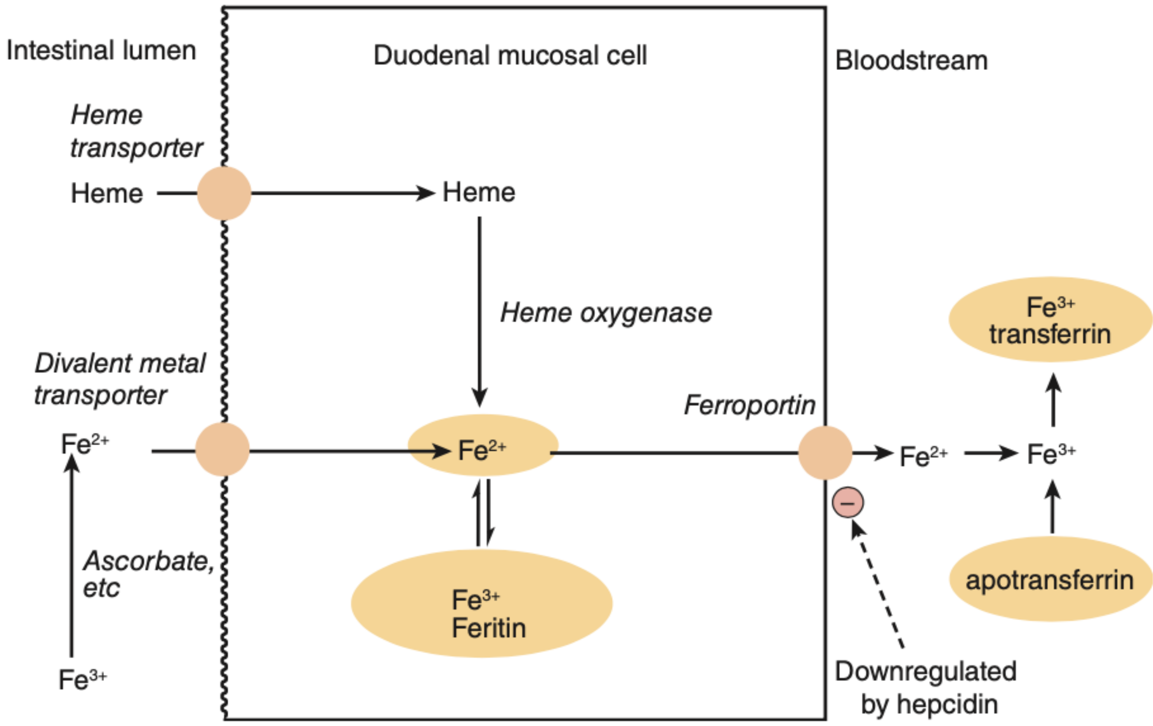

Figure 4. Iron absorption (1)

4.4 Impact of breastfeeding and formula feeding

Providing sufficient nutrition in infancy is essential for supporting normal growth, enhancing immunity against infections, contributing to long-term health in adulthood, and promoting optimal neurological and cognitive development. This significance is heightened during the initial 6 months—a phase marked by remarkably accelerated growth and heightened nutrient demands relative to body weight. Additionally, infancy and early childhood emerge as pivotal windows for metabolic programming, potentially influencing the likelihood of later obesity or metabolic syndrome during childhood.

A particularly beneficial nutritional practice during this period is breastfeeding, which has been linked to a diminished risk of various diseases in infants, children, and mothers alike. The act of breastfeeding not only provides essential nutrients but also establishes a unique bond between the mother and child, contributing to overall well-being and health outcomes in the long run (17).

4.4.1 Composition of breast milk

Human breast milk is a sophisticated and ever-changing liquid rich in nutrients essential for infant growth and development. It contains a balanced mix of carbohydrates, proteins, fats, vitamins, and minerals, along with vital digestive enzymes and hormones. Beyond these basic nutritional components, breast milk is endowed with a unique array of immune cells, such as macrophages and stem cells, and a plethora of bioactive molecules, which include both protein-derived and lipid-derived substances, as well as indigestible compounds like oligosaccharides. A notable characteristic of breast milk is the presence of human milk oligosaccharides (HMOs), which are crucial in protecting infants against gastrointestinal pathogens and in supporting the development of a healthy, balanced gut microbiota. This contributes significantly to the infant's immune responses and overall health.

The makeup of breast milk evolves to accommodate the shifting dietary requirements of an infant as they grow. It starts with foremilk, which is watery and quenches thirst, and transitions to hindmilk, which is richer in fats and calories, providing nourishment. This adaptability is influenced by various factors, including the mother's diet, her health status, and environmental conditions.

Proteins in breast milk, mainly casein and whey, are easily digestible and change in concentration throughout lactation, supporting the infant's digestive system and metabolic needs. The fat content in breast milk, crucial for energy and brain development, varies but is highly influenced by the mother's diet. It includes essential fatty acids necessary for numerous bodily functions, including growth and immune response.

Breast milk also contains essential vitamins, though supplementation of vitamins D and K might be necessary to prevent deficiencies. It provides all the necessary minerals for infant health, closely matching the mineral content of bovine milk but tailored for human infants. Additionally, breast milk contains a variety of bioactive elements, including hormones and growth factors, which contribute to the infant's overall development and well-being (18).

4.4.2 Breastfeeding

Human milk and breastfeeding represent the gold standard and universally accepted norms for nourishing and providing nutrition to infants. (18) The unparalleled health benefits of human milk for both infants and their mothers make it the optimal choice for infant feeding. 6 months of solely breastfeeding is recommended unanimously by Global health authorities such as the World Health Organization (WHO), the American Academy of Pediatrics (AAP), the American College of Obstetricians and Gynecologists (ACOG), and the U.S. Preventive Services Task Force (17).

The AAP specifically recommends human milk as the exclusive intake of nutrients for the first 6 months, with ongoing intake for the initial year and beyond, based on individual preferences. Breastfeeding not only offers immediate advantages for infant neurodevelopment but also establishes a foundation for long-term health, reducing the risks of various illnesses in both children and mothers (17). Unfortunately, notably, breastfeeding rates continue to decrease in the modern world, particularly in countries experiencing high and rising levels of wealth (19).

The greatest advantages of breastfeeding are most evident in studies involving young children. Several theories aim to elucidate the connection between breastfeeding and cognitive ability. The nutritional profile of breast milk, notably its content of critical long-chain fatty acids such as docosahexaenoic acid (DHA) and arachidonic acid (AA), might be a contributing factor. These fatty acids, which account for about 20% of the fatty acid composition in the brain, are essential for brain development. They are involved in diverse neurodevelopmental processes, including the modulation of cell growth, the biosynthesis of membrane lipids, and myelination. Beyond fatty acids, breast milk also includes sialic acid, an essential component for the construction of brain ganglioside, along with other critical nutrients such as choline, zinc, and vitamin B12, which are indispensable for the synthesis of myelin. It is significant to mention that breastfeeding is linked to a faster pace of white matter development in areas of the brain associated with advanced cognitive functions (20).

Another way breastfeeding might influence outcomes could be through the physical and emotional interaction between the mother and child during nursing, for example, increased brain activation in mothers during breastfeeding has been associated with greater maternal sensitivity. In turn, this is positively associated with the development of language in infants. Moreover, it makes sense to suggest that direct breastfeeding is linked to increased physical interaction between mother and child, potentially including skin-to-skin contact. These interactions, along with variations in maternal touch exposure, indicate their potential impact on neurodevelopment (20).

A wealth of evidence suggests that breastfeeding acts as a safeguard against mortality in low-income environments. Twenty-eight meta-analyses have delved into this subject, refining their approaches to account for differing definitions of breastfeeding found in the original studies (such as ever versus never breastfed, or short versus extended breastfeeding periods). Despite these discrepancies, there's a robust agreement that breastfeeding substantially decreases mortality rates, with reductions observed between fourfold and tenfold in settings with limited resources (19). In various settings, breastfeeding has shown potential benefits in lowering child mortality and morbidity. Meta-analyses in high-income countries show a 58% reduction in necrotizing enterocolitis and a 36% decrease in sudden infant death syndrome among infants who have ever been breastfed. In settings with low income, strong evidence supports breastfeeding's protection against respiratory infections and diarrhea, with reductions estimated at about 33% for respiratory infections and 50% for diarrhea. Particularly in younger children, the protective effects of breastfeeding are more pronounced in severe cases that require hospitalization, with estimates showing a 75% reduction for diarrhea and a 57% reduction for respiratory infections. In higher-income areas, breastfeeding is linked to a reduced incidence of otitis media in children younger than 2 years, although this protective effect diminishes in older children. As for shielding against food allergies, eczema, allergic rhinitis, and asthma, the evidence is still not definitive. Marginal protection against asthma (9%) fades away in studies that apply more stringent controls for confounding factors. An analysis of 49 studies indicates that breastfeeding provides protection against dental caries in young children for dental health. Yet, in children over 12 months old, prolonged breastfeeding (beyond 12 months) and breastfeeding at night are associated with a two- to threefold rise in the risk of dental cavities (19).

Advocating for human milk as the optimal nutritional source is relevant not only for full-term infants but also for preterm infants, especially those born extremely preterm. The intake of human milk has markedly diminished prematurity-related complications such as necrotizing enterocolitis, retinopathy of prematurity, bronchopulmonary dysplasia, and late-onset sepsis. Additionally, human milk feeding enhances feeding tolerance, which in turn reduces the time required to achieve full enteral feeding. Long-term advantages include a reduced risk of rehospitalization because of infectious diseases, especially respiratory conditions, and the enhancement of brain development and neurocognitive outcomes.

Recent research indicates that the cumulative effect of feeding with human milk on accumulating fat-free mass appears to positively influence cognitive outcomes (21).

Significant disruptions in the development of the central nervous system (CNS) can occur due to adverse fetal conditions in early development, which can subsequently affect brain maturation. Increasing evidence links impaired brain growth in neonates and preterm infants with neurological and psychiatric diseases in adulthood, highlighting nutritional status during development as a critical variable.

Breastmilk, with its diverse constitutive elements, plays a key role in the healthy development of newborns through breastfeeding. During breastfeeding, the dietary intake of specific nutrients by the mother can alter the nutritional composition of her milk, thereby affecting the infant's nutrition and brain development. Lactoferrin (Lf), a key protein present in colostrum and breast milk, is crucial for the advantages associated with breastfeeding in the postnatal period. Lf's antimicrobial and anti-inflammatory capabilities may help lower the risk of conditions like sepsis and necrotizing enterocolitis (NEC), which are prevalent in preterm infants. Additionally, Lf's ability to mitigate inflammation can help prevent complications related to childbirth by decreasing the secretion of pro-inflammatory agents and hindering the premature ripening of the cervix. This is associated with abnormalities in the commensal microbiome, which could interfere with brain development. Preclinical studies indicate that Lf can diminish inflammation and shield the developing brain from neuronal damage in experimental models of perinatal inflammation, intrauterine growth restriction (IUGR), and neonatal hypoxia-ischemia. It also enhances neurotrophin production and brain connectivity. Within this framework, Lf offers nutritional backing for the development of the brain and cognitive functions, potentially averting the emergence of neuropsychiatric disorders in later life (22).

4.4.3 Formula feeding

Despite initiatives to encourage exclusive breastfeeding until 6 months, fewer than 50% of mothers persist with breastfeeding at this milestone. The decision on how to feed infants is often made early during pregnancy by most women. The primary reason for choosing infant formula is parental preference. Nonetheless, there are specific situations where infant formula becomes necessary for infants, such as those with inborn errors of metabolism or when maternal conditions contraindicate breastfeeding. Furthermore, infant formula serves as an adjunct to breastfeeding when infants do not gain sufficient weight (23).

The bulk of infant formulas available are based on cow's milk and include added iron; it is advised to choose iron-fortified options unless a health care professional recommends otherwise. Formula producers are now incorporating a range of nutrients and biological elements that are present in breast milk, such as fatty acids, nucleotides, and both pre- and probiotics, aiming to closely emulate its benefits. For babies with allergies to cow's milk, soy formulas are an option, though it's worth noting that some of these infants may also react to soy. For those unable to tolerate standard or soy formulas, hypoallergenic versions are available, featuring proteins broken down into simpler forms for easier absorption. There are also specific formulas tailored for the needs of premature or low-weight newborns. While the standard carbohydrate source in these formulas is lactose, alternatives without lactose exist for intolerant infants. With a caloric density like breast milk, these formulas are designed to ensure adequate caloric intake through a diet rich in fats. Nonetheless, there's an observed tendency towards a higher risk of obesity in children fed on formula, possibly due to differences in how caloric intake is self-regulated compared to breastfed infants (17).

While infant formulas are produced following strict manufacturing practices and modulated by the food and drug administration (FDA), safety concerns still exist. Ready-to-feed and concentrated liquid formulas are sterile, but powdered formulas are not, posing a risk of bacterial contamination. Although powdered formulas typically have bacterial levels below the permitted thresholds, there have been cases of infections caused by Cronobacter sakazakii, particularly in premature babies. These powders may also carry other coliform bacteria, though they haven't been associated with illnesses in healthy, full-term infants. It's crucial to adhere to mixing guidelines carefully, use boiled or sterilized water, and employ the manufacturer's provided scoops to prevent incorrect formula concentration. Boiled water should be cooled completely to preserve heat-sensitive nutrients like vitamin C. For those using well water, regular testing for contaminants is advised. In areas where municipal water has high fluoride levels, using defluorinated bottled water is recommended to prevent fluoride toxicity (23).

4.5 Nutritional deficiencies

Nutritional deficiencies in pediatrics represent a significant aspect of child health, encompassing a range of conditions that can impact growth, development, and overall well-being. Among these, iron deficiency anemia is a common concern, characterized by a lack of sufficient iron to produce hemoglobin, leading to symptoms like fatigue and pallor. Adequate iron intake through diet or supplementation is crucial for preventing this condition.

Vitamin D deficiency is another important issue, vital for bone health and immune function, with insufficiency potentially leading to rickets in children. Adequate exposure to sunlight and consuming enough vitamin D in the diet can help reduce this risk.
Hypoproteinemia, or low blood protein levels, often results from inadequate dietary protein intake and can impact growth and immune response. A balanced diet with sufficient protein sources is essential for prevention and management.
The importance of unsaturated fatty acids, especially omega-3 and omega-6 fatty acids, is crucial in the field of pediatric nutrition. These fats are crucial for brain development, visual acuity, and overall health. Incorporating sources of these healthy fats into a child's diet supports cognitive and physical development.
Addressing these nutritional deficiencies involves a comprehensive approach, including dietary assessment and guidance, supplementation when necessary, and regular monitoring of growth and development indicators to ensure optimal health outcomes for children (24)(25).

4.5.1 Iron deficiency anemia

Iron deficiency anemia represents the most prevalent nutritional deficiency among children (26). It impacts children's growth, development, and overall health (24). Iron deficiency occurs when the body's total iron content is too low to support normal biological functions. This condition is identified in pediatric populations by a serum ferritin level below 15 micrograms per liter across all age groups. Anemia is generally characterized by a hemoglobin level that is more than two standard deviations below the mean for a similar healthy group of individuals of the same gender and age range. According to the World Health Organization, the hemoglobin thresholds utilized to diagnose anemia are as follows: for children aged 6 months to less than 5 years, the threshold is 11 g/dL; for those aged 5 to less than 12 years, it's set at 11.5 g/dL; and for adolescents aged 12 to less than 15 years, the cutoff is 12 g/dL.
Iron deficiency anemia in pediatric populations can be specifically delineated based on age-related criteria. In children who are between 6 months and less than 5 years old, this condition is identified when the serum ferritin levels are below 15 micrograms per liter coupled with hemoglobin concentrations under 11 g/dL, which is applicable to children within the 0.5 to 5-year age range. Moving to the older age bracket, children who fall into the 5 to under 12-year category are diagnosed with iron deficiency anemia when their ferritin levels are also below 15 micrograms per liter, but the threshold for hemoglobin is set slightly higher at less than

11.5 g/dL, tailored to the 5 to 12-year age group. These criteria help healthcare providers in diagnosing and managing iron deficiency anemia effectively in children, ensuring that interventions are age-appropriate and targeted.

The pathophysiology of iron deficiency anemia (IDA) in children revolves around the imbalance between iron intake, absorption, and the body's demands, particularly during rapid growth phases. Iron, crucial for forming hemoglobin and myoglobin, is predominantly recycled from old red blood cells, with a minor fraction sourced from the diet. In children, however, a significant portion of daily iron requirements must be met through dietary intake due to their rapid growth and increased muscle mass.

Regulation of iron homeostasis is primarily managed at the intestinal level, influenced by the hormone hepcidin, which modulates iron absorption based on the body's iron stores, erythropoietic activity, and inflammatory states. Various perinatal factors can predispose infants to IDA, including maternal iron deficiency, prematurity, and conditions leading to reduced iron stores at birth or increased iron requirements.

Diet plays a pivotal role in the risk of developing IDA during infancy and early childhood. Key dietary factors include insufficient iron intake, particularly in exclusively breastfed infants without supplemental iron after six months, early introduction of cow's milk, and diets high in substances that inhibit iron absorption. Conditions that impair gastrointestinal absorption or cause blood loss can also contribute to IDA, highlighting the multifactorial nature of this condition (26).

A tentative diagnosis of iron deficiency anemia (IDA) in children can be established when clinical risk factors align with lab results indicating a mild microcytic anemia. The definitive diagnosis is established when oral iron therapy, dosed at 3 mg/kg of elemental iron daily, leads to a hemoglobin increase of at least 1 g/dL in four weeks for those with mild anemia, and a 2 g/dL increase for children experiencing moderate to severe anemia (27).

Effectively addressing IDA in young individuals requires a comprehensive approach that encompasses three main strategies. First, oral iron therapy must be administered in the correct dosage and according to a precise schedule. This step ensures that the child receives an adequate amount of iron to replenish depleted stores and support the production of healthy red blood cells.

Second, dietary adjustments are crucial. These modifications aim to rectify the nutritional imbalances or deficiencies that may have contributed to the development of IDA. Incorporating iron-rich foods and possibly adjusting the intake of other nutrients that affect iron absorption can play a significant role in overcoming iron deficiency.

Lastly, monitoring the effectiveness of the treatment through follow-up assessments is vital. These evaluations allow healthcare providers to track the child's response to the intervention, gauging improvements in hemoglobin levels and overall health. Adjustments to the treatment plan can be made based on these assessments to ensure optimal outcomes.

For parents and caregivers, understanding these steps and working closely with healthcare professionals can help ensure the successful management of IDA in children. For detailed guidance on each of these steps, including specific dietary recommendations and follow-up care protocols, consulting with pediatric healthcare providers or referring to specialized medical resources is advisable (27).

4.5.2 Vitamin D deficiency

Vitamin D, vital for calcium regulation and skeletal integrity, when deficient, can cause significant health issues. In children, a profound shortage can result in rickets, and in individuals of all ages, osteomalacia, sometimes accompanied by dangerously low calcium levels leading to muscle spasms or convulsions. These health problems are predominantly seen in undernourished children in low-resource environments. Yet, even in areas with abundant resources, children can be at risk if they don't receive enough vitamin D from supplements, fortified foods, or sunlight, especially if they also have a low calcium diet or ongoing health conditions (28).

Vitamin D deficiency is recognized as a significant nutritional health issue, with the threshold for deficiency commonly set at 20 ng/mL by numerous professional societies. The vast majority of vitamin D deficiency cases stem from inadequate dietary intake of vitamins D_3 (cholecalciferol) and D_2 (ergocalciferol), or insufficient production of cholecalciferol in the skin due to limited sun exposure.

Prolonged and severe deficiency of vitamin D can lead to hypocalcemia and symptoms that signal rickets, which impairs bone development in children. These symptoms can include delayed growth or short stature, thickening of wrists and ankles, bowing of the long bones, rachitic rosary (a beading along the rib cage), and pectus carinatum, characterized by a protruding breastbone.

Diagnosis of vitamin D deficiency relies on the serum 25-hydroxyvitamin D level test, considered the definitive method for assessing an individual's vitamin D status. Treatment typically involves vitamin D replacement therapy, administered either daily or weekly, to rectify

the deficiency. Once vitamin D levels are restored to within the normal range, the dosage can be adjusted to a lower maintenance level.
The prognosis for vitamin D deficiency is generally positive, with most affected individuals responding well to standard replacement therapy. This intervention helps achieve normal levels of 25-hydroxyvitamin D, preventing the onset of complications associated with prolonged deficiency (29).

4.5.3 Hypoproteinemia

Hypoproteinemia refers to abnormally low levels of protein in the blood, often resulting from inadequate dietary protein intake, as seen in conditions like Kwashiorkor. Additionally, malabsorption issues, such as those caused by celiac disease or inflammatory bowel disease, can also lead to hypoproteinemia by preventing the body from properly absorbing nutrients from the diet.

Kwashiorkor is a form of malnutrition caused by inadequate dietary protein intake. It disrupts the body's ability to manage fluid, leading to edema due to compromised lymphatic system function. This condition is most observed in underdeveloped countries during periods of famine, but it can also occur in developed nations among individuals with chronic malabsorption issues (such as those with cystic fibrosis), those following extreme diets, or in children on specialized diets that eliminate milk (for example, using rice milk to manage atopic dermatitis).
Diagnosis involves taking a detailed medical history and conducting a physical examination to identify characteristic signs, such as fluid retention with pitting edema, a swollen abdomen, irritability in infants, potential anorexia, and a unique skin condition. This skin condition features a crusting, peeling dermatitis with what looks like adherent scales, known as the "flaky paint" or "enamel paint" sign, which is highly distinctive. Laboratory tests for diagnosing kwashiorkor typically include a serum total protein test, which often shows reduced levels indicative of a protein deficiency. In terms of treatment, the strategy focuses on cautiously reintroducing milk products or alternative protein sources back into the diet. It's crucial to manage the pace of this reintroduction because introducing protein too quickly can overwhelm the liver's ability to process it, which in extreme cases, could result in fatal complications (30).

Celiac disease results from gluten consumption leading to damage in the small intestine lining, which can cause malabsorption issues and nutritional deficiencies. It is prevalent in roughly 1% of the population and is commonly found alongside other conditions such as type 1 diabetes and autoimmune thyroiditis. Symptoms range from gastrointestinal discomfort, like diarrhea and bloating, to non-GI effects including bone thinning and skin rashes. The diagnosis is typically made through blood tests for certain antibodies and confirmed by a biopsy of the small intestine, which would show damage such as loss of villi. The primary treatment is a strict diet devoid of gluten, which involves careful monitoring of food intake to avoid gluten-containing products. Patients usually begin to feel better within a few weeks of starting the gluten-free diet, though full healing of the intestine may take several months (31).

Inflammatory Bowel Disease (IBD) predominantly emerges in the teenage years but can manifest at any stage of life, including Crohn's disease (CD), which can impact any part of the digestive tract, and ulcerative colitis (UC), limited to the colon. The occurrence rate of IBD is on the rise, especially in developed nations, and is associated with genetic predispositions, environmental factors, and lifestyle habits such as smoking. Cases of IBD appearing early in life may be related to immunological abnormalities and display a range of symptoms depending on the area of the digestive system involved.

For diagnosis, methods include blood tests to detect inflammation, stool tests for inflammatory markers, genetic screenings for early-onset IBD, and endoscopic procedures to assess the disease's scope and characteristics. Treatment for UC typically involves medications like aminosalicylates, corticosteroids, immunosuppressive drugs, and in severe instances, surgery. Management of CD might incorporate dietary interventions, corticosteroids, immune-modifying drugs, biological therapies, and surgical interventions to address complications. Both disorders stress the importance of limiting prolonged use of corticosteroids and preserving as much of the intestinal tract as possible during surgical procedures to effectively control symptoms and prevent complications (31).

4.5.4 The role of unsaturated fatty acids

Omega-3 fatty acids, notably docosahexaenoic acid (DHA), play a vital role in health, being essential unsaturated fats from prenatal development throughout the entire lifespan. DHA, a crucial element of brain and eye cell membranes, is vital for the development of cognitive and visual functions. The final trimester of pregnancy and the first two years of a child's life represent the most crucial period for DHA accumulation in the brain. The body's ability to produce DHA internally is limited, highlighting the necessity for dietary intake to support optimal brain growth (32).

Research reviews have delved into the relationship between DHA levels and neural development, revealing the essential functions of DHA in the development and diversification of neuronal cells and in facilitating neuronal signaling. While most human studies have focused on DHA's influence on visual acuity development, emerging evidence suggests DHA also plays a significant role in brain function during infancy. Additionally, newer studies suggest that the impact of DHA may vary based on gender and genetic variations related to the body's natural DHA production. This points to the potential broader implications of DHA, not only in early development but also in affecting cognitive abilities and mental health throughout life.

Numerous randomized controlled trials (RCTs) have explored the effects of supplementing omega-3 long-chain polyunsaturated fatty acids (LCPUFAs) during pregnancy, lactation, and early childhood. These studies examined the effects on infants' and children's visual acuity, psychomotor development, mental capabilities, and physical growth. (33) While certain RCTs have indicated beneficial outcomes from DHA supplementation, particularly for visual acuity and some neurodevelopmental aspects, the evidence on growth and long-term cognitive benefits remains inconclusive, with methodological challenges in studies necessitating careful interpretation of findings (34).

The significance of omega-3 fatty acids during pregnancy is profound, as they are crucial for fetal brain and retina development, may influence pregnancy duration, and can lower the risk of perinatal depression. However, dietary concerns about mercury and other pollutants in seafood, a primary source of DHA and eicosapentaenoic acid (EPA), have led to decreased fish consumption among expectant mothers. This review emphasizes the need for dietary guidelines that ensure adequate omega-3 intake while addressing contaminant risks.

In summary, DHA, and other omega-3 LCPUFAs are indispensable for the development of the brain and eyes, with implications for cognitive function and mental well-being that may last a lifetime. Although RCTs present mixed outcomes, the collective evidence supports the critical role of these fatty acids during key developmental phases. Ongoing research is essential to refine supplementation guidelines and to unravel the mechanisms through which DHA and omega-3 fatty acids contribute to developmental and health outcomes (34).

4.6 Future projections and challenges of pediatric nutrition

The future of pediatric nutrition is marked by significant challenges and projections, notably impacted by climate change, food security, obesity, and the rise of processed and ultra-processed foods. Climate change threatens the availability of diverse and nutritious food sources, essential for children's growth and development. Concurrently, obesity emerges as a critical concern, fueled by sedentary lifestyles and the consumption of high-calorie, low-nutrient foods. The prevalence of processed and ultra-processed foods further exacerbates the situation, contributing to poor dietary habits from a young age.

Addressing these issues necessitates a comprehensive strategy that includes policy reform, educational initiatives, and community engagement to promote sustainable food practices and healthy eating habits. The goal is to build a robust nutritional foundation for children, ensuring their well-being in the face of evolving environmental and societal challenges.

4.6.1 Climate change and food security

Over recent decades, the escalating issue of climate change, marked by global shifts in weather patterns and rising Earth temperatures, has profound implications for food safety and security. The phenomenon of climate variability, which refers to significant changes in weather variables and their occurrence, is closely linked to climate change, posing multiple threats to the integrity of the food supply chain. One critical concern is the potential for climate change to amplify foodborne diseases by affecting the lifecycle, resilience, virulence, and sometimes toxicity of pathogenic microorganisms. Additionally, the safety of our food is jeopardized by various chemical hazards, including pesticides, mycotoxins, and heavy metals, which may become more prevalent or concentrated owing to changing weather patterns, including reduced precipitation, higher temperatures, and an increase in extreme weather occurrences.

These climatic shifts bring forth several emerging food safety issues. For instance, the reduced availability of safe water for irrigating crops can lead to diminished food quality and safety. Increased pest resistance may necessitate greater reliance on pesticides, and maintaining the cold chain becomes more challenging with higher ambient temperatures, leading to potential temperature abuse. Flash floods and other extreme weather events can cause the runoff of chemical contaminants into natural water bodies, further compromising food safety.

The repercussions of these changes are significant, potentially leading to increased instances of foodborne infections and intoxications, the gradual accumulation of toxic chemicals and heavy metals in the human body and an increase in antibiotic resistance. Moreover, the severity and frequency of extreme weather events and natural calamities, driven by climate variability, can disrupt food safety measures either directly or indirectly.

Given the complexities of climate change and its multifaceted impact on food safety, there's a pressing need for robust mitigation and adaptation strategies. These strategies must be geared towards addressing the root causes of global warming and climate change, as well as managing the emerging risks to food safety. Highlighting the urgency of this issue, climate change significantly challenges food safety by not only increasing the risk of chemical contamination in food and exacerbating the occurrence and virulence of foodborne pathogens but also by posing significant challenges through the frequent occurrence of extreme weather events. Securing food safety amidst climate change challenges requires comprehensive adaptation measures and a proactive approach to safeguard against these growing risks (35).

4.6.2 Obesity

Childhood obesity is a growing concern, characterized by an imbalance where energy intake surpasses expenditure, leading to significant health and psychosocial issues. In 2008, the UK saw a significant prevalence of obesity in children between the ages of 2 and 15, with 16.8% of boys and 15.2% of girls being categorized as obese. This condition not only predisposes children to long-term health problems but also to social challenges like marginalization and low self-esteem. Alarmingly, most obese adolescents continue to be obese in adulthood.

A systematic review focusing on lifestyle and surgical interventions for childhood obesity highlighted various strategies, including behavioral changes, dietary adjustments, increased physical activity, and in some cases, bariatric surgery. The evidence, graded for quality, suggests that lifestyle interventions can be effective in managing obesity (36).

Exposure to screen media has been recognized as a major contributor to obesity among children and adolescents. It is linked to increased food intake during screen time, exposure to unhealthy food marketing, and decreased sleep duration, all of which contribute to weight gain. However, emerging research indicates the potential of interactive media in promoting healthier eating and physical activity behaviors (37).

Addressing childhood obesity requires a multidisciplinary approach, incorporating interventions to reduce screen time and leveraging digital media positively. Future research should explore the impact of new digital media on obesity and develop interventions to counteract media exposure's adverse effects.

4.6.3 Processed and ultra-processed foods

Recent research underscores the growing concerns around the consumption of ultra-processed foods (UPFs) and their association with obesity and related health conditions. Observational studies consistently indicate that UPF consumption correlates with an increased risk of weight gain in both adults and children, as well as a heightened risk of adiposity-related comorbidities in adults. Mechanistic studies have shown that UPFs, which are often more energy-dense than nutrient-dense, can lead to increased energy intake and subsequent weight gain compared to whole foods (38).

The evidence suggests a strong link between higher intake of UPFs and obesity, metabolic syndrome, elevated fasting glucose levels, and increased total and LDL cholesterol, alongside hypertension risks. However, it remains to be clarified whether these associations are directly attributable to the processing of these foods or their nutrient content. Despite the majority of studies supporting the link between UPF consumption and negative health outcomes, the need for further research, particularly longitudinal studies with adequate control for confounding factors, is evident to confirm these associations across different populations (39).

During childhood and adolescence, the consumption of UPFs such as snacks, fast foods, and sugary drinks has been positively associated with increased body fat. This relationship underscores the urgent need for standardized classifications of food processing levels to enhance comparability across studies and to better understand the impact of UPFs on youth obesity rates (40).

To identify UPFs, the NOVA classification system can be employed, which categorizes foods based on the extent and purpose of their processing. Characteristics of UPFs include the use of ingredients not typically used in home cooking, such as high-fructose corn syrup and hydrogenated oils, and a range of additives aimed at enhancing flavor, appearance, and shelf-life. The increasing consumption of UPFs, driven by their convenience, palatability, and aggressive marketing, poses a significant challenge to public health, emphasizing the need for comprehensive strategies to reduce their intake and promote healthier dietary choices (41).

5. Discussion

In the realm of pediatrics, optimizing growth and development is a multifaceted challenge that hinges on ensuring adequate intake of essential nutrients. These nutrients, including proteins, lipids, vitamins, and minerals, serve as the foundation for healthy growth, development, and the prevention of various nutritional deficiencies. The role of each nutrient, the impact of their deficiencies, and the ongoing debate between breastfeeding and formula feeding are critical components in the discourse on pediatric nutrition. Furthermore, the field faces evolving challenges, including those posed by climate change, food security, obesity, and the prevalence of processed and ultra-processed foods.

Proteins are indispensable for growth, immune function, and the repair of tissues. Pediatric populations are particularly vulnerable to the consequences of inadequate protein intake, which can manifest as hypoproteinemia, characterized by poor growth and edema. Ensuring that children's diets contain sufficient high-quality protein is paramount for their development.

Lipids, especially unsaturated fatty acids, are vital for the development of the brain and the preservation of cell integrity.

Omega-3 fatty acids, found in fish oil and certain plant oils, are essential for cognitive development and the prevention of chronic diseases. The balance between omega-3 and omega-6 fatty acids is vital for maintaining health and preventing inflammation.

Vitamins and minerals are involved in a wide array of physiological processes. Vitamin D, crucial for bone health and immune function, is often deficient in children, leading to conditions such as rickets. Iron deficiency is another common issue, leading to anemia and affecting cognitive and physical development. Ensuring that children receive adequate amounts of these and other micronutrients is critical for preventing deficiencies and supporting healthy growth.

The discussion surrounding the choice between breastfeeding and formula feeding carries profound implications for infant nutrition and maternal health. Breastfeeding is widely recommended for its unparalleled ability to furnish infants with a comprehensive array of nutrients and immune-protective factors, meticulously attuned to their developmental needs. This natural form of nourishment is replete with bioactive compounds that are essential for optimal growth and immune system development, elements that formula feeding strives to emulate, albeit with varying degrees of success. Despite advancements in formula composition, which now includes fortification to better support infant development, there remains a gap in replicating the intricate makeup of breast milk.

The advantages of breastmilk extend beyond the immediate nutritional needs of the infant, offering significant long-term health advantages for the mother as well. Notably, engaging in breastfeeding for an extended period, particularly beyond three months, can induce enduring metabolic changes in the mother. These changes are instrumental in substantially diminishing the likelihood of developing type 2 diabetes in later years, a concern particularly significant for obese women who face a heightened risk of experiencing gestational diabetes while pregnant. This metabolic shift underscores the protective and restorative impact of breastfeeding on maternal health.

Moreover, the act of breastfeeding offers protective benefits against certain forms of cancer. Research has demonstrated a tangible reduction in the incidence of breast and ovarian cancers among mothers who breastfeed. This protective effect adds another layer to the multitude of breastfeeding benefits, emphasizing its role not only in fostering infant health but also in enhancing maternal well-being (19). The compelling evidence supporting the long-term health benefits of breastfeeding for mothers, including its role in mitigating the risk of cardiovascular diseases, further advocates for the promotion and support of breastfeeding as a comprehensive approach to nurturing the health of both mother and child.

As we look to the future, the field of pediatric nutrition is confronted with several challenges. Worldwide food production and safety is significantly endangered by the climate change, potentially exacerbating malnutrition, and nutrient deficiencies, particularly in vulnerable pediatric populations. The rising prevalence of obesity in children, fueled by sedentary lifestyles and the consumption of calorie-dense, nutrient-poor processed and ultra-processed foods, underscores the need for effective dietary interventions and public health policies that encourage healthy eating habits from an early age.

In summary, optimizing growth and development in pediatric populations requires a comprehensive approach that includes ensuring adequate nutrient intake, addressing common nutritional deficiencies, and making informed choices between breastfeeding and formula feeding. Facing future challenges such as climate change, food security, obesity, and the prevalence of processed foods will necessitate a concerted effort from healthcare providers, policymakers, and families to promote healthy dietary practices and safeguard the health and well-being of children worldwide.

6. Conclusion

In conclusion, optimizing growth and development in pediatrics through a nutritional biochemical approach underscores the intricate interplay between essential nutrients and the pivotal roles they play in ensuring the health and well-being of children. Proteins, lipids, vitamins, and minerals each contribute uniquely to various physiological functions, with deficiencies in these nutrients leading to significant health implications. The debate between breastfeeding and formula feeding highlights the importance of providing infants with the best possible start, with breast milk offering a superior nutritional profile that is closely matched to the infant's needs.

The challenges facing pediatric nutrition are multifaceted, ranging from the need to address common nutritional deficiencies to navigating the complexities of modern dietary patterns, including the rising consumption of processed and ultra-processed foods. The impact of external factors such as climate change and food security further complicate the landscape, posing additional risks to food availability and quality, which in turn affects the nutritional status of pediatric populations.

As we move forward, a concerted effort from healthcare providers, researchers, policymakers, and caregivers is essential to promote healthy dietary practices from infancy through adolescence. This includes fostering environments that support breastfeeding, developing interventions to prevent and address nutritional deficiencies, and advocating for public health policies that encourage the consumption of whole, minimally processed foods.

The nutritional biochemical approach to pediatric health offers a comprehensive framework for understanding and addressing the nutritional needs of children, with the goal of optimizing growth and development. By focusing on the foundational role of nutrition and the complex interactions between diet and health, we can work towards a future where all children can achieve their full potential, supported by a strong foundation of good nutrition.

7. Summary

Optimizing pediatric growth and development through a nutritional biochemical lens highlights the essential importance of proteins, lipids, vitamins, and minerals in maintaining child health. Each nutrient category is vital for specific physiological functions, and their deficiencies can lead to significant health issues. The choice between breastfeeding and formula feeding is crucial, with breast milk's comprehensive nutrition being the preferred start for infants. Pediatric nutrition faces challenges like addressing nutritional deficiencies and adapting to modern dietary trends, including the increased intake of processed foods. External factors like climate change and food security add complexity by affecting food availability and quality. Moving forward, a collaborative effort among healthcare professionals, researchers, policymakers, and caregivers is vital to promote healthy eating from infancy. The nutritional biochemical approach provides a framework for meeting children's nutritional needs, aiming for a future where all children can reach their full potential, underpinned by sound nutrition.

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9. Curriculum Vitae

Sirin Noelle Riedel, born on January 5th, 1997, in Göppingen, Germany. She started her educational journey in 2003, attending primary school. Her academic path led her through eight years at the Gymnasium, including a transformative year at Whistler Secondary High School in Canada. Sirin culminated her secondary education by achieving her Abitur in 2016.

Immediately following her high school graduation, Sirin dedicated a year to volunteering at a kindergarten for deaf and handicapped children, deepening her commitment to service and care in Germany.
In 2017, she pursued her passion for medicine by enrolling at the University of Rijeka in Croatia.

In addition to her medical studies, Sirin actively pursued and participated in different internships within various medical disciplines during her summer vacations, gaining essential hands-on experience and expanding her practical understanding of the medical profession.