ISSN: 2754-4745

Journal of Physical Medicine Rehabilitation Studies & Reports

SCIENTIFIC Research and Community

Review Article

Open Access

Nutritional and Dietary Management of Inborn Errors of Metabolism: A Review

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ABSTRACT

Inborn errors of metabolism (IEMs) are a heterogeneous category of inherited genetic illnesses caused by mutations leading to the lack or complete absence of enzymes, transport proteins or critical cofactors involved in metabolic pathways. These defects disturb normal biochemical pathways and cause the accumulation of toxic metabolites and/or the deficiency of essential metabolic products. Metabolic disorders, if left untreated, can result in severe morbidity, irreversible organ damage, neurodevelopmental disability, and premature mortality. Nutritional and dietary therapy is the cornerstone of management in many IEMs especially the disorders of amino acid metabolism, organic acidemias, fatty acid oxidation disorders and carbohydrate metabolism disorders. Early discovery through increased newborn screening programs and rapid, individualised dietary management afterward have drastically improved survival, neurocognitive outcomes and general quality of life in affected individuals. Dietary management depends on the specific metabolic defect and generally consists of restriction of substrates which cannot be metabolised appropriately, provision of alternative sources of nutrients and energy, supplementation of deficient metabolites or cofactors and prevention of catabolic states by adequate caloric intake and appropriate feeding strategies. Ongoing nutritional surveillance and periodic metabolic assessment by a multidisciplinary team of health care professionals including metabolic physicians, dietitians, nurses, geneticists and laboratory specialists are essential for optimising growth, neurologic development, metabolic stability and long-term health outcomes. Recent advances in metabolic medicine such as precision nutrition, specialised medical foods, enteral nutritional support, enzyme replacement therapy, and gene-based therapeutic approaches have further improved the efficacy of nutritional management and expanded treatment options for several IEMs. Here we discuss basic concepts, existing tactics, emerging breakthroughs, problems and future views of nutritional and dietary therapy in patients with inborn errors of metabolism.

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Received: July 22, 2026; **Accepted:** July 28, 2026; **Published:** July 30, 2026

Keywords: Inborn Errors of Metabolism, Diet Therapy, Medical Nutrition Therapy, Metabolic Diseases, Phenylketonuria, Newborn Screening

Introduction

Inborn errors of metabolism (IEMs) are a wide heterogeneous set of inherited genetic diseases caused by pathogenic mutations in genes encoding enzymes, transport proteins, receptors, or cofactors involved in intermediary metabolic processes. These molecular defects result in abnormal biochemical processes that lead to the accumulation of toxic metabolic intermediates or the deficiency of essential metabolic products required for normal cellular function. Since the pioneering work of Sir Archibald Garrod in the early twentieth century who introduced the concept of 'inborn errors of metabolism' through his studies on alkaptonuria and later phenylketonuria (PKU) remarkable advances have been achieved in understanding the molecular basis, diagnosis and treatment of these disorders. Currently identified IEMs exceed 1,500 distinct entities and new disorders are being discovered with progress in molecular genetics, whole-exome sequencing, and metabolomics [1].

While each individual IEM is an uncommon condition, collectively they are a major problem. The estimated frequency worldwide is between 1 in 800 and 1 in 2,500 live births, depending on geographical region, ethnicity and availability of newborn screening programs Consanguinity is common in many populations and the prevalence is much higher because many IEMs are inherited in an autosomal recessive pattern [2]. IEMs are therefore an important public health problem, especially in developing countries where newborn screening services, molecular diagnostic facilities and specialised metabolic care are still scarce. Delayed diagnosis sometimes leads to irreparable neurological damage, severe disability or death in infancy and early childhood.

The clinical manifestations of IEMs are highly variable and depend on the affected metabolic pathway, residual enzyme activity, age of onset and environmental factors such as diet and infection. Some disorders present in the neonatal period with acute metabolic decompensation with poor feeding, vomiting, lethargy, seizures, metabolic acidosis, hyperammonemia, hypoglycemia, or coma. Others may present later in childhood or adulthood with developmental delay, intellectual incapacity, mobility abnormalities, repeated metabolic crises, cardiomyopathy, liver dysfunction, renal impairment, muscle weakness, visual changes or psychiatric symptoms Timely detection and management of these is critical as many of these illnesses advance swiftly to lifelong brain impairments or early fatality [3].

IEMs are often caused by one of three pathophysiologic causes or a combination: accumulation of hazardous substrates proximal to the metabolic block, insufficiency of important downstream products, or deficient energy production. For example, in phenylketonuria, a lack of phenylalanine hydroxylase causes an excessive buildup of phenylalanine. This is neurotoxic and interferes with proper brain development. In maple syrup urine disease (MSUD) too, branched-chain amino acids are incorrectly metabolised, leading to accumulation of leucine and related ketoacids which, if untreated, result in cerebral oedema and severe neurological impairment. Organic acidemias lead to the accumulation of toxic organic acids which impair mitochondrial function. Fatty acid oxidation disorders affect the ability to produce energy during fasting, making affected individuals prone to hypoglycemia and sudden metabolic crises [4].

Understanding of these biochemical mechanisms is the basis for rational nutritional intervention.

Among the available therapeutic approaches for IEMs, the nutritional and dietary therapy is the cornerstone of treatment for most of the disorders. Dietary substrate intake directly affects metabolic disorders and well-designed nutritional interventions can minimise the formation of hazardous metabolites and provide appropriate nutrients for growth, development and optimal physiological function. Medical nutrition therapy changes the intake of certain nutrients implicated in the faulty biochemical pathway, rather than treating the symptoms as pharmaceutical interventions do [5].

The major objectives of dietary management are to preserve metabolic homeostasis, prevent acute metabolic crises, foster normal physical growth and neurocognitive development, correct nutritional deficiencies, minimise long-term complications and enhance the overall quality of life. The dietary prescriptions are individualised for each patient based on his/her age, body weight, metabolic diagnosis, biochemical profile, clinical state and residual enzyme activity. Many IEMs require therapy for life therefore nutritional care carries on through childhood, youth, adulthood, pregnancy and old age. Therefore, long-term adherence is important but often challenging due to dietary restrictions, psychosocial factors, treatment burden and financial constraints [6].

One of the major successes in the control of IEMs has been the introduction of newborn screening (NBS) programs. Expanded neonatal screening using tandem mass spectrometry has transformed early diagnosis, enabling detection of various metabolic abnormalities prior to clinical manifestations. Early detection allows for early beginning of nutritional therapy in the presymptomatic phase, averting permanent neurological damage and greatly boosting survival rates. Disorders including as phenylketonuria, medium-chain acyl-CoA dehydrogenase deficiency (MCADD), maple syrup urine disease and various organic acidemias have been shown to have good outcomes when the nutritional treatment is started soon after birth [7]. However, comprehensive newborn screening is patchy in many low- and middle-income countries, resulting in disparities in patient outcomes [8].

The provision of medical nutrition therapy for IEMs is highly specialised and needs interdisciplinary collaboration among healthcare experts including metabolic physicians, clinical dietitians, nurses, genetic counsellors, psychologists, chemists, and laboratory scientists. The role of clinical dietitians is especially pivotal in the calculation of personalised nutrient needs, provision of specialised diets, biochemical marker monitoring, patient and carer education, and modification of nutritional prescriptions based on age, growth, illness, pregnancy and metabolic control [9]. Regular biochemical monitoring (plasma amino acids, organic acids, acylcarnitines, ammonia, glucose, micronutrient levels and growth parameters) is necessary to assess the efficacy of treatment and to prevent nutritional deficiencies [10].

Remarkable breakthroughs have significantly boosted nutritional management of IEMs in recent years. Enhanced palatability of improved medical foods, low protein modified foods, amino acid supplements, enteral feeding strategies, computerised dietary analysis, mobile health applications, telemedicine and continuous glucose monitoring and precision nutrition approaches have led to significant improvements in treatment adherence and metabolic outcomes. Besides, new therapeutic strategies including enzyme replacement therapy, substrate reduction therapy, liver transplantation, mRNA technology, genome editing and gene therapy are increasing the treatment options for certain diseases. Even if new medicines are available, nutritional therapy is an integral part of the overall metabolic care, because food impacts directly on metabolic stability [11].

Dietetic and Nutritional Management of Inborn Errors of Metabolism

Medical nutrition therapy is the cornerstone of treatment for most inborn errors of metabolism, providing specific dietary interventions based on the specific metabolic defect. The main goal is to supply sufficient quantities of energy, protein, essential fatty acids, vitamins, minerals and trace elements without allowing toxic metabolites to accumulate. The main nutritional strategies are: substrate restriction, substitution of deficient metabolic products, supplementation with vitamins or cofactors, prevention of catabolic states, achievement of optimal energy balance and continuous nutritional monitoring through life [12].

Protein restriction is the main therapy approach for amino acid abnormalities, including phenylketonuria (PKU), maple syrup urine disease (MSUD), homocystinuria, and tyrosinemia. In PKU, phenylalanine intake from the food is strictly controlled and phenylalanine-free amino acid formulas supply appropriate protein for optimal growth and development. The blood phenylalanine content is regularly monitored and the diet adjusted to maintain therapeutic objectives and avoid irreparable brain damage. Likewise, MSUD patients require a lifetime, stringent restriction of branched-chain amino acids, notably leucine, with the use of special medical formulations and proper consumption of other critical nutrients. In the course of illness, increased carbohydrate and fat intake is recommended to suppress protein catabolism and to reduce endogenous production of toxic metabolites [13].

A careful regulation of protein intake is also needed in organic acidemias, such as propionic acidemia and methylmalonic acidemia, to decrease the synthesis of harmful organic acids. Carnitine supplementation is frequently employed to facilitate the elimination of harmful metabolites and to enhance mitochondrial energy metabolism. In metabolic stress or infection more calories in carbohydrates are needed to reduce endogenous protein breakdown and to avoid metabolic decompensation [14].

Management of dietary carbohydrate is particularly critical in diseases of carbohydrate metabolism. The treatment of classic galactosemia is the lifetime avoidance of lactose- and galactose-containing foods to prevent liver dysfunction, cataracts and neurological sequelae. Similarly, people with inherited fructose

intolerance must avoid fructose, sucrose and sorbitol to avoid severe liver injury, hypoglycemia and renal impairment. These sugars are commonly found in processed foods and medicines and thus require careful nutritional counselling.

Metabolic diseases of fatty acid oxidation demand a distinct nutritional approach to avoid extended fasting and to maintain a continuous supply of energy [15]. Patients with medium chain acyl-CoA dehydrogenase deficiency (MCADD) require frequent carbohydrate-rich meals and emergency glucose supplementation during illness to prevent hypoglycemia and unexpected metabolic crises. Medium-chain triglyceride (MCT) supplementation is an alternate energy source in some long-chain fatty acid oxidation problems, bypassing impaired long-chain fatty acid metabolism [16].

Some IEMs respond to vitamin or cofactor supplementation showing the importance of precision nutrition. Homocystinuria responsive to pyridoxine is effectively treated with high doses of pyridoxine and biotinidase deficiency has its clinical symptoms reversed by biotin supplementation [17]. Similarly, hydroxocobalamin (vitamin B12) therapy is helpful in vitamin B12-responsive methylmalonic acidemia and tetrahydrobiopterin supplementation improves metabolic control in certain patients with phenylketonuria. These tailored nutritional interventions demonstrate how individualised dietary management can lead to dramatically improved clinical outcomes [18].

Long-term nutritional follow-up is still necessary throughout life. Regular assessment of anthropometric measurements; growth velocity; body composition; biochemical monitoring; dietary adherence; micronutrient status; and neurodevelopmental assessment. Dietary prescriptions should be adjusted from time to time to allow for growth, physical activity, pregnancy, ageing and intercurrent illnesses. Women with PKU require very strict metabolic control before conception and throughout pregnancy to prevent maternal PKU syndrome which is associated with congenital heart defects, microcephaly, developmental delay and foetal growth restriction [19].

Recent advances have revolutionised the nutritional care of IEMs. Better taste and nutritional composition of medical foods, low-protein modified foods, enteral nutrition, digital applications for dietary tracking, telemedicine, continuous glucose monitoring for selected disorders, and precision nutrition based on genomic profiling have all improved treatment adherence and long-term metabolic control. Nutritional therapy remains the cornerstone of lifelong management as it directly addresses the biochemical consequences of the underlying metabolic defect and continues to play an essential role in optimizing patient outcomes [20]. New promises of emerging therapies such as enzyme replacement therapy, liver transplantation and gene therapy offer new hope for selected metabolic disorders [21].

Conclusion

Nutritional and dietary management continues to be the mainstay of treatment for most inborn errors of metabolism (IEMs). Advances in neonatal screening, early diagnosis, personalised medical nutrition therapy, and ongoing metabolic monitoring have altered the prognosis of many diseases, with significant improvements in patient survival, growth, neurocognitive development, and overall quality of life. Dietary interventions tailored to the individual, including substrate restriction, specialised medical foods, cofactor supplementation and strategies to prevent catabolic states, can maintain metabolic stability and reduce the risk of acute metabolic crises and long-term complications.

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