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NUTRITION IN RARE CARDIOMYOPATHIES: FROM SUPPORTIVE CARE TO TARGETED THERAPY

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ABSTRACT – Rare cardiomyopathies (CMPs) may result from infiltrative disorders, such as amyloidosis, as well as from inherited metabolic diseases, where pathophysiological mechanisms vary depending on the specific defect, including impaired energy production, accumulation of toxic metabolites, or substrate storage. Across this spectrum, nutritional factors play a dual and often underappreciated role: they may drive disease mechanisms or modulate prognosis through malnutrition, sarcopenia or cachexia. In several inborn errors of metabolism, such as glycogen storage diseases and organic acidemias, a targeted diet constitutes etiological therapy, preventing life-threatening metabolic crises and stabilizing cardiac function. In others, including systemic amyloidosis and Fabry disease, nutritional disturbances, such as malabsorption, sarcopenia and cachexia, exacerbate organ involvement and worsen survival despite disease-specific treatments. Importantly, treatable nutritional deficiencies may themselves present with CMPs: primary carnitine deficiency can cause dilated cardiomyopathy reversible with supplementation, while riboflavin has shown therapeutic benefit in ACAD9-related mitochondrial cardiomyopathy.

The interaction between nutrition and cardiomyopathy is complex and bidirectional: metabolic blocks, gastrointestinal involvement, and chronic inflammation precipitate malnutrition, while nutritional deterioration independently predicts worse outcomes. Conventional tools, such as body mass index (BMI) and serum albumin, are often inadequate; refined techniques, including bioelectrical impedance analysis, dual-energy X-ray absorptiometry and functional tests, provide a more accurate assessment.

Evidence indicates that malnutrition, cachexia, and sarcopenia are strong prognostic factors, while targeted interventions ranging from cornstarch protocols in glycogen storage disorders to cofactor supplementation in mitochondrial and metabolic CMPs can stabilize patients and improve quality of life.

This review synthesizes disease-specific paradigms, highlights cross-cutting mechanisms, and outlines principles of personalized intervention, with emphasis on the role of multidisciplinary teams. Nutrition should no longer be regarded as supportive care, but as a therapeutic axis central to rare cardiomyopathy management, with direct implications for survival, function, and patient-centered outcomes.

Keywords: Rare diseases, Nutrition, Amyloidosis, Fabry disease, Cardiomyopathies.

Abbreviations: ACAD9: acyl-CoA dehydrogenase 9; B12: vitamin B12 (cobalamin); BIA: bioelectrical impedance analysis; CMPs: cardiomyopathies; GSD: glycogen storage disease.

INTRODUCTION

Rare cardiomyopathies (CMPs) represent a heterogeneous group of myocardial disorders, defined by their low prevalence but associated with substantial morbidity and mortality[1]. Although individually uncommon, they collectively account for a significant proportion of heart failure and sudden death in both children and adults. Most have a genetic or metabolic basis, often manifesting in childhood, though many are increasingly recognized later in life[2]. Regardless of their diversity, rare CMPs frequently share a common feature: a high burden of progressive disability, multisystem involvement, and reduced survival[3,4].

The management of rare CMPs has traditionally focused on genetic counselling, disease-specific pharmacological treatments, advanced heart failure therapies, and organ transplantation. Nutrition, by contrast, has long been considered supportive or marginal. This underestimation contrasts with growing evidence that nutritional status is a key determinant of prognosis, quality of life, and treatment adherence[5]. In some CMPs, dietary intervention is the cornerstone of therapy, as in glycogen storage diseases or organic acidemias[6,7]. In others, such as amyloidosis or Fabry disease, nutrition does not modify the underlying pathology but decisively influences symptoms, functional capacity, and survival[8].

Although these conditions differ markedly in pathophysiology, the examples discussed in this review reflect broader mechanistic categories in which nutritional factors influence cardiac involvement. Other inherited metabolic diseases, such as Pompe disease or fatty-acid oxidation defects, may also present with CMP through energy failure or substrate accumulation, even though nutritional therapy is not central to their management. Nutrition, therefore, emerges as a transversal dimension of care in rare CMPs, shaping both clinical presentation and outcomes. Figure 1 summarizes the overarching framework linking metabolic derangements, systemic involvement, and nutritional status. The following sections address the challenges of nutritional assessment in these patients, the prognostic implications of nutritional decline, and the principles of targeted dietary and metabolic intervention.

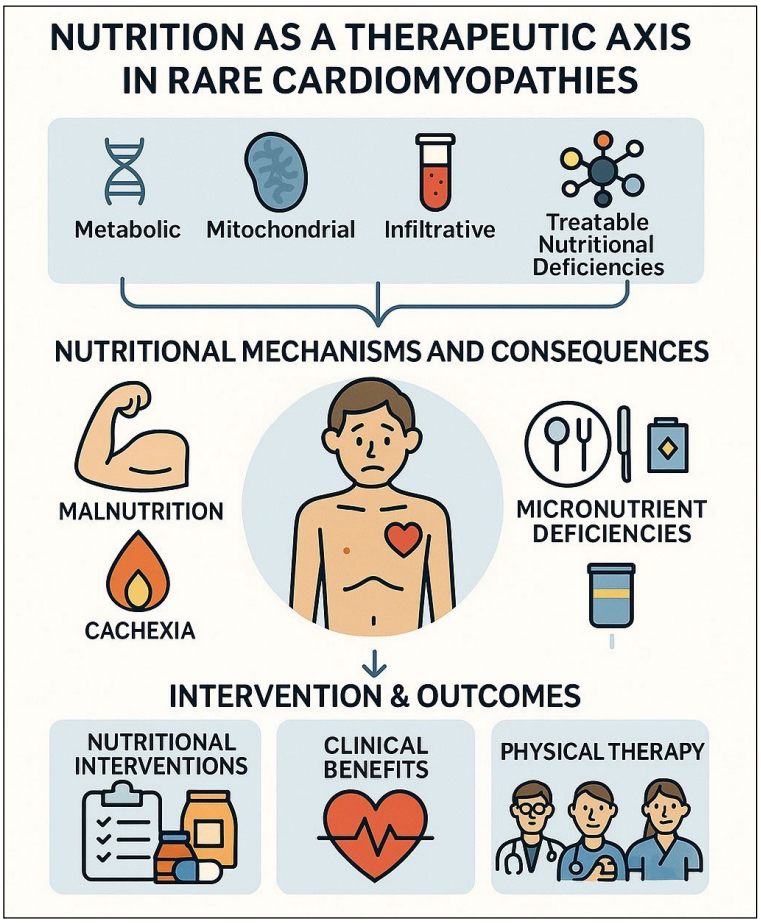

Figure 1. Conceptual framework of nutrition as a therapeutic axis in rare cardiomyopathies.
Nutrition contributes to the pathogenesis and management of rare cardiomyopathies through multiple pathways. Disease groups include metabolic, mitochondrial, infiltrative disorders, and treatable nutritional deficiencies. Nutritional mechanisms and consequences encompass malnutrition, cachexia, and micronutrient deficiencies. Interventions range from nutritional strategies and supplementation to physical therapy, with potential clinical benefits across the disease spectrum.

Methods

This article is a narrative review summarizing current evidence on nutritional mechanisms and interventions in rare CMPs. A targeted literature search was conducted in PubMed, Scopus, and Google Scholar up to September 2025, focusing on clinical studies, guidelines, position papers, case series, and mechanistic reviews relevant to nutritional assessment and management in rare cardiomyopathies and inborn errors of metabolism. Additional references were identified through citation tracking of key publications.

Studies were selected based on clinical relevance, contribution to understanding the nutritional–cardiac interface, and consistency with current metabolic and cardiology classifications. Evidence was synthesized qualitatively and organized to highlight mechanistic categories, shared nutritional features, and disease-specific paradigms.

This review is based exclusively on previously published literature and did not involve human subjects, patient data, or institutional review board approval.

NUTRITIONAL CHALLENGES IN RARE DISEASES

The nutritional consequences of rare CMPs arise from a complex interplay of mechanisms: defective metabolic pathways, chronic inflammation, gastrointestinal dysfunction, endocrine alterations, and reduced physical activity due to skeletal muscle involvement[9]. These processes often coexist, producing unique nutritional phenotypes that directly influence cardiac performance and prognosis.

In systemic amyloidosis, amyloid deposition in the gastrointestinal tract and autonomic nervous system leads to dysmotility, malabsorption and anorexia[10]. The result is a pattern of protein–energy malnutrition and cachexia that is partly nutritional and partly inflammatory[11]. In Fabry disease, abdominal pain and diarrhea restrict food intake, contributing to weight loss and selective deficiencies[12]. In mitochondrial disorders, impaired oxidative phosphorylation translates into a chronic energy deficit with fatigue, early satiety, and catabolism despite adequate intake[12,13], while the myocardium is directly affected, leading to dilated or hypertrophic CMP. Glycogen storage diseases illustrate the dual impact of nutrition on the heart: strict dietary regimens prevent hypoglycemia, but non-adherence can accelerate cardiomyopathy progression[14]. Importantly, treatable deficiencies such as primary systemic carnitine deficiency can cause dilated CMP reversible with supplementation[15], while ACAD9-related cardiomyopathy may respond to riboflavin therapy[16].

A common theme emerges: nutritional disturbances are not secondary or trivial but integral components of the CMP phenotype, shaping prognosis and interacting with therapies. Nutritional needs evolve over time, often changing dramatically during disease progression, initiation of new treatments, or the transition from pediatric to adult care (Supplementary Table 1)[16].

The Problem of Assessment

Assessing nutritional status in rare CMPs is deceptively complex. Traditional tools such as body mass index or serum albumin often fail to capture the true picture[8]. For example, a patient with amyloidosis and edema may appear “normal weight” on BMI yet be profoundly malnourished. Similarly, albumin levels fall not only with malnutrition but also with inflammation[17].

More refined tools, such as bioelectrical impedance analysis (BIA), dual-energy X-ray absorptiometry, and CT/MRI-based muscle assessment, offer deeper insights into body composition and prognosis[18]. Functional measures such as hand grip strength or timed walking tests provide meaningful prognostic data[19]. Laboratory markers can reveal deficits in vitamin D, B12, folate, zinc, and thiamine, or identify disease-specific abnormalities such as elevated ammonia in organic acidemias[20].

Even so, no single tool is universally reliable in rare CMPs. Cut-off values validated in oncology or geriatrics may not apply to a young adult with mitochondrial cardiomyopathy. What matters most is longitudinal monitoring: progressive weight loss, declining grip strength, or a drop in bioelectrical impedance analysis (BIA) phase angle frequently anticipate clinical deterioration (Supplementary Table 2)[18].

Nutritional Status as a Prognostic Determinant

Evidence increasingly shows that nutritional deterioration is a driver of prognosis, not a bystander, in rare CMPs. Protein–energy malnutrition independently predicts higher mortality and hospitalization in chronic rare diseases[21]. Cachexia, with inflammation-driven catabolism, is an adverse prognostic factor in amyloidosis, reducing survival even when cardiac or renal involvement is not advanced[17]. Sarcopenia predicts functional decline and mortality in Fabry disease, hereditary myopathies, and cardiac amyloidosis[22].

Obesity also carries risks. In glycogen storage disorders (GSDs), obesity may coexist with metabolic fragility, masking malnutrition ("sarcopenic obesity"). In GSD types I and III, two of the most common hepatic glycogen storage disorders, obesity and insulin resistance may also arise from overtreatment, particularly excessive cornstarch or carbohydrate administration intended to prevent hypoglycemia[23]. This phenotype predisposes to cardiovascular and metabolic complications, accelerating disability and worsening cardiac remodeling[24]. Micronutrient deficiencies add further risk. Vitamin D deficiency is linked to fractures and cardiovascular mortality, while B12 and folate deficits exacerbate neurological dysfunction[25,26]. In metabolic CMPs, uncorrected deficiencies of cofactors such as carnitine, riboflavin, or thiamine can precipitate rapid deterioration or trigger life-threatening crises[15,16].

Composite indices such as the Prognostic Nutritional Index, the Geriatric Nutritional Risk Index, and the CONUT score have shown prognostic utility in systemic and infiltrative CMPs[17]. These indices, though not designed for rare CMPs, reinforce the concept that nutrition is a measurable and modifiable determinant of survival (Supplementary Table 3).

Principles of Nutritional Intervention

Effective management requires a personalized, dynamic, and multidisciplinary approach. Three principles stand out:

Adequate support

Ensuring sufficient caloric and protein intake, tailored to disease stage and comorbidities, is fundamental. Oral nutritional supplements are preferred, with escalation to enteral or parenteral nutrition when needed. Micronutrient monitoring and supplementation (vitamin D, B12, folate, iron, zinc, thiamine) should be systematic[27].

Targeting mechanisms

Nutritional support must address underlying drivers. In cachexia, anti-inflammatory strategies can enhance efficacy. In metabolic CMPs, strict control of substrate load (e.g., protein restriction in propionic acidemia, a prototypical organic acidemia, and timed cornstarch regimens primarily in glycogen storage disease type I, with occasional use in type III) is essential. Supplementation with cofactors such as L-carnitine or riboflavin can support mitochondrial metabolism, while other compounds such as coenzyme Q10 and thiamine may stabilize function in selected subgroups[28].

Rehabilitation and empowerment

Adapted physical activity is crucial to counteract sarcopenia, restore function, and improve autonomy. Nutritional rehabilitation integrates diet, exercise, and psychological support. Education of patients and caregivers sustains adherence, particularly during the transition from pediatric to adult care, where discontinuity often leads to nutritional decline[29].

These principles illustrate how nutrition moves from a supportive measure to a therapeutic axis, influencing outcomes across rare disease populations.

Setting the Stage for Disease-Specific Paradigms

The general framework highlights a recurring theme: nutrition is central to rare CMP management. It shapes prognosis, modifies therapy, and determines quality of life. Its role becomes clearest in specific conditions where nutritional intervention exemplifies broader principles: in amyloidosis, cachexia reflects inflammatory catabolism; in Fabry disease, gastrointestinal dysfunction undermines intake; in glycogen storage disorders, diet is the therapy; in mitochondrial disease, cofactors and caloric modulation support energy balance; in propionic acidemia, protein restriction prevents metabolic crises; in primary systemic carnitine deficiency and ACAD9 deficiency, supplementation with L-carnitine or riboflavin can reverse or stabilize cardiomyopathy.

The next sections, therefore, examine these paradigms in detail, using them as models for understanding the role of nutrition across the rare CMP spectrum.

DISEASE-SPECIFIC PARADIGMS OF NUTRITION IN RARE DISEASES

Systemic Amyloidosis

Nutritional impairment in amyloidosis is frequent but often underestimated, especially early in the disease course (Table 1). Cardiac amyloidosis typically presents with a restrictive cardiomyopathy characterized by increased wall thickness, diastolic dysfunction, and progressive heart failure; however, the degree of cardiac involvement varies markedly across amyloidosis subtypes[30]. When present, this cardiac phenotype further worsens nutritional vulnerability because reduced cardiac output, venous congestion, gastrointestinal dysmotility, and autonomic dysfunction synergistically impair appetite, nutrient absorption, and metabolic reserve. In variant transthyretin amyloidosis (ATTRv), weight loss, diarrhea, and early satiety due to gastrointestinal dysautonomia may precede the diagnosis by years. Amyloid fibril deposition in the gastrointestinal tract and autonomic nervous system disrupts motility and absorption, leading to malnutrition and micronutrient deficiencies[31]. In wild-type *ATTR* (ATTRwt), prevalent in the elderly, cachexia is compounded by reduced appetite, systemic inflammation, and visceral congestion due to heart failure. AL amyloidosis is even more complex: beyond fibril deposition, circulating light chains and chemotherapy toxicity further impair liver, gut, and muscle metabolism[32].

The nutritional phenotype typically evolves from subtle weight loss to sarcopenia and cachexia, with edema often masking true lean mass loss. Malnutrition is an independent predictor of mortality, sometimes preceding biomarker deterioration[33]. When cardiac amyloidosis is present, progressive heart failure (HF) contributes substantially to morbidity, hospitalization burden and overall prognosis[34]. Early recognition of hypoalbuminemia, falling BIA phase angle, or reduced hand grip strength enables timely intervention[35].

Supportive protocols emphasize high-calorie, high-protein diets, texture adaptation for dysphagia, and early use of enteral nutrition when intake becomes insufficient. In refractory cases, parenteral nutrition stabilizes patients through critical periods. Adjunctive strategies, such as omega-3 fatty acids for catabolic modulation or midodrine for postprandial hypotension, may facilitate tolerance and improve intake. Integration of dietitians into amyloidosis centers is therefore crucial[36].

Fabry Disease

Fabry disease, a lysosomal storage disorder, exemplifies the interplay between gastrointestinal dysfunction and nutrition (Table 1). Abdominal pain, bloating, and diarrhea affect more than half of patients, often leading to avoidance of meals, reduced caloric intake, and selective micronutrient deficiencies. These alterations are further aggravated by renal impairment and chronic inflammation, resulting in weight loss and sarcopenia[8].

Although enzyme replacement therapy improves the systemic phenotype, nutritional disturbances frequently persist. Dietary management, therefore, requires a dual strategy:

- Symptom-oriented: low-FODMAP regimens to reduce diarrhea and bloating, texture adaptation for dysphagia.
- Supportive: adequate energy and protein intake aligned with enzyme replacement therapy, regular monitoring of lean mass, and supplementation of renal-sensitive nutrients (e.g., vitamin D, iron, folate).

Educational interventions such as Fabry's Kitchen and Rare Book projects (https://www.rare-bz.net/it/news/il-progetto-fabrys-kitchen-e-il-ricettario-rare-book) have provided patients with culturally tailored recipes and evidence-based dietary advice, improving adherence and quality of life.

Table 1. Nutritional aspects across groups of rare diseases.

Disease group	Nutritional mechanism	Typical manifestations (including cardiac)	Dietary intervention	Key challenges
Systemic protein-depositing CMPs (cardiac amyloidosis) and lysosomal storage disorders (Fabry disease – sphingolipidosis)	GI infiltration, autonomic dysfunction, chronic inflammation	Malabsorption, dysmotility, anorexia, sarcopenia; HF progression; HF hospitalization	High-protein, high-calorie diet, supplements, enteral/parenteral nutrition	Early detection, poor tolerance, variable response to ERT or chemotherapy
Energy metabolism disorders (GSD I/III, mitochondrial CMP, ACAD9 deficiency)	Defects in glycogenolysis, gluconeogenesis, or oxidative phosphorylation	Hypoglycemia, fatigue, lactic acidosis, skeletal myopathy; dilated/ hypertrophic CMP	Strict cornstarch/glucose regimens; cofactor supplementation (thiamine, riboflavin, CoQ10, carnitine)	Compliance, nocturnal regimens, risk of overfeeding or obesity; variable riboflavin response
Organic acidemias (propionic, methylmalonic)	Enzyme block in amino acid catabolism → toxic metabolite accumulation	Metabolic crises, growth delay, neurologic impairment; dilated CMP in severe forms	Controlled protein restriction, specific precursor-free formulas (restriction of Ile, Val, Thr, Met), emergency protocols; carnitine, B12 in responsive methylmalonic acidemia	Balancing restriction *vs.* growth needs, recurrent crises, and sarcopenia
Primary systemic carnitine deficiency	Defective carnitine transport → impaired fatty acid oxidation	Dilated CMP, hypoketotic hypoglycemia, skeletal myopathy	Oral L-carnitine supplementation	Early diagnosis is essential; rapid deterioration without treatment
Other metabolic/lysosomal disorders (Pompe – lysosomal glycogenosis, Wilson disease – copper metabolism disorder, others)	Myopathy, hepatosplenomegaly, cholestasis	Dysphagia, early satiety, vitamin deficiencies, sarcopenia; CMP reported in Wilson and late-onset Pompe	High-protein diets, vitamin supplementation, supportive nutrition	Multisystemic involvement, transplant phases, variable cardiac expression

ACAD9: acyl-CoA dehydrogenase 9; B12: vitamin B12 (cobalamin); CMPs: cardiomyopathies; CoQ10: coenzyme Q10; ERT: enzyme replacement therapy; GI: gastrointestinal; GSD: glycogen storage disease; HF: heart failure.

Glycogen Storage Diseases

Glycogen storage diseases (GSDs) are paradigmatic because nutrition is integral to their management (Table 1). Among classical hepatic GSDs, CMP is most consistently associated with glycogen storage disease type III (Cori/Forbes disease), particularly the IIIa subtype with skeletal muscle involvement, in which glycogen accumulation in the myocardium can lead to hypertrophic or dilated cardiomyopathy. By contrast, cardiac involvement is not typical in GSD type I, while PRKAG2-related cardiomyopathy and Danon disease represent distinct glycogen storage cardiomyopathies that are not primarily modified by dietary therapy.

In type I GSD, fasting hypoglycemia, due to defective glucose-6-phosphatase activity, requires frequent use of carbohydrates. Uncooked cornstarch is the cornerstone, administered every 3-4 hours, including during the night, and extended-release starch preparations reduce nocturnal dosing and improve sleep quality[37].

Pediatric regimens may require continuous gastric infusion, whereas in adulthood, strict adherence to timed starch intake remains essential. The macronutrient profile revolves around increased complex carbohydrates to provide sustained glucose release, restriction of simple sugars to limit hyperlactacidemia and hyperlipidemia, and maintaining normal protein intake to support growth and metabolic needs[38]. Despite these strategies, obesity and sarcopenic obesity may arise from chronic overfeeding and overtreatment aimed at preventing hypoglycemia.

In GSD type III, nutritional therapy serves different objectives: reducing glycogen accumulation in the liver, muscle, and heart, particularly in adulthood. This includes a relative reduction in total carbohydrate intake, increased protein consumption to support gluconeogenesis, and, in selected cases, higher lipid intake, including ketogenic or medium-chain triglyceride (MCT)-enriched regimens. Several reports have shown that providing alternative energy substrates, especially higher-protein or ketogenic approaches, can lead to significant improvement or stabilization of GSD III-associated cardiomyopathy[39-43]. Long-term complications such as hepatic adenomas and renal dysfunction are strongly influenced by nutritional control.

Ongoing clinical trials (e.g., NCT03970278) are evaluating modified starches with prolonged release profiles, aiming to improve compliance, maintain euglycemia overnight, and reduce treatment burden. These developments highlight how nutritional innovation continues to reshape the therapeutic landscape of GSDs[44].

Mitochondrial Disorders

Mitochondrial dysfunction leads to defective oxidative phosphorylation, chronic energy deficits, and lactic acidosis. Nutritional decline is driven by both impaired intake (due to gastrointestinal dysmotility and early satiety) and increased metabolic demands. Patients often develop sarcopenia and cachexia despite apparently adequate diets (Table 1).

Management focuses on caloric adequacy while avoiding overfeeding. Supplementation with cofactors (thiamine, riboflavin, carnitine, coenzyme Q10) forms the so-called “mitochondrial cocktail”. Although evidence remains largely observational, many patients report improved energy tolerance and quality of life. Ketogenic diets have been explored in selected subgroups (particularly mitochondrial epilepsies), though long-term safety is debated[45].

Adjunctive physiotherapy and psychosocial support are essential components of “nutritional rehabilitation”, preserving autonomy and slowing decline. Clinical studies such as MMPOWER-3 (NCT03308764), which evaluated the efficacy and safety of elamipretide in primary mitochondrial myopathy using functional performance, patient-reported outcomes, and biochemical markers of mitochondrial function as key endpoints, illustrate the growing integration of metabolic and nutritional parameters in mitochondrial research.

Organic Acidemias

Propionic and methylmalonic acidemias illustrate the delicate balance between protein restriction and anabolic preservation. Propionic acidemia is the organic acidemia most consistently associated with cardiomyopathy, with dilated cardiomyopathy, arrhythmias and conduction disease reported from infancy

to adulthood. Methylmalonic acidemia appears to carry a lower but clinically relevant risk of cardiac involvement, with cardiomyopathy and heart failure described in a subset of patients. Protein intake must be carefully limited to avoid accumulation of toxic precursors, while maintaining adequate essential amino acid provision to support growth and prevent catabolism. In both disorders, management relies on specific precursor-free amino acid formulas that exclude isoleucine, valine, threonine, and methionine, combined with carnitine supplementation and, in B12-responsive forms of methylmalonic acidemia, parenteral or high-dose oral vitamin B12 (Table 1).

Emergency protocols are critical: during illness or surgery, rapid institution of glucose infusion and temporary protein restriction prevent catabolic decompensation. Without such measures, hyperammonemia and metabolic acidosis rapidly progress to life-threatening crises. Long-term therapy requires vigilant metabolic monitoring and frequent adjustments, particularly during growth or puberty. Sarcopenia, growth delay, and micronutrient deficiencies remain significant risks, highlighting the need for continuous nutritional supervision[46].

Primary Systemic Carnitine Deficiency

Carnitine plays a central role in long-chain fatty-acid oxidation, and deficiency, whether primary or secondary, can impair myocardial energy production. While primary systemic carnitine deficiency is a well-recognized cause of reversible dilated cardiomyopathy, secondary forms may also present with cardiac involvement. These include nutritional deficiency (e.g., strict vegetarian or vegan diets with low carnitine intake), malabsorption, nephrotic-range urinary losses, or chronic use of valproate, which increases carnitine depletion.

Several case reports and small series have described complete reversal of dilated cardiomyopathy after carnitine supplementation in secondary deficiency, confirming its pathogenic relevance[47,48]. This example illustrates that, even outside genetically defined metabolic pathways, nutritional deficiencies can occasionally act as primary drivers of cardiomyopathy rather than mere modulators of disease severity[15].

ACAD9 Deficiency

ACAD9 deficiency, a disorder of mitochondrial fatty acid β-oxidation and respiratory chain complex I assembly, is increasingly recognised as a cause of mitochondrial cardiomyopathy. Patients typically present with dilated or hypertrophic CMP, exercise intolerance, and lactic acidosis. Muscle biopsy often reveals lipid accumulation, providing early diagnostic clues. Importantly, riboflavin supplementation has shown therapeutic benefit in several cases, improving cardiac function and stabilizing disease course. Empirical treatment with riboflavin and carnitine may be justified based on biopsy findings, even before genetic confirmation[16,49]. This highlights how targeted nutritional interventions can have disease-modifying effects in selected rare CMPs.

Other Rare Disorders with Nutritional Relevance

Beyond amyloidosis, Fabry disease, glycogen storage disorders, mitochondrial dysfunctions, and organic acidemias, several additional rare conditions demonstrate how nutritional disturbances significantly affect clinical course and quality of life. The common denominators across these disorders are malabsorption and metabolic imbalance, which act as primary mechanisms driving deterioration. By contrast, sarcopenia and cachexia are downstream consequences of these metabolic and gastrointestinal abnormalities rather than mechanisms themselves.

Urea cycle disorders exemplify the delicate balance between substrate restriction and anabolic preservation. Preventing catabolism, such as by avoiding fasting and ensuring adequate non-protein energy intake, is essential to reduce the risk of hyperammonemic crises. Dietary management relies on Foods for Special Medical Purposes (FSMPs) specifically designed to provide essential amino acids while limiting nitrogen load. Long-term follow-up must include frequent metabolic reassessment, particularly during periods of rapid growth or intercurrent illness[50].

Pompe disease illustrates another scenario in which nutritional factors interact with multisystem involvement. In infantile-onset Pompe disease, hypertrophic cardiomyopathy is a hallmark feature and contributes significantly to early morbidity and mortality. By contrast, in late-onset Pompe disease, cardiac involvement is usually mild or absent, while dysphagia, respiratory muscle weakness, and increased energy expenditure often lead to malnutrition and sarcopenia. High-protein, energy-enriched diets integrated with enzyme replacement therapy can support functional maintenance and improve tolerance to rehabilitation[51].

Gaucher disease presents a different nutritional profile, where hepatosplenomegaly causes early satiety and malabsorption. Despite the transformative impact of enzyme replacement therapy, structured nutritional support remains necessary to prevent secondary malnutrition[52].

Metabolic liver diseases, such as Wilson's disease and progressive familial intrahepatic cholestasis, also illustrate the nutritional dimension of systemic dysfunction. In Wilson's disease, copper overload leads primarily to hepatic and neurological manifestations, but case reports describe dilated cardiomyopathy, arrhythmias, and conduction defects[53]. Malnutrition is common, driven by liver dysfunction, gastrointestinal symptoms, and poor dietary intake. Malabsorption of fat-soluble vitamins and protein–energy malnutrition complicate growth, bone health, and, in advanced cases, eligibility and recovery after transplantation. Nutritional support, including specialized supplementation of vitamins A, D, E, and K and tailored high-protein, high-calorie regimens, is therefore integral to management, with potential benefits not only for systemic outcomes but also for cardiac function in selected patients[54].

Taken together, these examples demonstrate that nutritional care is not confined to metabolic or mitochondrial cardiomyopathies. Rather, it is a cross-cutting theme across the rare disease spectrum, where nutritional decline magnifies vulnerability and appropriate intervention can stabilize patients even when disease-specific therapies are limited (Table 2).

CROSS-CUTTING THEMES, RESEARCH ADVANCES, AND FUTURE PERSPECTIVES

Cross-Cutting Clinical Themes

Despite the heterogeneity of rare CMPs, several nutritional issues recur across conditions. Sarcopenia is perhaps the most universal, arising from reduced intake, systemic inflammation, immobility, and anabolic resistance. It independently predicts mortality, hospitalization, and loss of autonomy, and often persists even in patients who appear to have adequate caloric intake. Managing sarcopenia requires integrated strategies: adequate protein and energy supply, resistance training, and, potentially in the future, targeted anti-catabolic therapies[55].

Malabsorption and secondary malnutrition also represent common denominators. In amyloidosis, infiltration of the gastrointestinal tract impairs motility and absorption; in Fabry disease, neuropathic diarrhea limits intake; in Gaucher disease, hepatosplenomegaly reduces meal capacity; and in cholestatic liver disorders, fat-soluble vitamin deficiencies are frequent. These mechanisms highlight the need for routine screening for deficiencies of vitamin D, iron, folate, thiamine, and cofactors such as carnitine and riboflavin, which may otherwise remain clinically silent until cardiac deterioration occurs[56].

Artificial nutrition, though rarely discussed in guidelines, plays a crucial stabilizing role in advanced cases. Enteral or parenteral support can bridge patients through crises, improve treatment tolerance, or serve as a pre-transplant intervention. Initiating such measures requires a careful balance between medical necessity and quality of life, ideally within a multidisciplinary framework[57].

Finally, multidisciplinary care itself is indispensable. Cardiologists, dietitians, metabolic specialists, physiotherapists, psychologists, and patient organizations each contribute to a holistic model of care. Particular attention is required during transitions, such as the shift from pediatric to adult follow-up, where adherence often declines, and nutritional deterioration accelerates.

Ongoing Studies and Clinical Trials

Research in this field is expanding, though still constrained by small cohorts and clinical heterogeneity (Box 1).

Table 2. Consolidated dietary protocols in selected rare diseases.

Disease	Standard dietary intervention	Level of evidence	Key limitations
Glycogen storage disease type III	High-protein, relatively lower-carbohydrate diet; in selected cases, high-fat or MCT-enriched/ketogenic regimens to provide alternative cardiac energy substrates	Low–moderate (case series, small cohorts) tolerability of high-fat regimens	Heterogeneous phenotype; limited prospective data; variable
Primary systemic carnitine deficiency	Oral L-carnitine supplementation (100-400 mg/kg/day) with regular meals and avoidance of fasting	Moderate–high (case series, pathophysiological evidence; cardiomyopathy often reversible)	Delayed diagnosis may lead to irreversible myocardial damage; adherence to lifelong supplementation required
Propionic / Methylmalonic acidemia	Controlled protein restriction, precursor-free amino acid formulas (Ile, Val, Thr, Met), carnitine supplementation, and emergency regimens; B12 in responsive methylmalonic acidemia	Moderate (observational studies, expert consensus)	Growth failure, recurrent metabolic crises, sarcopenia; limited prospective trial data; cardiac involvement often under-recognized
Mitochondrial disorders (including ACAD9 deficiency)	Caloric adequacy with mitochondrial cofactors (thiamine, riboflavin, carnitine, CoQ10); ketogenic diet in selected subgroups	Low-moderate (case series, pilot trials)	High heterogeneity; lack of RCTs; variable riboflavin response (notably in ACAD9-related CMP); limited long-term data
Urea cycle defects	Low-protein diet with specific FSMP formulas and nitrogen scavengers (sodium benzoate, phenylbutyrate)	Moderate (registries, consensus guidelines)	Balancing growth with ammonia control, frequent hospitalizations, limited cardiac involvement, but nutritional lessons relevant to CMP care

ACAD9: acyl-CoA dehydrogenase 9; B12: vitamin B12 (cobalamin); CMP: cardiomyopathy; CoQ10: coenzyme Q10; Phe: phenylalanine; 3–4 h: Every 3–4 hours; RCTs: randomized controlled trials.

Box 1. Methodological challenges in nutrition research for rare cardiomyopathies.

- Small sample sizes – due to fragmentation of patient populations and limited multicenter collaboration.
- Marked clinical heterogeneity – variable phenotypes and nutritional needs, even among patients carrying the same mutation.
- Lack of standardized endpoints – survival, quality of life, body composition, and metabolic markers are rarely harmonized across studies.
- Limited randomized trials – most available data derive from case series, registries, or expert consensus rather than controlled designs.
- Under-reporting of long-term outcomes – especially regarding adherence to dietary regimens, functional independence, and impact on cardiac prognosis.
- Translational gaps – promising nutritional biomarkers and cofactor therapies (e.g., riboflavin in ACAD9 deficiency) are seldom integrated into trial design or clinical guidelines.

In amyloidosis, ongoing observational studies (NCT05721676; NCT04685871) are validating the prognostic role of phase angle and nutritional indices such as the Prognostic Nutritional Index. If confirmed, these markers may become part of standard risk stratification.

In Fabry disease, a multicenter study (NCT04622676) integrates dual-energy X-ray absorptiometry and BIA into routine follow-up, exploring how enzyme replacement therapy modifies body composition and basal metabolism. Parallel efforts are investigating low-FODMAP approaches for gastrointestinal symptoms.

In glycogen storage diseases, trials such as NCT03970278 are assessing extended-release starches to reduce nocturnal dosing and improve sleep quality while maintaining normoglycemia.

In mitochondrial disorders, pilot studies (e.g., MMPOWER-3, NCT03308764) combine metabolic therapies with nutritional interventions. Although pharmacological agents, such as elamipretide, remain the primary focus, dietary cofactors (riboflavin, carnitine, coenzyme Q10, thiamine) continue to play a central role in patient management.

For organic acidemias, structured dietary protocols and emergency regimens are being harmonized across European networks, though randomized trials remain lacking. Registries are beginning to capture longitudinal nutritional data, laying foundations for future intervention studies.

Together, these initiatives illustrate a paradigm shift: nutrition is being recognized not only as supportive care but as a measurable and testable therapeutic variable in clinical research.

Local Experiences and Integrated Models

Beyond trials, innovative local projects demonstrate how nutrition can empower patients and enhance adherence. The Fabry's Kitchen initiative, developed in collaboration with clinicians and patient associations, translated dietary recommendations into culturally adapted recipes, producing the Rare Book to guide low-FODMAP diets. This approach improved both symptom control and treatment adherence.

Building on this, the Pizza Mara project linked rare disease nutrition to a universally recognizable cultural symbol. By using pizza as a platform for awareness and inclusion, the initiative promoted dialogue between patients, caregivers, and the wider community, showing how nutrition can bridge clinical care with social identity.

Such experiences underscore that nutritional support extends beyond the clinic. When integrated into cultural contexts and supported by patient organizations, nutrition becomes a tool for education, empowerment, and public awareness. Combining these models with emerging tele-nutrition platforms may further enhance access, especially for patients living far from referral centers.

CONCLUSIONS

Nutrition is a critical yet underappreciated determinant in rare CMPs. Across diverse conditions, from amyloidosis and Fabry disease to glycogen storage disorders, mitochondrial dysfunctions, organic acidemias, and treatable deficiencies such as carnitine and ACAD9 deficiency, altered nutritional status both reflects disease mechanisms and independently shapes prognosis. In some disorders, diet is the cornerstone of therapy; in others, it mitigates complications, preserves function, and improves quality of life.

Early recognition of malnutrition, sarcopenia, or micronutrient deficiencies, combined with personalized interventions and multidisciplinary care, can significantly influence outcomes. Emerging studies highlight the prognostic value of body composition and the efficacy of tailored nutritional strategies, while local initiatives and digital tools show how nutrition can also enhance adherence and patient empowerment.

Moving forward, integration of nutrition into routine CMP care, research protocols, and rare cardiomyopathy registries will be essential to shift its role from a supportive measure to a therapeutic axis, with direct benefits for survival and patient-centered outcomes.

Artificial Intelligence-Assisted Technologies:

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