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REVIEW ARTICLE

Nutritional Strategies for Managing Inborn Errors of Metabolism: Focus on Macro- Nutrient-Related Genetic Disorders

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Abstract

Inborn Errors of Metabolism (IEMs) are rare heritable disorders caused by enzyme deficiencies that disrupt macronutrient metabolism. These disturbances lead to either an accumulation of toxic metabolites or energy depletion and are often life-threatening from infancy. This review synthesizes nutritional management strategies for four exemplar macronutrient-related IEMs— Phenylketonuria (PKU), Maple Syrup Urine Disease (MSUD), Medium-chain Acyl-CoA Dehydrogenase Deficiency (MCADD), and Galactosemia. Nutritional therapy remains the cornerstone of care, ranging from substrate restriction (e.g., low-phenylalanine diet in PKU, lactose exclusion in Galactosemia) to supplementation with alternative fuels (e.g., uncooked cornstarch for GSD I, triheptanoin for LC-FAODs). The review was conducted through a narrative search of PubMed, Scopus, and Web of Science databases for studies published between 2000–2025 focusing on macronutrient-related IEMs. Clinical examples demonstrate that early dietary treatment prevents neurocognitive impairment, metabolic crisis, and organ dysfunction. Psychosocial, cultural, and economic challenges were also discussed with emphasis on multidisciplinary care. Nutritional therapy supported by medical foods, dynamic dietary monitoring, and policy regulation remains the first-line therapeutic approach, complemented by emerging innovations such as gene therapy and enzyme replacement therapy.

Keywords: Inborn Errors of Metabolism, Macronutrients, Nutritional Therapy, Phenylketonuria, Galactosemia, Metabolic Disorders, Medical Nutrition, Genetic Diseases, Nutrigenomics.

INTRODUCTION

1.1 Definition and Classification of Inborn Errors of Metabolism (IEMs)

Inborn errors of metabolism (IEMs) represent a heterogeneous group of genetic disorders characterized by enzymatic deficiencies that disrupt the normal metabolism of carbohydrates, proteins, or lipids. While individually rare, their cumulative prevalence is significant, making them an important consideration in pediatric and adult clinical practice [1]. The clinical presentation of IEMs can vary widely, ranging from acute life-threatening crises in the neonatal period to chronic progressive complications manifesting later in life [2]. Advances in biochemical and molecular diagnostics have considerably expanded the recognition of these disorders, enabling earlier identification and intervention [3].

Despite these improvements, the diversity of phenotypic expression and overlapping clinical features often complicate timely diagnosis and management [4].

The Inborn Errors of Metabolism (IEMs) are a spectrum of genetic diseases that is characterized with a set of diverse disorders caused by a deviation in the metabolic pathways, and when they are primarily inherited, the most typical scenario is autosomal recessive inheritance, though there are also other forms such as X-linkage and mitochondrial [5]. These disorders are characterized by gene mutation which encode enzymes, any cofactor or transport factors mediating any essential biochemical reactions. These enzyme deficiencies lead to toxic accumulation of intermediary products or shortage of important products of metabolism, a condition often portrayed in neonates and children by life-threatening conditions like hypoglycemia, metabolic acidosis, seizures, or growth and developmental delays [6,7].

Typically, IEMs have been classified by the nutrient or pathway of the metabolic defect. They are broadly grouped into carbohydrate (e.g. Galactosemia, Glycogen Storage Diseases), amino acid (e.g. Phenylketonuria (PKU), Maple Syrup Urine Disease (MSUD)), lipid (e.g. Medium- Chain Acyl-CoA Dehydrogenase Deficiency (MCADD), Very Long-Chain Acyl-CoA Dehydrogenase Deficiency (VLCADD)) and energy (e.g. mitochondrial respiratory chain disorders) disorders of metabolism. The IEMs associated with macronutrients are of critical importance among them because of their direct consequence on the dietary management, which is fundamental to therapy [8,9]. Contrary to some conditions that need pharmacologic or surgical treatment, the first approach to most IEMs is a special diet that nullifies biochemical unfoundedness in addition to promoting regular growth and improvement [10]. Table 1 provides an overview of the main categories of IEMs, organized by affected metabolic pathway, representative examples, and common clinical features. This classification follows current nosologies in clinical genetics and metabolic medicine [2, 5, 6, 8].

Table 1: Classification of Inborn Errors of Metabolism

Category	**Examples**	**Affected Pathways**	**Clinical Features**
Carbohydrate metabolism	Galactosemia, Glycogen storage diseases	Glycolysis, Glycogenolysis	Hypoglycemia, hepatomegaly, failure to thrive
Amino acid metabolism	Phenylketonuria, Maple syrup urine disease	Phenylalanine, Branched-chain amino acids	Neurological deficits, seizures

Organic acidemias	Methylmalonic acidemia, Propionic acidemia	Organic acid catabolism	Vomiting, metabolic acidosis, developmental delay
Fatty acid oxidation defects	MCADD deficiency, Long-Chain 3-Hydroxyacyl-CoA Dehydrogenase Deficiency (LCHAD) deficiency	β-oxidation	Hypoketotic hypoglycemia, liver dysfunction
Urea cycle disorders	Ornithine Transcarbamylase (OTC) deficiency, Carbamoyl Phosphate Synthetase I (CPS1) deficiency	Urea cycle	Hyperammonemia, encephalopathy
Lysosomal storage disorders	Gaucher disease, Tay-Sachs, Niemann-Pick	Lysosomal enzyme activity	Organomegaly, neurodegeneration

The main categories of IEMs depend on the affected metabolic pathway or nutrient [2]. Usually, metabolic disorders are sorted into the following three main categories: Some disorders are related to amino acids, organic acids, and carbohydrates, some affect energy production such as mitochondrial and fatty acid oxidation defects, and other disorders involve

processing complex molecules in lysosomes and peroxisomes. The disorders involving carbohydrates, proteins, and lipids are clinically significant because they affect both food intake and diet treatment [3].

An example is Phenylketonuria (PKU), which alters the metabolism of amino acids. Galactosemia leads to difficulty breaking down carbohydrates, and MCADD affects lipid processing in the body [4]. These conditions need to be spotted early and proper diets need to be followed carefully so that metabolic crises and permanent harm to organs do not happen [5]. Understanding how these disorders are classified and their biochemical cause is necessary to help with clinical care and nutritional recommendations.

1.2 Epidemiology and Prevalence of Macronutrient-Related Inborn Errors of Metabolism

Although these inborn errors of metabolism are individually uncommon, they still greatly impact health worldwide, leading to major problems among children [5]. Around 1 in 1,500 to 1 in 5,000 live births is the average worldwide estimate for the number of IEM cases, although this may change due to ethnicity, interrelationships, and the scope of new-born screening programs [6]. Certain parts of the Middle East, South Asia, and North Africa have a higher rate of disorders like IEMs due to increased rates of close family marriages [23].

About a third of all IEMs are connected to carbohydrates, proteins, or lipids, each of which can lead to health challenges [7]. One well-known example is Phenylketonuria (PKU), which happens in around 1 out of every 10,000 to 15,000 births worldwide. In other countries such as Turkey or Ireland, it can occur as often as 1 in 4,000 new-borns [8]. Many cases of Maple Syrup Urine Disease are observed in Old Order Mennonites in the United States and Canada because they live in groups with limited interbreeding [4]. In developed countries, many new-borns have disorders such as Galactosemia (1 in 30,000 to 60,000 births) [5] and MCADD (1 in 10,000 to 20,000 births) routinely found through expanded new-born screening [7, 14].

New technologies for neonatal screening have made it possible to catch issues earlier, lowering the rates of illness and death [9]. For instance, tandem mass spectrometry (MS/MS) has transformed newborn screening by allowing the simultaneous detection of over 30 metabolic disorders, including aminoacidopathies, organic acidemias, and fatty acid oxidation disorders, from a single dried blood spot [45]. More recently, next-generation sequencing (NGS) is being integrated into neonatal screening programs, enabling the identification of pathogenic variants that may not manifest biochemical abnormalities at birth, thereby expanding early diagnostic capacity [110]. Even today, there are problems in health systems and access to equipment in some countries. Consequently, we do not have a complete picture of the worldwide burden of IEMs involving macronutrients, and the current data is likely low.

1.3 Importance of Early Diagnosis and Nutritional Intervention

Early detection and appropriate nutrition are important for managing macronutrient-related IEMs. Most of these disorders are present from soon after birth or in childhood, and may be diagnosed by symptoms like lethargy, sickness, difficulty feeding, delays in development, or serious changes in metabolism [28]. If these signs are not noticed or addressed at the right time, neurological damage, failure of multiple organs, or death may quickly result. For this reason, finding out about the disorder early can help provide timely nutritional support and improve health outcomes. Table 2 summarizes commonly used diagnostic methods for IEMs, including biochemical assays, metabolic profiling, and genetic testing, along with representative disorders detected by each approach. These tools

Table 2: Common Diagnostic Tools for Inborn Errors of Metabolism

Diagnostic Method	Purpose	Examples of Detectable Disorders
Tandem mass spectrometry	Screens amino acids and acylcarnitines	Phenylketonuria (PKU), MCADD deficiency, MSUD
Gas chromatography–mass spectrometry (GC-MS)	Profiles urine organic acids	Methylmalonic acidemia, Propionic acidemia
Enzyme assay	Measures specific enzyme activity	Glycogen storage diseases, lysosomal disorders
DNA sequencing	Detects mutations in metabolic genes	Any genetically linked IEM
Ammonia and lactate levels	Assesses metabolic crisis or decompensation	Urea cycle defects, mitochondrial disorders

In many cases, the only way to treat IEMs is through nutritional intervention, which needs to be managed carefully for life [6-10]. This also requires providing fuel, nutrients, and growth- supporting substances to promote the patient's health. Health professionals typically recommend using specific prescription formulas, reduced-protein diets, and dietary supplements. However, it is important to keep monitoring nutritional therapy, guide caregivers, and receive support from many teams to maintain health and quality of life [12]. A quick diagnosis and proper nutrition control can turn life-threatening IEMs into chronic illnesses with positive long-term prospects [5]. Table 3 outlines major therapeutic strategies for IEMs, highlighting dietary modification, cofactor supplementation, enzyme replacement, transplantation, and emerging gene therapies. These approaches are tailored to the underlying metabolic defect and have been validated in both clinical practice and translational research [10, 12].

Table 3: Treatment Approaches for Inborn Errors of Metabolism

Therapeutic Strategy	Mechanism of Action	Examples of Application
Dietary modification	Eliminates toxic substrates and supplies missing nutrients	PKU (phenylalanine-restricted diet), Galactosemia (lactose-free diet)
Cofactor supplementation	Enhances residual enzyme activity	Biotinidase deficiency (Biotin), Methylmalonic Acidemia (MMA) (Vitamin B12)
Enzyme replacement therapy	Replaces deficient or nonfunctional enzymes	Gaucher disease (Imiglucerase), Fabry disease
Liver transplantation	Provides source of functioning enzymes	Ornithine Transcarbamylase (OTC) deficiency, Tyrosinemia type I
Gene therapy (experimental)	Corrects the underlying genetic mutation	Trials ongoing in OTC, Mucopolysaccharidoses (MPS) types I & II, and others

1.4 Aim and Scope of the Review

This review also shifts the goals of clinical knowledge of nutritional interventions in IEMs towards new technologies in molecular diagnostics, digital applications, and the process of personal dietary planning. There is nothing new in identifying IEMs, as such they are well- documented in dietary therapy, but what is new and important is bringing the current and novel strategies of macronutrient-specific dietary therapy together into one document. These are the use of tetrahydrobiopterin (BH4) therapy in responsive people with PKU, triheptanoin oil in disorders of fatty acid occupation (FAO), real-time digital tracking of the diet to improve compliance, and nutritional modeling, which is

case-based [11-13]. This is enhanced further based on the examination of psychosocial and economic impediments of nutritional care, which have not been adequately tackled in literature.

Instead of giving a superficial review, this review will be based on translating biochemical mechanisms into practice in multidisciplinary dietary interventions. There is particular focus on the incorporation of metabolic data into dietary algorithms, an evolving role of medical foods and the logistics of paediatric to adult nutritional transitions. In situating conventional dietary therapy in the context of contemporary medicine, this piece provides a complete revision necessary in the practice of clinicians, dieticians, and researchers in the field of metabolic medicine [14-16].

1.5 Methodology

The narrative review was done via the use of different biomedical databases such as PubMed, Scopus, and Web of Science until April 2025. Combined search terms utilizing the Boolean operators are as follows: inborn errors of metabolism, nutritional therapy, dietary management, macronutrients, phenylketonuria, maple syrup urine disease, galactosemia and medium-chain acyl-CoA dehydrogenase deficiency. Articles were considered for inclusion if they (i) were

published in English between 2000–2025, (ii) focused on macronutrient-related IEMs, and (iii) provided clinical, nutritional, or therapeutic data. Priority was given to systematic reviews, randomized controlled trials (RCTs), meta-analyses, and high-quality cohort studies. Expert consensus guidelines, case reports, and narrative reviews were included as complementary evidence to provide clinical context [14, 53, 106]. Evidence was synthesized thematically according to the metabolic pathway involved (carbohydrate, protein, or lipid metabolism) and the nutritional strategies applied.

2.0 Pathophysiology of Macronutrient-Related Inborn Errors of Metabolism

Inborn errors of metabolism (IEMs) include several genetic conditions that hinder the body’s ability to use carbohydrates, proteins, and lipids [14]. These conditions are caused by abnormalities in enzymes or coenzymes involved in breaking down or forming major nutrients [15]. When IEMs disturb metabolism of macronutrients, problems with enzymes can build up poisonous substances in the body or reduce the production of essential metabolites, which may severely harm health. To manage IEMs and design new treatments, it is essential to understand the metabolic processes of carbohydrates, proteins, and lipids, along with the pathophysiology of the top IEMs in those groups [16].

2.1 Overview of Metabolic Pathways Involving Carbohydrates, Proteins, and Lipids

Metabolism covers all the chemical processes used by living organisms to maintain life. These processes rely heavily on the pathways that handle the use and modification of macronutrients. carbohydrates, proteins, and lipids [17]. Their main function is to supply energy and to build body tissues, and how they are metabolized is strictly controlled. Changes in genes may cause inborn errors of metabolism (IEMs) and these often seriously impact health and development.

2.1.1 Carbohydrate Metabolism

Glucose and other carbohydrates are the main sources of fast energy used by the body [18]. The process of digestion begins in the mouth and ends in the small intestine, where polysaccharides are split into monosaccharides. Glucose travels into the cell with the help of specific transporters and becomes glucose-6-phosphate when it is phosphorylated, which signals the beginning of glycolysis [19]. During glycolysis, enzymes change glucose into

pyruvate and allow two adenosine triphosphate (ATP) molecules and two NADH molecules to form for every glucose.

In aerobic conditions, pyruvate becomes acetyl-CoA and then moves to the citric acid cycle (Krebs cycle) in mitochondria, where additional oxidation occurs and this produces electron carriers like NADH and FADH2 [20]. These electrons are used by the electron transport chain to create ATP by means of oxidative phosphorylation. When there’s no oxygen or mitochondria, pyruvate is changed into lactate.

Glycogen is formed from extra glucose and is stored in the liver and skeletal muscle. Glycogen in our liver is released as glucose when we are fasting or using higher amounts of energy [21]. The body produces glucose from non-carbohydrates through gluconeogenesis, giving constant glucose to the brain and red blood cells.

2.1.2 Protein Metabolism

Proteins are primarily functional and structural molecules, but they also serve as energy sources when necessary. Dietary proteins are digested into amino acids, which are absorbed and utilized in protein synthesis or catabolized for energy [22]. Each amino acid follows a unique catabolic pathway based on its side chain, yielding intermediates such as pyruvate, acetyl-CoA, or tricarboxylic acid (TCA) cycle intermediates [44].

Deamination, or the elimination of an amino group, is important for splitting amino acids during catabolism. Ammonia, which is very dangerous, is quickly turned into urea by the liver and excreted in urine. Depending on how they are used, the carbon skeletons of amino acids are considered glucogenic, ketogenic, or both. These two types of amino acids are metabolized differently because glucogens enter gluconeogenesis while ketogens become ketone

bodies. Proper enzymatic action is necessary for managing the number of amino acids in the body. If there is a defect in these pathways from inherited enzyme deficiencies, harmful substances build up while important products are unavailable [24]. These sorts of disorders include phenylketonuria, in which phenylalanine hydroxylase is lacking, and maple syrup urine disease, where branched-chain amino acid metabolism is disturbed.

2.1.3. Lipid Metabolism

Lipids provide much more energy than carbohydrates or proteins, with one gram of lipid giving about twice as much energy as one gram of the other two [25]. Dietary lipids are processed into fatty acids and monoacylglycerols, which are absorbed into small sacs known as chylomicrons

where they are made into triglycerides for transportation through the blood. During times when the body needs extra energy, triglycerides are released from adipose tissue through lipolysis. In mitochondria, fatty acids undergo β-oxidation to form acetyl-CoA, NADH, and FADH2. When fasting or carbohydrate intake is low, acetyl-CoA is often diverted to ketone bodies in the liver [26]. Peroxisomal β-oxidation deals with long-chain fatty acids, but α-oxidation handles branched-chain fatty acids.

The synthesis of important substances such as steroid hormones, bile acids, and phospholipids depends mainly on lipid metabolism [27]. Disorders of lipid metabolism like MCADD and LC-FAODs make it difficult for the body to access energy from fat.

2.1.4 Interconnectivity and Regulation

Metabolism of carbohydrates, proteins, and lipids affects one another. Excess carbohydrates can change into fatty acids using de novo lipogenesis, and amino acids can either transform into glucose or fatty acids depending on the energy available [28]. A balance between anabolic and catabolic states depends on hormones such as insulin, glucagon, epinephrine, and cortisol. Lacking enzymes or having issues with transport in these systems can lead to a build-up of substrates, lack of energy, and problems with organs, which are main features of macronutrient- related IEMs [3,14].

2.2 Genetic and Enzymatic Defects Affecting Macronutrient Metabolism

These genetic mutations lead to partial or complete loss of enzyme function, causing metabolic blockages, substrate accumulation, alternative pathway activation, and deficiency of vital end- products. The impact is particularly severe in infancy and childhood, where rapid growth and metabolic activity are essential [29].

2.2.1 Nature of Genetic Mutations and Inheritance Patterns

Most IEMs follow an autosomal recessive inheritance pattern, meaning two defective copies of a gene must be inherited, one from each parent for the disorder to manifest [30]. However, some are X-linked or dominant. Mutations may include missense, nonsense, frameshift, or splice-site mutations, each affecting the enzyme's structure or function

differently. Affected individuals may produce a dysfunctional enzyme or none at all, depending on the mutation's severity. Genetic defects disrupt the metabolism of carbohydrates, proteins, or lipids by impeding crucial steps in their catabolic or anabolic pathways [31]. These disruptions may

result in toxic accumulation of intermediates, such as organic acids or ammonia, or an energy deficit due to blocked ATP-generating steps.

2.2.2 Enzymatic Deficiencies in Carbohydrate Metabolism

Carbohydrate metabolism involves glycolysis, glycogenolysis, gluconeogenesis, and the pentose phosphate pathway, all of which are enzymatically driven [27]. Defects in these processes are commonly associated with disorders such as:

- *Galactosemia*: Lack of galactose-1-phosphate uridyltransferase (GALT) in galactosemia causes an increase in the levels of galactose-1-phosphate and galactitol [32]. If galactose is not controlled early by following a low-galactose diet, the result can be liver problems, cataracts, and nerve damage [5].
- *Glycogen Storage Diseases (GSDs):* Low levels of enzymes for glycogen production or breakdown lead to these disorders [33]. As an example, GSD type I (von Gierke disease) occurs when the body lacks glucose-6-phosphatase and can’t release glucose from the liver. Because of this, severe low blood sugar, a build-up of lactic acid, and swollen livers develop [6].

2.2.3 Enzymatic Deficiencies in Protein Metabolism

Amino acids are processed for metabolism, first by transamination, then deamination, and finally broken down into substances that can take part in the TCA cycle or in gluconeogenesis [27]. An abnormality in one of these pathways can lead to an aminoacidopathy.

- Phenylketonuria (PKU): When phenylalanine hydroxylase is absent, phenylalanine builds up and leads to toxic effects [34]. Early diet management is crucial to avoid intellectual disability, frequent seizures, and such behavioural issues in PKU.
- Maple Syrup Urine Disease (MSUD): A malfunction in the branched-chain α-keto acid dehydrogenase complex is responsible for MSUD, resulting in higher levels of leucine, isoleucine, and valine [35]. The presence of these branched-chain amino acids and their ketoacids in babies can lead to brain damage, poor appetite, extreme tiredness, and urine that smells sweet [4].

Ornithine transcarbamylase deficiency, a disorder involving protein metabolism, can damage the urea cycle and increase ammonia levels in the body, which can be fatal if it's not treated rapidly [22].

2.2.4 Enzymatic Deficiencies in Lipid Metabolism

β-oxidation in mitochondria, peroxisomal oxidation, and the process of remodelling complex lipids are the primary means to metabolize lipids [36]. Problems in these pathways may cause hypoglycemia, enlarged liver, heart disease, and sudden death, this occurs primarily during periods of illness or inadequate food intake.

- ***Medium-chain acyl-CoA dehydrogenase deficiency (*MCADD)**: This disorder is one of the most frequently found in fatty acid oxidation disorders. Because medium-chain fatty acids cannot be oxidized when a person does not consume foods, this causes the body to become low in energy and hypoglycemic [37]. The signs of Niemann-Pick generally appear during infancy and can be lethargy, vomiting, seizures, and going into a coma [12].
- **Long-chain fatty acid oxidation disorders (LC-FAODs):** CPT II deficiency and VLCAD deficiency are two examples of these [38]. Such disorders can be dangerous, as they interfere with cardiac and muscle function, usually leading to heart weakness, muscle breakdown, and liver problems [8].

2.2.5 Metabolic Consequences of Enzyme Deficiencies

For all three groups, carbohydrates, proteins, and lipids, an enzyme being disrupted causes excess metabolites (which can be toxic) or a drop in the metabolites needed for energy, toxin removal, or biosynthesis [39]. Accumulating galactose-1-phosphate in galactosemia damages the liver, and having too little energy in MCADD can bring on acute metabolic problems. Many poisons bring about systemic reactions, especially on the liver, brain, muscles, and heart.

2.2.6 Important of Early Diagnosis and Treatment

Since IEMs share many signs with usual paediatric diseases, they are sometimes incorrectly diagnosed or treated late [40]. With the adoption of tandem mass spectrometry for new-born screening, it has now become much easier to find cases of PKU, MSUD, and MCADD early in life. Being able to diagnose early makes it possible for nutritional and metabolic treatments to stop further problems before they become permanent.

2.3 Carbohydrate Metabolism Disorders: Galactosemia and Glycogen Storage Diseases

Defects in the processes that regulate how sugars, like glucose, are broken down, stored, and used are what lead to carbohydrate metabolism disorders [27]. As a result of these conditions, the body cannot convert carbohydrates into

energy, causing more substrates to build up, using up energy, and leading to dangerous toxicity in the whole system. Two traditional types of

inborn errors in carbohydrate metabolism are named Galactosemia and Glycogen Storage Diseases (GSDs) [41]. Both of these conditions illustrate how a lack of enzyme activity in infancy or early childhood can influence many organs in the body.

2.3.1 Galactosemia

In people with galactosemia, there is a problem processing galactose, which is made from lactose and belongs to a kind of monosaccharide [32]. Common and very severe is Classic Galactosemia (Type I), which happens because the body doesn't have enough of the GALT enzyme [32]. There are two different kinds of less frequent variants: Type II without galactokinase and Type III not having uridine diphosphate-galactose-4-epimerase (UDP- galactose-4-epimerase).

Galactosemia causes an accumulation of galactose-1-phosphate, galactitol, and galactonate, which results from the enzymatic block [42]. They are harmful to the liver, brain, kidneys, and eyes. In most cases, jaundice, vomiting, an enlarged liver, low blood sugar levels, being too weak, and failure to thrive are the early signs of the condition in new-borns. If not treated, a patient can suffer from sepsis, *E. coli*, liver failure, brain damage caused by infections, and even death. Doctors use new-born screening or special biochemical tests to arrive at a diagnosis. Diagnosis is confirmed by noticing that galactose and galactose-1-phosphate are high in the blood, and that the GALT enzyme is reduced in amount [42]. This form of testing can determine exactly which mutations are in the GALT gene, which helps with genetic counselling.

Taking care of the patient's nutrition is the most important part of treatment. Strictly denying galactose and lactose to the patient by forbidding milk and dairy products can reduce the chances of acute toxicity and help the patient survive [43]. Still, some children may keep experiencing speech problems, lower intellect, and may prematurely lose their ability to have children, despite recovery from the metabolic condition. This points out that exposure to metabolites during pregnancy and in the first weeks of life may create hard-to-reverse problems [5].

2.3.2 Glycogen Storage Diseases (GSDs)

Glycogen Storage Diseases are a set of inherited issues that occur due to a lack of certain enzymes needed to store or break down glycogen [44]. Having glycogen in the liver and muscles helps provide the steady supply of glucose needed in times when you're fasting [44].

If enzymes do not function correctly, it can lead to changes in glucose levels and organ problems.

There are over a dozen recognized types of GSDs, but the most clinically relevant in childhood include:

- GSD Type I (Von Gierke Disease) is the result of low levels of glucose-6-phosphatase, hindering the final part of gluconeogenesis and glycogenosis. Patients are unable to change glucose-6-phosphate into free glucose, so they face severe hypoglycemia in fasting, an increase in lactic acids, higher lipids, and larger than normal livers [6].
- GSD Type II, also known as Pompe Disease, occurs when a person does not have enough acid alpha-glucosidase and so cannot break down glycogen properly in lysosomes [45]. Primary symptoms are related to muscle, such as heart and skeletal, so the disease may involve cardiomyopathy, weak muscles, and breathing difficulties in infants [12].
- In GSD Type III (Cori or Forbes Disease), the lack of a debranching enzyme means glycogen is only partly broken down for use. It results in an enlarged liver, low blood sugar, and muscle disorders [6].
- People with GSD Type V, also called McArdle Disease, have insufficient muscle phosphorylase, causing them to tire easily, get muscle cramps, and pass myoglobin in their urine [37].

Depending on the type, the main clinical signs are swelling of the liver, being underweight, low blood sugar levels, and muscle weakness after physical activity. The doctor will test the activity of enzymes, look for genetic changes, and examine biopsies of liver or muscle tissue. In certain cases, having higher levels of lactate, triglycerides, and uric acid in the blood can help confirm the diagnosis [46]. Treatment for GSDs varies by type but generally deals with changes to the diet to control the risk of hypoglycemia [47]. For patients with GSD Type I, regular meals with sufficient complex carbohydrates and uncooked cornstarch (1.6–2.5 g/kg every 3–6 hours in children) are required to maintain euglycemia and prevent hypoglycemia [114]. In contrast, infantile-onset Pompe disease, also known as GSD Type II, is effectively treated with enzyme replacement therapy (ERT) using recombinant acid α-glucosidase. The recommended ERT regimen is 20 mg/kg body weight administered intravenously every 2 weeks, which has significantly improved survival and cardiac outcomes [117, 118].

2.3.3 Broader Implications

Both these conditions, Galactosemia and GSDs, demonstrate how important it is for carbohydrate metabolism to be balanced and the major problems that can happen when it is not. Hence, doctors need to pay attention to early detection, continuous metabolic test results, and involve nutritionists, geneticists, and metabolic experts in care. Chronic impacts, such as delays in neural development and growth of hepatic adenomas, need to be keep an eye on for a long time [48].

2.4 Protein Metabolism Disorders: Phenylketonuria (PKU) and Maple Syrup Urine Disease (MSUD)

Problems with protein metabolism can happen when certain enzymes in the body do not work properly and disrupt the breakdown of amino acids [49]. As a result of these problems, more amino acids or their toxins accumulate, which leads to brain damage, serious illness, and delays of growth. PKU and MSUD are some of the best studied and most important conditions in the field [50]. It is important to diagnose these disorders early and use a proper diet to avoid permanent problems.

2.4.1 Phenylketonuria (PKU)

Phenylketonuria results from deficiency of phenylalanine hydroxylase, leading to toxic accumulation of phenylalanine and its metabolites [51]. Tyrosine, used in the making of dopamine and norepinephrine, is made from phenylalanine with the help of this enzyme. Reduced PAH enzyme activity due to mutations in the gene results in phenylalanine and its metabolites (including phenylpyruvate) building up in the blood and the brain [51].

Neurological issues make up most of the side effects caused by phenylalanine. Excessive levels block the brain's growth and myelin creation, which results in intellectual problems, behavioural issues, seizures, and the build-up of phenylacetate, making a person smell musty [52]. In children who do not receive treatment, the symptoms appear during the first few months of their life. PKU is commonly found by testing for phenylalanine levels in new-borns using tandem mass spectrometry. Confirmatory tests are the phenylalanine hydroxylase (PAH) enzyme assay and performing genetic testing [2].

For treating PKU, the approach of changing the diet is considered the best option. Ensuring blood phenylalanine levels do not go above a certain limit is done mainly by eating a low- phenylalanine diet throughout life. Among the non-allowed foods are meat, milk, eggs, nuts, and other foods that are rich in protein. People with phenylketonuria are given special food and

formulas that ensure they get their required nutrients and not too much phenylalanine [53]. In recent years, sapropterin dihydrochloride, a synthetic form of the PAH cofactor tetrahydrobiopterin (BH4), has been used to enhance residual PAH activity in responsive patients. It is very important to take the recommended diet especially during pregnancy with PKU (also called maternal PKU), because too much phenylalanine could harm the fetus [54]. Even though dietary changes are made early, a small number of people with PKU may still show signs of mild intellectual difficulties, which is why regular checks for growth and development are important. Periodic checkups are imperative towards changes in therapy. The individuals affected by PKU, who strictly control their diet, still demonstrate some neurocognitive impairment, diminished executive abilities, and psychiatric problems in comparison with healthy individuals [52, 54].

2.4.2 Maple Syrup Urine Disease (MSUD)

MSUD is a serious illness brought on by the deficiency of an enzyme complex called BCKDH, which helps break down the branched-chain amino acids in the body: leucine, isoleucine, and valine. Both BCKDHA and BCKDHB are components of this complex. Mutations in their genes cause a build-up of BCAAs and their related ketoacids, which are harmful to the brain [55]. The disorder got its name from the maple syrup-like scent of the urine, which is caused by too much of the chemical sotolone [56]. About a week after birth, signs of clinical presentation appear and include being tired, poor appetite, vomiting, touching and crying a lot, odd changes in muscle tone, and developing seizures and coma if the condition is not treated. Like PKU, leucine and other branched-chain amino acids are universally measured on new- borns for MSUD screening. Both measuring the BCKDH enzyme activity and doing molecular genetic tests confirm the diagnosis [56].

Proper diagnosis and management of MSUD relies on quickly fixing the patient's eating habits and stabilizing the metabolism. When a metabolic crisis occurs, glucose and lipid solutions are given intravenously to help stop the breakdown of muscle and cut back on BCAA presence. In the long run, patients remain on a limited BCAAs diet and are given BCAA-free amino acid supplements to promote proper growth and development [56]. It is very important to observe leucine in the blood since it can be highly harmful to the brain. For some persons with classic MSUD, having a liver transplant is helpful, as this enables the liver to manage BCAA in a healthy way [56]. However, having a transplant means dealing with many surgical dangers and possible effects in the future, such as lessening the immune system.

3.0 Nutritional Management Principles In IEMs

The management of many IEMs relies heavily on adjusting the nutritional intake, especially related to macronutrients [57]. Dietary interventions try to either limit the harmful substances a person eats, supply what is missing in their diet, or support other ways to process food so they don't experience serious and life-threatening problems. Since the symptoms of IEMs are not the same, a tailored diet plan that matches each condition is usually required [37].

3.1 Dietary Restriction of Substrates

Dietary restriction is the principle treatment method in addressing most IEMs to deter the build- up of toxic metabolites but allow normal development and growth. In conditions like PKU, MSUD and Galactosemia the metabolic blockage is directly correlated with a substrate that has to be heavily limited to avoid organ injury or neurotoxicity. Nevertheless, these diets are not dietary elimination regimes, but they should also be balanced carefully to prevent tertiary nutrient deficiencies and maintain metabolism balance [1-3]. The history of dietary management in IEMs reflects evolving clinical knowledge and patient-centered interventions. Particularly, the treatment of phenylketonuria (PKU) has shifted to inflexible low phenylalanine diets, to more liberal diets via sensitivity to sapropterin

dihydrochloride and the emergence of gene medicine. This evolutionary trend can be seen in Figure 1, which shows the highlighting of some milestones in the utilization of low-phenylalanine diets (e.g soy protein isolate contains approximately 2,000 mg of phenylalanine per 100g, other high-phenylalanine foods include meat, fish, eggs, dairy products, nuts, and legumes) since the 1950s as well as contemporary and prospective treatment developments.

PKU is managed through lifelong restriction of phenylalanine using low-protein diets and medical formulas, supplemented with tyrosine and BH4 [4]. Excessive restriction

can lead to growth failure or protein-energy impairment, this is particularly true with children, and periodical re-evaluation of the diet and biochemical monitoring is essential [5]. More recent treatment options like sapropterin dihydrochloride [6] (a synthetic analog of BH4), have now helped liberate the diets of some patients by augmenting remaining PAH activity and lowering the amount of phenylalanine, not as severely avoided by diet [6].

The most recent changes have focused on the digital dietary tools of PKU. For example, mobile applications now allow real-time tracking of phenylalanine intake, improving adherence and clinical outcomes [106]. Moreover, research in maternal PKU has refined phenylalanine tolerance ranges during pregnancy, highlighting genotype-dependent variation and the necessity of individualized care [16]. In low-resource settings, limited access to medical foods remains a barrier, underscoring the need for cost-effective local alternatives [11]. Systematic reviews and randomized trials confirm that lifelong dietary restriction of phenylalanine prevents neurocognitive impairment in PKU [106]. Recent RCTs have further demonstrated the efficacy of sapropterin (BH4) supplementation in responsive patients, allowing dietary liberalization without loss of metabolic control [112]. Similarly, meta-analyses on glycogen storage disease management support the use of uncooked cornstarch and modified cornstarch to sustain normoglycemia [11].

To avoid redundancy, detailed case-specific outcomes are summarized in the case study section, whereas this section highlights general dietary principles [37, 53].

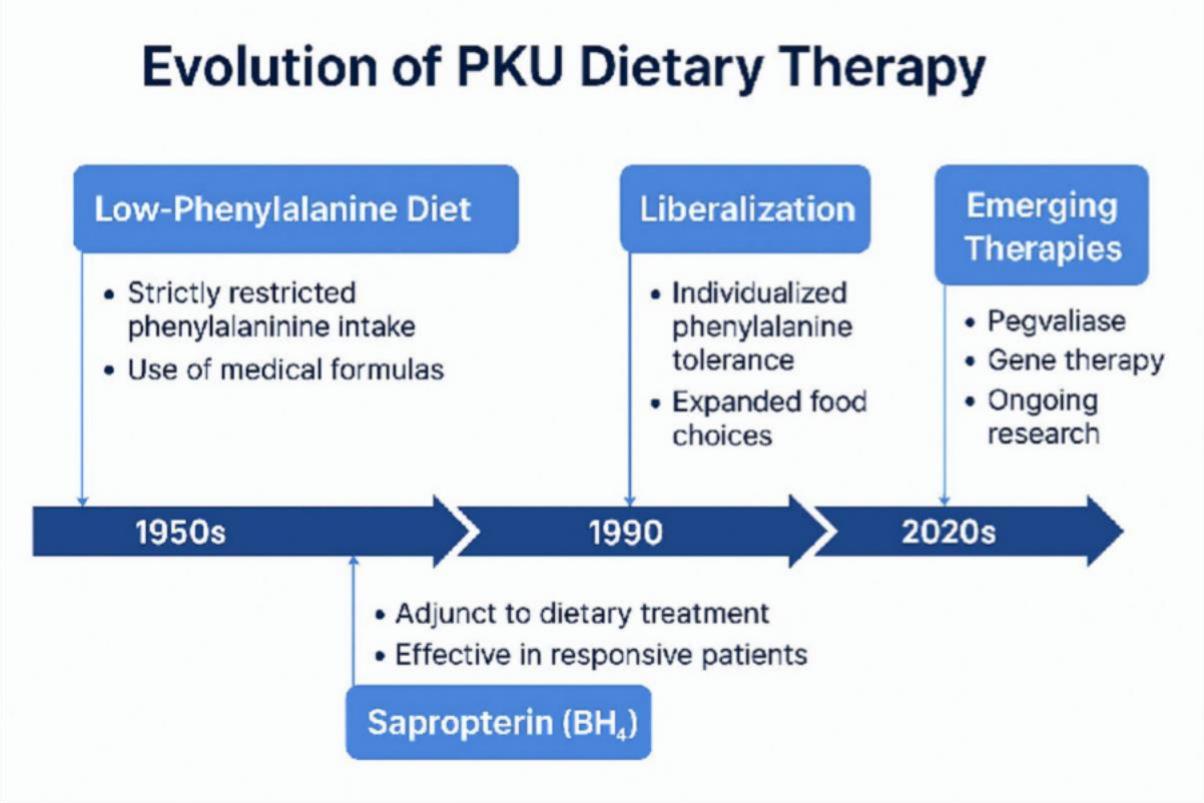

Fig. 1. Evolution of PKU Dietary Therapy. A timeline illustrating the progression of dietary management strategies for Phenylketonuria (PKU) from the 1950s to the present, including key milestones such as sapropterin introduction and emerging gene therapy options [53].

It is also important to restrict the branched chain amino acids (leucine, isoleucine, valine) in MSUD. Eggs – a single large egg contains about 1.3 g of BCAAs, primarily leucine, making it a high-quality protein source commonly used in clinical nutrition and metabolic studies [119]. Other notable examples include chicken breast, beef, dairy products (milk, whey protein), soy protein, and legumes [7-8].

Treatment of galactosemia involves a permanent ban on lactose, galactose and lactose and galactose-containing foods like milk and dairy products and certain legumes. Despite the acute symptoms that have a high probability of prevention with the use of diet therapy, long-term complications, including primary ovarian insufficiency, speech abnormalities, and mental retardation, are still most common, probably as a result of exposure to metabolites during gestation and early life [9]. The new studies focus on new dietary thresholds and evaluation of the residual enzyme activity used to customize the limit of galactose tolerance [10].

In the case of Glycogen Storage Disease Type I (GSD I), dietary management looks at prevention of the fasting hypoglycemia. Uncooked cornstarch therapy is employed to deliver a slow release of glucose to preserve euglycemia

in prolonged fasting state, especially in the overnight fasting. A practical dosage of 1.62.5 g/kg q3-6 hours in children and 1.72.5 g/kg 4- 6 hours in adolescents and adults or about 6-8 g/kg/day in divided doses is recommended. A bedtime cornstarch feed is essential to prevent nocturnal hypoglycemia [114, 115]. The enteral nutrition is usually protocol-dependent every 3-4 hours, sometimes continuous during the night. Nevertheless, new experiments with modified cornstarch (Glycosade 126) prove hopeful in changing the feed volume frequency and quality of life enhanced [11].

Nutritional management therefore needs to be dynamic- altered with age, metabolic needs, growth and response to treatment [12]. Dynamic metabolic modeling has emerged as effective in providing an improved list of substrate restrictions based on real time monitoring of the biomarkers. As an example, an increase in the tolerance of higher levels of phenylalanine in sapropterin-responsive PKU patients contributes to the decreased dietary strictness and quality of life [18]. On the same note, low glycemic index therapies have also been established to reduce cases of nocturnal hypoglycemia in GSD types I and III, which reduces cases of overnight tube feeding [19]. These strategies account the change of blanket-restriction to risk- adaptive nutritional algorithms. Likewise, there has been great improvement in the management of Glycogen Storage Disease Type I (GSD I). The conventional cornstarch treatment that entailed rigorous feeding times at nights and frequent administration of starch has been enhanced with invention of modified cornstarch products such as Glycosade (R), which offers longer periods of glycemic control, and extends the span of fasting.

3.2 Adding Extra Nutrients and Aiding Factors

In a lot of situations, just blocking substrates is not enough to fully arrest IEMs. In order to have normal growth and steer clear of nutritional deficiencies, some patients need to add extra nutrients and enzyme components [62].

- Amino acids: Those with protein restrictions need their diets to include artificial mixtures of amino acids that lack the toxic acids but contain all other essential ones. Many of these products have added vitamins and minerals.
- Fat-Soluble and Water-Soluble Vitamins: People may not get enough nutrients because they are restricted in their food sources or do not absorb them well [63]. Adding vitamin D, calcium, and iron to the diets of patients with GSDs can shield them from

  osteoporosis and anaemia. MSUD and MADD often require riboflavin and thiamine among the B-complex vitamins to be treated.

- Cofactor Therapy: A few IEMs are affected by the right amount of cofactor supplements.
- BH4 (sapropterin): BH4 makes PKU management easier by improving the remaining activity of the phenylalanine hydroxylase enzyme [64].

- Riboflavin: Helps bring back function in MADD that is controlled by riboflavin.
- Vitamin B12: helps in treating both methylmalonic acidemia and homocystinuria.
- Biotin: Treats biotinidase deficiency as well as holocarboxylase synthetase deficiency.
- Carnitine Supplementation: In fatty acid oxidation diseases, carnitine is involved in taking up fatty acids by mitochondria and supporting the elimination of harmful acyl- CoA compounds [65].
- Monitoring: To prevent overdosing or off-balance levels, you should get your blood tested every so often for your vitamin and mineral intake, paying extra attention to zinc, selenium, and copper.

3.2.1 Personalized Nutrition and Dynamic Modeling

One of the most popular innovations related to IEM care is the transition to a flexible system of nutrition to an adaptive one. With the help of genotyping, metabolic flux analysis, and application of wearable technologies, clinicians can now personalize macronutrient ratios and can see and monitor the patient-specific response to diet on their watch [13]. As an example, genotype-phenotype correlation and the chances of response are anticipated in BH4-responsive PKU and dietary liberalization is carried out together with phenylalanine tolerance trials [14]. In the same token, there are differences in clinical trials (mentioned below in case-studies) of decision-support algorithms to assist in optimizing substrate loads in MSUD and GSDs, on the basis of growth parameters and biochemical markers [15]. Table 4 presents a comparative summary of nutritional strategies applied in selected macronutrient-related IEMs. It highlights established interventions, key supplements, and emerging approaches, providing a concise overview of clinical practice and ongoing innovations [11, 13, 53].

Table 4: Comparative Nutritional Strategies for Selected IEMs

Disorder	**Main Nutritional Strategy**	**Key Supplement**	**Emerging Approaches**
PKU	Low-phenyalanine	Tyrosine, BH4	Gene therapy, digital
	diet		tracking.
MSUD	BCAA restriction	BCAA-free amino acid formula	Liver transplant, adaptive algorithms
Galactosemia	Lifelong lactose/galactose exclusion	Calcium, Vitamin D	Enzyme replacement under study

MCADD	Avoid fasting, frequent carbohydrates feeds	Carnitine (in some cases)	Digital monitoring of sick-day protocols

Interindividual variability also emerged with the emergence of nutrigenomics and metabolomics regarding nutrient processing, absorption and tolerance. Such tools are particularly relevant in adult patients and when there are special stages during which nutrient needs change significantly such as during adolescence or when pregnant [16]. Even though this review dwells on PKU and GSD I, other IEMs, like Maple Syrup Urine Disease (MSUD), Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCADD) which have different nutritional management. A comparative summary of such disorders is outlined in Figure 3 illustrating, the foundational dietary steps of corrective therapy and supporting management strategies of the significant importance in the patient outcome behavior in such disorders. Figure 3 provides a comparative summary of the dietary management in a few of the IEMs. It has suggested dosages based on age, growth, and metabolism regulation; however, they are oriented in accordance with consensus statements. In MSUD, dietary therapy focuses on leucine restriction (20–40 mg/kg/day) with valine and isoleucine supplementation (20–40 mg/kg/day each) to maintain balance [121, 122]. In MCADD, fasting must be strictly avoided, with carbohydrate intake maintained at approximately 2–3 g/kg for every 3–4 hours in infants, and carnitine supplementation (50–100 mg/kg/day) considered in deficient patients [114, 123]. For LCHADD, long-chain triglycerides are restricted to 10–15% of daily energy, with medium- chain triglycerides supplemented at 2–4 g/kg/day to support energy needs [124]. In galactosemia, lifelong elimination of galactose/lactose is required, with additional calcium (500–1,000 mg/day) and vitamin D (400–800 IU/day) supplementation to preserve bone health [125].

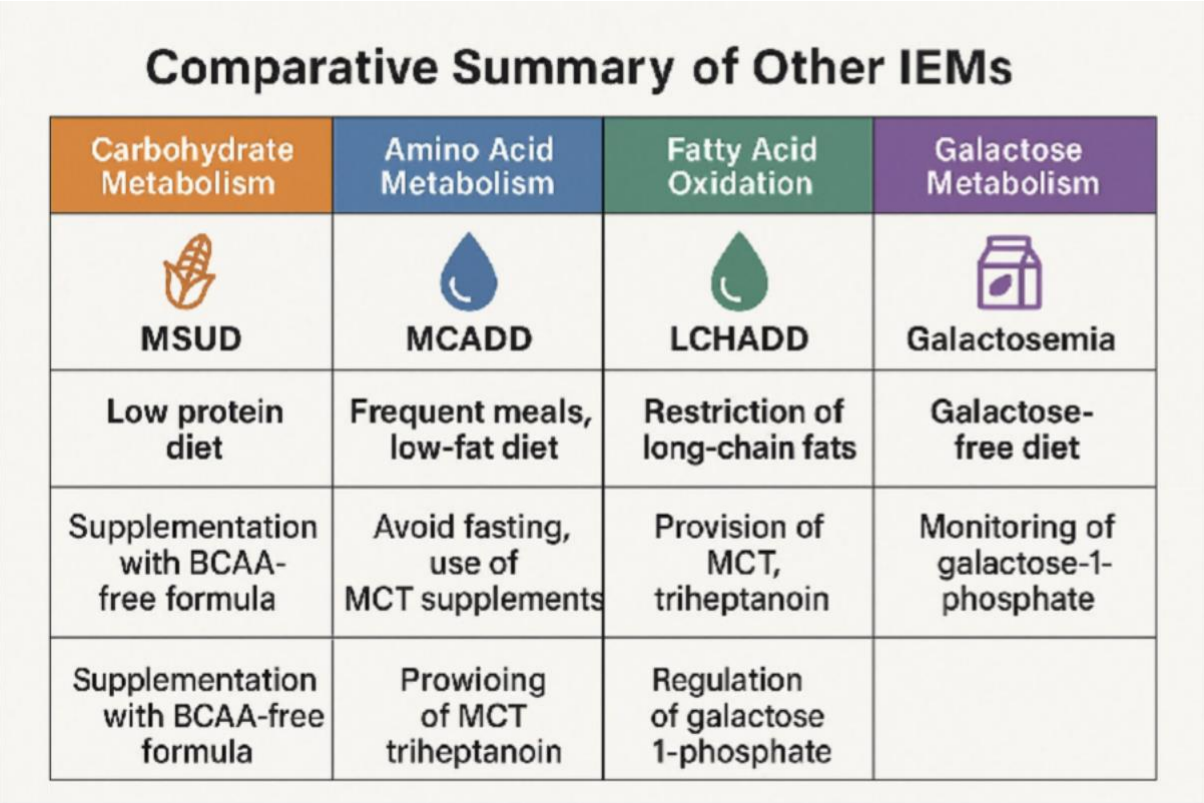

Fig. 3. Comparative Summary of Other IEMs. A comparative overview of dietary approaches and key management strategies for Maple Syrup Urine Disease (MSUD), Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCADD), Long-Chain 3- Hydroxyacyl-CoA Dehydrogenase Deficiency (LCHADD), and Galactosemia [11,13].

3.3 Provision of Alternative Metabolic Pathways and Energy Sources

For IEMs with blocked or malfunctioning pathways, providing certain nutrients can support other ways for the body to make energy and prevent the build-up of metabolites [66].

- Medium-Chain Triglycerides (MCTs): For those with LC-FAODs, using MCTs for energy is more effective since it avoids the carnitine shuttle and is oxidized in the mitochondria [35]. They are frequently found in custom recipes and dishes.
- Triheptanoin (C7 Oil): A recent development in LC-FAOD treatment, triheptanoin is a type of odd-chain triglyceride that helps the body regain propionyl-CoA and acetyl- CoA, thus making energy production more stable [35].

- Uncooked Corn-starch: In this type of GSD, the slow-release carbohydrate help prevent low blood sugar, especially at night. It delivers a consistent level of glucose without causing a quick increase in insulin [6].
- Ketogenic Diet: If pyruvate dehydrogenase complex deficiency (PDCD) is present, glucose cannot be used, so ketones supply the energy for the body instead [67].

Precautions: Switching to new fuels should always be monitored properly. MCTs may lead to gastrointestinal side effects or too much fat, and ketogenic diets should always be kept under check for acidosis, possible growth problems, and dietary deficiencies.

3.4 Managing the Body During Times of Catabolism and Sickness

When people with IEMs experience anything stressful such as fever, infections, injury, fasting, or surgery, it can bring on an unsafe metabolic state [68]. They cause more energy to be used, and they mobilize internal substances, worsening the metabolic issue.

- Emergency Protocols: Having a personal "sick-day" plan is helpful for patients to manage their disease better. IV dextrose (10–12% solution) is given to prevent lipolysis and proteolysis from happening. Electrolyte correction, acidosis management with bicarbonate, a close check must be kept on the levels of blood glucose, ammonia, and lactate [50].
- Temporary Diet Relaxation: While sick, patients may eat more, but this change is only meant to help remove extra acid from their system and is stopped as soon as they improve [69].
- Prophylactic Measures: In individuals with IEMs who also suffer from asthma, additional prophylactic measures are needed to prevent respiratory stress, as this could exacerbate metabolic imbalance. This includes avoiding asthma triggers, staying hydrated, and ensuring vaccinations are up to date [50].
- Patient Empowerment: It is important for families to be taught how to recognize early problems (e.g., tiredness, throwing up, rapid breathing), use emergency sources of nutrients, and how to care for their loved ones.

3.5 Role of Specialized Medical Foods and Monitoring

They are customized products that provide the nutrients needed by people with IEMs [70]. They are usually the main source of food that prevents health problems.

- *Low-Protein Products*: For people with PKU and MSUD, breads, pasta, rice, and reduced-protein baking mixes must be included in their diet.

- *Medical Formulas* : These personal recipes omit harmful amino acids or fats and supply your patient with necessary vitamins, minerals, and essential nutrients.
- *Regulatory and Access Issues*: Most of these products are expensive, are accessed with prescriptions, and often cannot be paid for by insurance [71]. Lack of medical foods in low-resource places hurts the ability to treat certain health issues.
- *Patient Adherence*: How palatable, easily available, socially accepted, and well- received food is, plays a role in maintaining nutrition for the long term. Adolescents are more likely than adults to not stick to required treatments, causing their metabolism to become unbalanced.
- *Multidisciplinary Team*: Nutritionists, metabolic professionals, paediatricians, nurses, social workers, and psychologists all contribute to successful care [71].
- *Regular Monitoring*: Nutritional management is not static and involves a range of different measures.

It is important to differentiate between well-established dietary strategies, such as low- phenylalanine diets in PKU or lactose-free diets in galactosemia, which are supported by decades of clinical evidence [9, 53], and experimental strategies like gene therapy, genetically engineered probiotics, or triheptanoin supplementation, which are promising but remain in early clinical trials [109, 111]. Such critical review of these therapies suggests that we are in need of additional randomized controlled trials as well as longitudinal follow studies of these therapies to establish their safety, expense-efficiency and long term outcomes.

3.6 Psychosocial and Ethical Considerations

It is important to remember that lifelong dietary therapy affects much more than how medical care is delivered. Families run into emotional, budgeting, and time-related difficulties in following a healthy diet.

1. Social and Psychological Impact: People may miss out on social gatherings, lose class time, and have to avoid participating in family meals because of their diets [73]. Kids can feel separated, and parents may worry about their health, such as any diet issues or emergency situations.

2. Transition of Care: It is important to plan and teach patients well as they move from paediatric to adult medical care to ensure they continue following their treatment.

3. Cultural and Religious Dietary Considerations: The preferences for food in a culture must be considered and included in any diet planning [74]. In regions with limited dietary diversity, modifying traditional meals can be challenging. Informed Consent and Autonomy: For adolescent and adult patients, shared decision-making is crucial in respecting autonomy and promoting adherence.

Case Studies of Nutritional Management In Specific IEMs

IEMs refer to a range of genetic illnesses that disrupt the normal breakdown of large molecules in the body [75]. The biochemical reasons behind these disorders are well understood, but managing the disorders, especially through nutrition, depends a lot on what the metabolic condition is, when it is diagnosed, and the patient's particular situation. It provides real-life examples of dietary plans used in clinical treatment, grouped according to the main affected macro-nutrient.

Often, these types of disorders become apparent in early infancy by causing symptoms such as vomiting, low blood sugar, an enlarged liver, and excessive lactic acid in the body. Classic Galactosemia was identified in a new-born on the fourth day because of the usual set of symptoms [42]. As soon as the diagnosis was made through screening, treatment started by having the infant replace breast milk with a lactose- and galactose-free, typically soy-based formula. Dairy products were completely avoided by the child, and their calcium and vitamin D were carefully watched. Since the acute metabolic problems were handled, it was later discovered that the diet could not prevent problems with brain development.

Glycogen Storage Disease Type I (GSD I) is another useful example, as it occurs due to a lack of glucose-6-phosphatase [72]. The case study presented the history of a six-month-old patient diagnosed as GSD Type I presenting with a case of lactic acidosis and hepatomegaly. Nutritional therapy entailed regular feeding, intake of uncooked corn starch, and micronutrient supplementation. The counseling referenced was provided to the patient's caregivers and involved detailed dietary planning, emergency protocols, and adherence strategies [75]. With regular feeding and keeping blood sugar levels stable by means of medication, GSD I was prevented from causing sudden metabolic problems and allowed for normal growth in the patient [74-75].

For some conditions such as PKU and MSUD, it is very important to control the diet precisely. When PKU is detected in new-born screening, treatment with a phenylalanine-limited diet started around the second week [75]. A baby in PKU was treated using phenylalanine-free diet and a measure of natural protein whose amount was calculated individually and depending on

the tolerance limit. To maintain metabolic control, the state of the plasma phenylalanine was monitored weekly up until the age of birth. Dietary management was initially successful, but dietary problems often arose during school-going years with symptoms of food fatigue and peer pressure. By performing specific behavioral counseling and organized community support, the compliance increased. At the age of ten, the patient had shown normal intellectual

and physical development, and this showed that PKU should be managed early and frequently by a proper diet [2,3,13].

Maple Syrup Urine Disease (MSUD), as compared to other metabolic diseases, in general, has a rapidly progressive course and tends to rapidly worsen [55]. An example of a recorded case was that of a two week old baby with classic MSUD showing symptoms of lethargy, poor feeding, seizures and the odor of maple syrup in the urine. To decrease catabolism, acute treatment involved using glucose and insulin intravenously, and dialysis in certain cases was used to enable a quick elimination of the build-up of the branched-chain amino acids (BCAAs). Nutritional Long-term treatment included infusion of a medical formula free of BCAA as well as close titration of natural sources of protein in a bid to prevent leucine, isoleucine, and valine overload, but to achieve essential growth [54]. Detailed dietary education and emergency procedures were offered to family members and caregivers to have proper control of the disease at home and in the community.

Neurological damage can be avoided, and normal development can be ensured in MSUD patients through proper and early control of their metabolism. Family members and care givers were informed to look out early symptoms of catabolic stress and how they could address diet needs during illness [55]. To prevent metabolic crises in Medium-chain Acyl-CoA Dehydrogenase Deficiency (MCADD), patients must avoid prolonged fasting and maintain regular carbohydrate intake. In one case, a two-year-old with MCADD developed hypoglycemia and seizures following a 20-hour fasting period during a viral illness. After diagnosis, the child was placed on a diet consisting of frequent, carbohydrate-rich meals and snacks. Caregivers were instructed to use glucose-based rehydration solutions during illness and to seek emergency care when necessary. Over the following four years, the patient experienced no metabolic decompensation, underscoring the critical role of dietary management. While MCADD primarily requires avoidance of fasting, Long-chain 3- Hydroxyacyl-CoA Dehydrogenase Deficiency (LCHADD) involves additional restrictions on long-chain fatty acid intake and often requires MCT supplementation. [35].

The problems of nutrition in long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency (LCHADD) are considerable because of poor oxidation of long-chain fatty acids [8]. One of the cases presented an infant of five months presenting with cardiomyopathy and hepatomegaly. The management of the diet included the limitation of the long-chain triglycerides to below 10 percent of total energy as intake, and the medium-chain triglycerides (MCTs) were given as an alternative source of energy since they do not affect the impaired enzyme pathway. The essence of the supplementation of docosahexaenoic acid (DHA) and other essential fatty acids was to facilitate the best neurological and visual development. It was essential to check catabolic-stress and keep the metabolism stable via continuous feeding, including overnight. Following careful monitoring, the heart function recovered by age two, but hypotonia was still present afterwards. It shows that LCHADD patients must manage both their fat consumption and their proper nourishment [59]

There are a number of important themes that emerge from all of the cases mentioned. Preventing severe illness and promoting the best outcomes greatly depends on catching the disease in its early stages. A nutrition plan should be adjusted to suit a patient's specific metabolic disorder and what food he or she can handle [61]. Keeping up with biochemical tests helps doctors catch and handle changes that might lead to metabolic decompensation. A well-rounded approach to education for the family including, eating habits, emergencies, and support for mental and emotional needs help patients stay on treatment in the long run. When people grow, what they need to eat changes along with their body's demands and daily habits, so their diet requires regular review and the help of specialists.

It is clear from these case studies that when nutritional therapy is used in IEMs, it promotes active changes that turn life-threatening conditions into diseases that people can live with. As more studies are conducted and advanced metabolic monitoring becomes available, specialized diet plans will continue to develop and help those with these uncommon, and important health problems.

CONCLUSION AND FUTURE PERSPECTIVES

The Inborn Errors of Metabolism (IEMs) that deal with biochemistry of macronutrient metabolism underscores the pivotal intersection between genetics, biochemistry and nutrition. Even though each of these disorders is infrequent, their overall burden, with a focus on children, is quite significant. To a large extent, nutritional management has become a primary pillar of treatment, and it has the potential to lead to a significant enhancement of health outcomes provided such an approach is started early and properly conducted.

In general, as has been reviewed, IEMs, which disrupt the metabolism of carbohydrates, proteins, and/or lipids have the potential to cause metabolic imbalances that are life- threatening. Nevertheless, in patients receiving individualized diet interventions (e.g. substrate restriction or supplementation with alternate sources of energy), most patients are able to attain metabolic stability, normal growth, and attainment of developmental milestones. The examples of dietary treatment in such conditions as Phenylketonuria (PKU), Glycogen Storage Diseases (GSD), and Medium-Chain Acyl-CoA Dehydrogenase Deficiency (MCADD) help to visualize the revolutionary role of nutrition in how treatment and support are provided to patients.

The nutritional management of IEMs associated with macronutrients is coming out of basic substrate avoidance. It is turning to precision guided, data-intensive and patient centered. This transformation is facilitated by the benefits of genomics, increased newborn screening, and online health websites that encourages food compliance. As an illustration, patients diagnosed with PKU or Maple Syrup Urine Disease (MSUD) can now use their mobile phones to check their intake of amino acids in real time, by means of dietary tracking applications, improving diet adherence. On the same note, combining metabolomics is facilitating earlier identification of poor diet and looming metabolic crises prior to the onset of clinical symptoms.

Although there are improvements in nutritional therapy and implementation of digital health tools, significant evidence gaps do exist. Few randomized controlled trials have evaluated long-term outcomes of novel interventions such as gene therapy, engineered probiotics, or triheptanoin supplementation [109, 111]. Policy implications include strengthening regulatory frameworks for medical foods, ensuring affordability and equitable distribution, particularly in low- and middle-income countries [11, 67]. Dietitians play a central role not only in individualized diet planning but also in guiding transitions from pediatric to adult care and in integrating cultural dietary preferences into medical nutrition [7]. Future strategies must also address the psychosocial burden of lifelong dietary therapy through structured counseling and community-based support [73].

Future Directions

In the future, more of the management of IEMs is likely to be optimized using genomics, telemedicine, wearable devices, and digital health tools, all of which are being integrated. The use of mobile applications and a remote watch can enhance patient adherence, diet accuracy,

and consumption in the long run. Furthermore, enhancements of newborn screening activities worldwide will be required to have an early intervention and an early diagnosis, particularly in disadvantaged countries. New treatment methods like enzyme replacement therapies, and gene editing are new trends in research. Although this is promising, it is necessary to underline that a majority of these therapeutic possibilities remain experimental, or at an early clinical level in regard to many IEMs and are not yet widely available in a normal clinical setting

Strategic Considerations

These developments notwithstanding, there are several challenges that still exist. The ability to access specialized medical foods, the economic requirements of undertaking constant metabolic surveillance as well as the psychosocial consequences of life-long dietary restriction, specifically in the adolescent phase are issues that must be prepared through integrated policy, health care system, and family-based interventions. A large number of long-term outcome studies have also been largely biochemical with little consideration on psychosocial health, cognitive growth, or adulthood quality of life.

Future research must prioritize the integration of nutritional genomics, behavioral science, and psychosocial support to develop more holistic and adaptable dietary strategies that address patients' needs across their lifespan. Nutritional therapy for IEMs should be envisioned as a dynamic intervention that evolves with patients' developmental, emotional, and physiological changes.

Conclusively, nutritional treatment comprises the primary modality in treating most of the macronutrient-related IEMs. Further development will be based on the integration of scientific innovation and fair access to care and patient-

focused solutions. By implementing worldwide cooperation and multidisciplinary initiatives, people living with such rare inherited syndromes can anticipate better clinical outcomes and the quality of life.

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