

# Adherence Issues in Inherited Metabolic Disorders Treated by Low Natural Protein Diets

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## Key Words

Adherence · Amino acids · Dietary management · Inborn errors of metabolism · Phenylketonuria · Urea cycle disorders

## Abstract

Common inborn errors of metabolism treated by low natural protein diets [amino acid (AA) disorders, organic acidemias and urea cycle disorders] are responsible for a collection of diverse clinical symptoms, each condition presenting at different ages with variable severity. Precursor-free or essential L-AAs are important in all these conditions. Optimal long-term outcome depends on early diagnosis and good metabolic control, but because of the rarity and severity of conditions, randomized controlled trials are scarce. In all of these disorders, it is commonly described that dietary adherence deteriorates from the age of 10 years onwards, at least in part representing the transition of responsibility from the principal caregivers to the patients. However, patients may have

particular difficulties in managing the complexity of their treatment because of the impact of the condition on their neuropsychological profile. There are little data about their ability to self-manage their own diet or the success of any formal educational programs that may have been implemented. Trials conducted in non-phenylketonuria (PKU) patients are rare, and the development of specialist L-AAs for non-PKU AA disorders has usually shadowed that of PKU. There remains much work to be done in refining dietary treatments for all conditions and gaining acceptable dietary adherence and concordance, which is crucial for an optimal outcome.

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## Introduction

Inborn errors of amino acids [AAs; phenylketonuria (PKU), maple syrup urine disease (MSUD), homocystinuria (HCU), type I and II tyrosinemia (TYR I and TYR

II), organic acidemias (OA) and urea cycle disorders (UCD)] are a heterogeneous group of conditions. Each of these is caused by a different single enzyme deficiency, causing a block in the respective metabolic pathway of a number of indispensable or dispensable AAs. All these disorders may result in some neurocognitive problems even when treated according to best clinical practice, and in conditions such as MSUD, OA and UCD, metabolic decompensations may result in high morbidity with severe neurological deficits, and may cause death [1].

These disorders necessitate a life-long diet restricting natural protein intake with addition of L-AA supplements that are free of the precursor AAs or provide essential L-AAs only. The poor palatability of many of these products renders dietary adherence arduous and therefore challenging, and may negatively impact on the clinical outcome and the family as a whole [2]. The anxiety and pressure experienced by patients and their families in adhering to their well-day diet as well as the treatment regimen given during acute and non-acute decompensations have so far received little attention. The primary aim of this report is to highlight the hurdles that need to be overcome in gaining dietary adherence across the range of classical AA disorders, OA and UCD in patients at various ages.

### **The Principles of the Low-Protein-Diet Treatment**

With the exception of UCD, the principles of dietary management are similar for all AA disorders [3], although the precise method of managing dietary management will vary from country to country, and even between centers in the same country. This primarily consists of three inseparable parts: (1) a measured but clearly restricted allocation of natural protein; (2) a precursor-free protein substitute with all other L-AAs, and (3) consumption of foods that are naturally very low in protein, such as special low-protein pasta or other protein-free energy sources to meet the energy requirements of the patient. In UCD, natural protein intake is severely restricted and most countries provide routine supplementation with essential AA [4, 5]. High-protein foods such as meat, fish and eggs are severely limited or completely prohibited, and foods moderate in protein content, such as potatoes and cereals, are given in small and controlled portions; the amount being determined on an individual basis according to the severity of the condition, age, growth rate and metabolic control. In AA disorders, adjustment of natural protein is titrated repeatedly against frequent

plasma concentrations of precursor AA to maintain them within target ranges and avoid essential AA deficiency. In UCD, natural protein intake (together with drug dosage) is adjusted according to regular ammonium, glutamine and quantitative plasma AA concentrations [6].

### **AA Supplementation**

Disorder-specific AA supplementation is an important source of protein in AA disorders treated by diet. These are available in a variety of presentations (powders, gels, liquids and even tablets for PKU). Many contain vitamins and minerals. Their fat and carbohydrate content is variable and they are an essential nutritional supplement for protein metabolism including protein homeostasis and growth. Their administration is demanding, partly because they are prescribed in at least 3 evenly distributed dosages throughout the day, in order to achieve stability of blood precursor AAs and to optimize their metabolic utilization [7]. Supplements may be administered orally or by enteral feeding tube. Generally, many patients have a poor acceptance of AA supplements even though their taste and presentation has improved over the years. Some conditions will also require permanent or temporary supplementation with additional AA, in addition to other deficient nutrients, co-factors of the defective enzyme and drugs. The amount of AA supplement per kilogram body weight may decrease with age in some conditions (e.g. PKU) whereas in other conditions maintenance of a high intake (e.g. MSUD) of suitable AA is crucial during acute illness to minimise metabolic decompensation, although there are no reports of adherence with emergency feeding protocols during illness.

### **Dietary Adherence**

Poor adherence to diet is a commonly reported problem for most conditions in all age groups, and it is known to deteriorate with age, especially from around 10 years of age. Dietary adherence is arguably more problematic in chronic disorders in which there are no risks of acute decompensation, e.g. PKU, HCU, and TYR I and II. In other disorders (UCD and MSUD), poor adherence to the diet can be rapidly 'penalized' with metabolic decompensation and its consequences. In PKU, approximately one third of patients have median/mean blood phenylalanine concentrations outside the target treatment range with maintaining control deteriorating further with increas-

ing age [8–11]. Comparable problems have been reported in MSUD [12]. In HCU, published information about the metabolic control achieved is scarce, but clinics report worsening adherence in older patients. Therefore, it is apparent that compliance is challenging in adolescents and adults, although poor adherence occurs in some families with younger children, especially when diagnosed by neonatal screening instead of clinical presentation or when the commands of culture demand treatment non-adherence.

One group of conditions where there are particularly little adherence data is UCD. Although there is clear guidance for protein prescription in UCD, there are surprisingly no publications reporting actual consumption of protein or energy of patient cohorts. It is possible that some patients may under-achieve their prescribed protein intake if they commonly use their protein-free emergency feeds due to illness, experience periodic vomiting, or if they are tube fed [13, 14]. Some may consistently over-restrict protein from fear of precipitating hyperammonaemia [5].

### **Comparison with Other Chronic Disorders**

Commonly these conditions of inborn errors of metabolism (IEM) have adherence issues similar to many other chronic non-IEM diet-treated conditions such as insulin-dependent diabetes or cystic fibrosis. It is well established that these children are about twice as likely as other children to have behavioural and emotional problems in the clinical range [15]. At the very least, the conditions are likely to have disruptive effects on the family lifestyle, and participation in normal activities such as holidays or sleepovers may be affected [16]. However, some of the barriers observed in IEM are particularly taxing not only because of the intricacies of dietary treatment and other treatment demands, but also the lack of treatment consensus and guidelines, and the child's physical condition and neuropsychological profile.

### **The Burden of the Disorder and the Diet Management**

Generally, in all conditions treated by strict diet therapy, the need to adhere every day to management is relentless (table 1) [17]. Treatment is not only about a rigorous dietary regimen, but an endless sequence of medications, procedures, home blood tests, emergency

procedures in MSUD, OA and UCD, and numerous visits to hospital to see a wide range of professionals, and this is shared and experienced by the entire family [18]. Children may have physical or behavioural feeding difficulties or have limited appetites [2], and may require constant coercion to take their AA supplement three to four times daily, which is exhausting for caregivers. In addition, because these conditions are inherited, and some population groups have large families, it is not unusual to have more than 1 child with the same IEM in the family unit, thereby increasing the workload.

### **The Paradox of Dietary Management**

Dealing with IEM conditions often involves ambiguities, including uncertain long-term outcome, variable treatment aims and conflicting information from large multi-disciplinary health professional teams. With better management, treatment aims are changing from preventing severe neurological deficits only towards achieving best-possible neuropsychological outcome with normal quality of life [19]. With such high expectations, the question is always if a demanding treatment like a low AA diet, which is essential to achieve optimal biological control and positive neurocognitive outcome, may negatively influence quality of life. Some may debate that a less strict dietary restriction may result in a better overall outcome for the patient through a greater tolerability of the dietetic treatment by the patient and its family, although this has not been studied in a controlled way. However, in conditions like PKU, the caring of a child on a special diet does not appear to affect the quality of life of the parents. However, factors such as loss of carer friendships and lack of emotional support have a large negative impact [20, 21].

### **Patient Responsibility**

As children mature, they are expected to take more responsibility for their diet therapy. This process of transition of responsibility implies that parents have to be willing to step down as primary caregiver and to lose their control. Patients on the other hand have to have more knowledge, both theoretical and practical. Apart from that, patients may have particular difficulties in managing the complexity of their treatment because of the impact of the condition on their neuropsychological profile. In poorly treated PKU, poor executive function-

**Table 1.** Factors affecting adherence in low-protein natural diets

	Positive factors	Negative factors	Additional associated factors
Adherence to AA supplementation	Palatable, attractive and trendy presentation, convenient, single-dose packaging (no weighing/measuring), low-volume (Gokmen-Ozel et al. [39]), good administration routine	Unpalatable, inconvenient, unattractive, limited product choice, high volume, coercion to take protein substitute	Availability, supply, cost
Burden of diet	Diet becomes way of life; consistent family support, good family cooking skills, appropriate access to special dietary foods	Need to adhere to diet every day regardless of circumstance or social occasion; social isolation; need for emergency dietary procedures; child feeding difficulties, limited appetite	Patient and caregiver personality, motivation, ability, education, and resourcefulness; costs of special low-protein dietary foods; loss of earnings and other 'unmeasured costs' associated with dietary care
Paradox of dietary treatment	Agreed long-term goals; child/patient appears well associated with good metabolic control	Child/patient appears well, regardless of 'metabolic control' achieved; inconsistent health professional advice, lack of treatment guidelines, dietary advice may oppose guidelines for 'healthy living'	Dichotomy between optimal outcome vs. quality of life; change/deterioration in health status irrespective of dietary adherence
Patient responsibility	Self-care, good knowledge of treatment, motivation, organised, development of cooking skills, peer and family support	Dislike of diet, poor knowledge, no interest in treatment, impaired neuro- psychological abilities affecting self-care or acceptance of need for diet; peer pressure, bullying	Age, child personality and temperament, ability, acceptance of diet
Family characteristics	Well-educated, good knowledge of conditions, family supportive and responsible, consistent message, well organised	Dysfunctional family, chaotic conditions, emotional stress, carer depression, low family cohesion or support, divorce, poor caregiver education or treatment knowledge	Coping ability, caregiver anxiety, parenting skills, family income, housing, level of education, living conditions
Cultural and religious influences	Good extended family support	May be >1 child with same IMD in family, illiteracy, poor access to information, low acceptance of treatment, low access to professional support	Family size, access to information, language, importance of food
Information	Comprehensive written and web-based information for PKU	Limited information for non-PKU conditions, unrestricted and unchecked web sites; few international patient associations for non-PKU conditions	Literacy and cognitive skills

ing, e.g. sub-optimal planning and organisational skills, poor attention [22] and short-term memory [23–25] may affect the ability to self-manage a low protein diet because of the day-to-day organisation and planning required [26]. In addition, in PKU, low impulse control and mood variations [22] may hinder the ability to comply by reducing self-control and motivation to adhere to dietary restrictions. In conditions such as HCU [27] (mainly late diagnosed) and UCD, behavioural problems, such as aggression, episodic depression and personality disorders, add to health care professionals difficulties in being able to convince patients that the diet is essential. These difficulties are a particular issue during times of higher risk (e.g. during puberty, pregnancy and post partum) [28].

In all of these conditions, some of the consequential patient developmental issues affecting adherence in-

clude limited abilities in risk assessment, conscious risk taking, and peer group pressures and the 'need to fit in'. It has been demonstrated in conditions such as coeliac disease that adherence to dietary restriction complicates social relationships when it made their condition visible to others [29]. A sense of being discriminated was experienced when other people either amplified or minimized the importance of their medical condition and dietary needs. It was embarrassing to be seen as special in the eyes of others, even when reactions were interpreted as misplaced kindness by people who became concerned about accommodating their needs [29]. Negative school experiences have been particularly reported in MSUD [30].

## The Patient's Family Characteristics

Overall outcome in children depends on parental ability, their discipline, motivation, organization skills and overall coping ability [31] to continually apply and supervise the dietary regimens. Caring for 1 affected child with an IEM together with healthy children may be particularly taxing, sometimes testing the personal conviction about the need for the severity of the dietary treatment for their child.

Generally, adherence of children to the dietary treatment expected in IEM is particularly complex because it frequently involves intricate family relationships and perspectives. Emotional stress has been reported in 78.4% of parents of MSUD patients [30] and it has been shown in conditions like asthma [32] that feeling emotionally depleted can compromise the parent's ability to respond to acute illness, and this may be analogous for MSUD, OA and UCD. Family climate has the potential to either support or derail adherence to dietary treatment. Households headed by 1 parent have increased in some countries, and low family cohesion and divorce has been shown to have a negative impact on compliance in PKU [29]. Family disengagement and criticism is associated with poor adherence in children with conditions such as diabetes, and although parental support is needed, it is important that this support does not become overinvolvement [33]. Some parents of children with PKU (n = 11) endorsed parenting strategies such as yelling, grounding or taking away privileges. These parents had children who were less adherent and had higher blood phenylalanine concentrations than those who were parented without these tactics [34]. Directly observed family interactions characterised as warm, supportive and responsive have been associated with better medical management in conditions such as cystic fibrosis [34, 35].

## Cultural and Religious Influences

IEM are more frequent in populations with a high level of consanguinity. MSUD, TYR I and UCD are particularly prevalent in Muslim communities originally from South Asia and the Middle East who are now living in western countries. Structural and practical constraints include living in poor housing with limited cooking facilities, large-sized families, illiteracy and/or poor language skills [36]; the latter is a major barrier to understanding and accessing basic information about the dietary treatments, which affects their ability to adhere to

treatment. In these populations, food is socially very important with food being readily available to serve to guests within the home. Due to cultural reasons, women (often the principal caregivers), may not be allowed to attend mixed gender educational events without an escort or may have limited direct access to a supermarket's special dietary products. It is common for fathers to communicate with the health care professionals at the outpatient clinic, although it is the mothers who can contribute the most valuable information about their dietary practices and dietary issues. One of the consequences is reliance on other people, often male family members, to access, translate and interpret health information on their behalf. There may be poor acceptance of the condition and occasionally misinterpretation of religious teachings with a belief that the condition is 'God's will' so there is a reluctance to administer treatment that may be seen as invasive to the child or not in accordance to the anticipated religious laws. There is commonly an unwillingness to use home tube feeds, partly due to the attention a tube would draw from others, and the inability to conceal the condition with a nasogastric tube in situ.

## Adherence and Information Sources

Caregivers encounter an overwhelming amount of unrestricted and unchecked information from websites, Facebook, Twitter and other sources. Although there is extensive information for PKU, professionally written, disorder-specific information is sparse for the rarer conditions such as MSUD, HCU and UCD. Equally, there are well-established national and even international patient associations for PKU, but due to the infrequent incidence (in most countries) of other conditions, support from other families experienced with managing the disorders is less available. Furthermore, families may receive care from a non-metabolic-specialist health professional care team who may lack the necessary experience to support and enable the family to deliver the optimum treatment, which may lead to conflicts between the primary caregivers and the clinician.

Sometimes medical doctors concentrate on drug therapy only and so leave the dietetic management as an adjunct therapy to other non-medical professionals, but families then may fail to accept the importance of this treatment. The lack of clear guidelines is also important as different targets between or within countries may unintentionally allow individual choices for patients and families, but also for individual members of the same

professional IEM team to give variable advice. This not only asks for guidelines with clear targets, but also for discussion on how to implement these guidelines in day-to-day care issues, so they can be attained by patients, their families and health care professionals [19]. The recently published UCD and glutaric aciduria type 1 guidelines are welcome [37, 38].

## Social Aspects

Another issue is the limitations that have affected the quality and variety of foods that can be offered to patients, ultimately negatively affecting adherence. In some countries, there is mainly incomplete, non-validated, food AA analysis available and for some foods, e.g. exotic fruits and vegetables, there is very limited information. This restricts the range of foods which can be allowed due to unavailability of food analysis to calculate and control their intake. In addition, although, internationally, there is a wide range of special low-protein foods available, a full range of products is usually not accessible to all patients in each country. A government in an individual country may expect families to purchase all low-protein special foods (creating a financial burden), or they supply them via a prescription system that is bureaucratic and cumbersome. Some systems may be so inflexible that they discourage families from using the special low-protein products to their full potential to improve the quality of the diet. The cost of some specialist foods may

be prohibitive in some countries. Furthermore, although precursor-free protein substitutes or essential L-AAs are an essential part of treatment, due to the low incidence of HCU, MSUD, TYR I and II and UCD, the development of protein substitutes/essential AA supplements has always lagged behind that of PKU. Consequently, the range and flavours available is restrictive, which may add to the non-adherence of dietary treatment in non-PKU.

## Conclusions

In IEM conditions requiring a protein-restricted diet, a collaborative study is essential to evaluate the effects of diet and education, develop consensus treatment guidelines, and to progress and refine dietary treatments for all conditions. To gain important insights into the effects of adherence of differing psychological, social, economic and medical/nutritional conditions, large-scale international studies (through registries or systematic investigation) are imperative for this group of conditions. The production of consensus-driven, international, web-based, educational tools for all conditions is likely to be significant in supporting patients and caregivers and standardizing educational messages. Above all, in IEM, when studying adherence and outcome, there is much to be learnt by community studies observing actual dietary patient practices and outcome measures rather than the theoretical recommendations suggested by health professionals working under hospital conditions.

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