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Dietary Considerations in Tyrosinemia Type I

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Abstract

Since the introduction of 2-(2 nitro-4-3 trifluoro-methylbenzoyl)-1, 3-cyclohexanedione (NTBC), life expectancy of HT1 patients greatly improved. However, due to treatment with NTBC, tyrosine concentrations greatly increase. As a consequence to possible neurocognitive problems, the main objective of dietary therapy in HT1 is to provide adequate nutrition allowing normal growth and development while strictly controlling tyrosine levels in blood (and tissues). Although no well-defined target levels exist, tyrosine concentrations below 400 µmol/L are considered to be safe. To achieve this aim a diet restricted in natural protein and supplemented with a special tyrosine and phenylalanine-free amino acid mixture is necessary.

Dietary management could be strenuous at diagnosis due to several different problems. If vomiting and diarrhea are a major issue at diagnosis, frequent feeding with additional energy from low protein food is needed

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for catch-up growth. Initiation of dietary treatment is usually easier if diagnosis is directly after birth. Based on newborn screening when infants are still reasonable healthy. If presenting clinically infants may experience serious difficulties in taking the amino acid mixtures probably due to feeding problems while when presenting after some 2–3 months taste development and the difference in the taste of amino acid mixtures compared to regular formula and breast milk increase difficulties with the treatment.

Following a dietary treatment is even harder than taking some medicine. Older children and adolescents often relax the diet and at some age become reluctant to stick to a strict regimen. Therefore, adequate training and information should be given to the patients and the family at regular intervals. To achieve this, a multidisciplinary approach involving pediatricians/physicians, dieticians, psychologists and social workers is an asset for the care of patients with HT1.

Keywords

Tyrosinemia type I • Diet • Amino acid • Phenylalanine • Tyrosine • Protein substitute

Abbreviations

HPPD	4-hydroxyphenylpyruvate dioxygenase
HT1	Hereditary Tyrosinemia type 1
NTBC	2-(2 nitro-4-3 trifluoro-methylbenzoyl)-1, 3-cyclohexanedione
PKU	Phenylketonuria

Until 1992 treatment for Hereditary Tyrosinemia type 1 (HT1) only consisted of a diet that was restricted in phenylalanine and tyrosine. Exclusively restricting dietary tyrosine is not enough as large parts of the precursor phenylalanine are converted to tyrosine. The diet sometimes led to temporary clinical stabilization but did not prevent development of liver cancer, renal tubulopathy and other serious sequelae. Thus, before the era of NTBC liver transplantation was necessary in every HT1-patient sooner or later (van Spronsen et al. 1994).

NTBC has led to a revolution of treatment in HT1. NTBC inhibits the activity of the enzyme 4-hydroxyphenylpyruvate dioxygenase (HPPD) upstream from the primary enzyme defect and thereby prevents production of toxic compounds (Lindstedt et al. 1992). NTBC gives rise to high tyrosine concentrations that might compromise neurocognitive development. Therefore, a diet low in phenylalanine and tyrosine is essential in all patients treated by NTBC.

It is essential to meet energy requirements to strictly prevent catabolism, which may give rise to elevated tyrosine levels. There are no well-defined target levels for tyrosine in blood, concentrations below 400 μmol/L are regarded as reasonably safe (de Laet et al. 2013; Mayorandan et al. 2014). To achieve this aim a diet restricted in natural protein and supplemented with a special tyrosine and phenylalanine-free amino acid mixture is necessary. The age at diagnosis (and thus the age at start of treatment) is variable (Mayorandan et al. 2014) and critically depends on the institution of a newborn screening programme for HT1.

18.1 Modes of Dietary Intervention

While the need for tyrosine (and phenylalanine) restriction is generally accepted, different modes of dietary intervention are used. In a recent multinational survey we found that there are differences in dietary treatment: 24% of centres used tyrosine and phenylalanine calculation, 38% of centres used protein restriction or tyrosine and phenylalanine calculation (depending on age), 19% of centres used protein restriction or tyrosine calculation (depending on age) and 19% of centres only recommended protein restriction (Mayorandan et al. 2014).

18.2 Dietary Management

18.2.1 Routine Dietary Management in HT1

For patients presenting in the first few months of life, severe vomiting and diarrhea may be a major issue. These children need frequent feeding with special food as well as additional energy for catch-up growth. The additional energy comes from low –protein food, and special protein-free modules with high energy content that are commercially available and provide energy without tyrosine/phenylalanine.

The intake of special amino acid mixtures is relatively easy when the patient can start with that regimen in the first few weeks of life. If newborn screening is not operative, most patients start treatment beyond the newborn period. Most of these babies experience serious difficulties in taking the amino acid mixtures. This probably relates to the taste development and considerable differences in taste of the amino acid mixtures compared to regular formula and breast milk.

The basic dietary principle is a restricted intake of phenylalanine and tyrosine. This regimen is comparable to phenylketonuria (PKU) where only phenylalanine intake is restricted (however, the intake of tyrosine is increased). In principle, the intake of phenylalanine in PKU and tyrosine in HT 1 can be calculated in milligrams per day or as protein equivalent in gram/day. Counting phenylalanine and tyrosine (in an exchange system) as well as counting natural protein is a strategy that works in HT1 as well as in PKU noticing that the content of phenylalanine in natural protein is generally 4.5–5% while the tyrosine content usually is somewhat lower (Table 18.1).

The food exclusively consists of mother's milk or formula supplemented with special tyrosine- and phenylalanine-free infant amino acid mixtures during the first 5–6 months of life which makes management by parents easy. Special tyrosine- and phenylalanine-free infant formula can be consumed ad libitum. For the first year of life, the dietitian should calculate nutrient intake at regular intervals. Supply of energy and natural protein/tyrosine intake is commensurate with weight development and tyrosine levels in blood. The total protein intake required is calculated based on the recommendations for the general population and "some" extra to compensate for the use of 70–90% of the recommendation of protein as amino acids mixture. Worldwide we see differences in recommendations in HT1 for the total protein based on different insights how much to calculate as com-

Table 18.1 Additional practical information for the dietary treatment

Estimation[a] of the amino acid content of foods (mg/g protein)		
Food	PHE	TYR
Fruits	25–30	25
Vegetables	35–40	25
Bread, crackers, pasta, cereals	50–55	33
Potatoes	40–49	59
Meat, poultry, fish	44–48	34–42
Dairy products	50	50
Egg	53	39

[a]USDA Agriculture Research Service, Nutrient Data Laboratory (http://www.nal.usda.gov/fnic/foodcomp/search/)

Table 18.2 Protein recommendations based on several age groups

	Protein [g] per kg body weight	Protein [g] per kg bodyweight via AAM
Age	Natural protein + protein via AAM	Adapted according to DACH 2000 recommendations
0–2 months	2.5	2.0–2.5 (to be checked by dietary protocol)
2–12 months	2.0	2.0
1–4 years	1.5	1.0
4–10 years	1.2	0.9
10–14 years	1.1	0.9
>14 years	1.0	0.9

The total protein recommendation is on the left side. On the right side is the protein recommendation only for the AAM. This corresponds to our DACH reference values. The difference between the two is the estimated protein intake of natural foods that you have specified in the supplementary data "Expected natural protein tolerance in HT1" (supplementary data 1) pensation. In the Table 18.2 we show 'DACH 2000' for the German-speaking countries.

A whole range of different commercial products with mixtures of l-amino acids devoid of phenylalanine and tyrosine, supplemented with vitamins and minerals, are available on the market providing essential amino acids and micronutrients (Table 18.3). For older children the amino acid mixture can be calculated according to 'DACH recommendation 2000'. The minimum protein requirement is completely supplied by special amino acid mixtures (see Table 18.3)

The phenylalanine requirements for healthy individuals are subject to discussion as reviewed by Pencharz et al. (2007). Such studies are necessary for all age groups and are very laborious. Initial data suggested that phenylalanine and tyrosine intake (in total for both) should be somewhere between 15 and 39 mg/kg per day with a ratio of 60:40. However, later studies have shown that phenylalanine intake by itself should be between 38 and 48 mg/kg per day. Therefore, the maximum phenylalanine requirement (if no tyrosine is given) is considered to be 42 mg/kg per day, while about 9 mg/kg per day is needed when enough tyrosine is provided.

Some children with HT1 on a phenylalanine/tyrosine -restricted diet have been found to have

Table 18.3 Special dietary products (metabolic formula) for tyrosinemia[a]

Product	Protein equivalent (g)	Energy (kcal)	Age indication	Flavored	Micronutrients added
Powdered (400–500 g cans); details shown for 100 g					
TYR Anamix Early Years	13.5	473	Infants, children <3 year	–	+
TYR Anamix Next	28	385	>1 year	–	+
XPhe, XTyr Maxamaid	25	324	Young children	+	+
XPhe, XTyr Analog	13	475	Infants, children <3 year	–	+
XPHEN, TYR Maxamaid	25	309	Young children	–	+
XPHEN, TYR Maxamum	39	297	Older children and adults	–	+
Tyrex-1 (Abbott)	15	480	0–12 month	–	+
Tyrex-2 (Abbott)	30	410	>1 year	–	+
Comida-TYRo A	11.8	506	0–12 month	–	+
Comida-TYRo B	31.1	420	1–14 year	–	+
Tyros 1 (Enfamil)	16.7	500	Infants, toddlers	–	+
Tyros 2 (Enfamil)	22	410	Children, adults	+	+
Zero TP Infant mix LCP	11	508	Infants	–	+
Zero TP Kid	72	289	4 month's-6 year	–S	+
Zero TP junior	75	300	7–14 year	–S	+
Zero TP Advance	77	309	>15 year	–S	+
Prepacked portions					
Tyr Gel (Vitaflo)	10	81	>1 year	–S	+
Tyr Express 15 (Vitaflo)	15	74	>3 year	–S	+
Tyr Express 20 (Vitaflo)	20	99	>3 year	–S	+
Zero TP minis (MetaX)	5	24	>3 year		+
Ready to use					
Cooler 10 (Vitaflo)	10	62	>3 year	+	+
Cooler 15 (Vitaflo)	15	92	>3 year	+	+
Cooler 20 (Vitaflo)	20	124	>3 year	+	+
Tylactin RTD (Cambrooke)	15	200	Children, adults	+	+
Tylactin restore (Cambrooke)	10	170	Children, adults	+	+

(continued)

Table 18.3 (continued)

Product	Protein equivalent (g)	Energy (kcal)	Age indication	Flavored	Micronutrients added
TYR Lophlex LQ	20	120	>4 year	+	+
PT-am infant	13	466	0–12 month	–	+
Milupa Tyr 1	50	290	> 0 month	–	+
Milupa Tyr 2 prima	60	289	1–8 year	–	+
Milupa Tyr 2 secunda	70	291	9–14 year	–	+
Milupa Tyr 3 advanta	70	297	>14 year	–	+
PT-am Anamix	29	374	>3 year	+	+
Frucht Vanille					
Tyr Anamix Junior LQ orange	8	95	<3 year	+	+
Tyr lophlex LQ 20 Juicy Berries	16	96	>4 year	+	+

[a]Worldwide, different products and other manufacturers are available; see country details on websites
+ = Yes; – = No; S = separate flavoring

low phenylalanine levels (Wilson et al. 2000; van Vliet et al. 2015). There has been concern that these low levels could be detrimental to the child's development, and it was thought that the addition of phenylalanine to the diet would increase levels in blood and tissues without increasing the tyrosine level. An initial study found that supplementing the diet with an additional 20–40 mg/kg per day phenylalanine increased the blood phenylalanine concentration while maintaining the tyrosine level (Wilson et al. 2000). Therefore, supplementation with phenylalanine may be beneficial, but the risk of high tyrosine should always be kept in mind. Further long-term studies are required before a recommendation for standard supplementation can be given. In this context, it should be considered whether normal bread instead of phenylalanine should be provided. This is based on the fact that normal bread contains more phenylalanine than tyrosine (Table 18.1). This relaxation is likely to improve dietary compliance.

18.2.2 Special Issues Regarding Diet in HT1

Diagnosis and initiation of dietary and pharmacological treatment are a big challenge for affected families. In "*Additional practical information for the dietary treatment*" (Table 18.1) we give practical recommendations to start dietary treatment.

A new period begins when the child can open the cupboard or fridge himself. When patients grow-up and become independent of their parents, new issues may arise: going to school and eating out, acceptance of dietary requirements by their peers, having parties etc.. Special attention has to be paid to new responsibilities and creative introduction of new roles to parents and the patient. Adolescence is a very difficult period for the patient, aspects like self-empowerment are important issues. The family and the child must be well trained and informed at regular intervals starting in early childhood and continuing during adulthood.

Following a dietary treatment is even harder than taking some medicine. A simple food selection is useful to improve dietary compliance (see Table 18.4). Young people often relax the diet and are reluctant to stick to a strict regimen. Before they stop sticking to their diet, a wider food selection should be considered. This should be discussed with physician and dietician.

Other issues may include the reimbursement of amino acid mixtures and low protein foods that varies around Europe already (Belanger-Quintana et al. 2012). From Mayorandan et al. (2014) we know that reimbursement of HT1 treatment varies considerably, similar to PKU (Ahring et al. 2009).

While age-specific target levels for phenylalanine exist in PKU, the situation in HT1 is less

Table 18.4 Simple recommendations for the older patient when choosing food

Very low protein food	Moderate protein food	
< 2–3 g protein per 100 g	< 6 g protein per 100 g	High protein food
Fruit	Normal bread and	Meat
Vegetables	Bakery products	Sausage
Potatoes, rice	(under 6 g E/100 g)	Egg
Butter, oil, mayonnaise, tartar sauce	Pasta	Poultry
Cream, creme fraiche, sour cream	Milk	Fish
Sugar,	Nuts	Seafood
Sugar confectionery		
Juice drinks and lemonade		
Rice milk, oat milk		
Special low protein foods		
You can eat as much as you like!	Be careful!	Not allowed
	May be taken depending on your tyrosine level	

clear. In PKU we know that diet for life is required in adults and women who aim to become pregnant have to stick to a stricter diet, we cannot give recommendations for HT1 yet.

Like in PKU, glycomacropeptide may be a dietary option, their role in the treatment of HT1 still has to be elucidated. In its pure form, glycomacropeptide does not contain phenylalanine nor tyrosine. Due to the fact that the glycomacropeptide has to be removed out of the whey protein, the product will contain some phenylalanine and tyrosine.

18.2.3 Dietary Management and Follow-Up

The objective of dietary therapy in HT1 is to provide adequate nutrition allowing normal growth and development while strictly controlling tyrosine levels in blood (and tissues). Changes in growth velocity, intercurrent illness and dietary indiscretions may result in large fluctuations of tyrosine concentrations. Therefore, especially during the early years, we need a very frequent follow-up by (home) blood sampling and frequent clinical and laboratory checks at the outpatient clinic with dietary assessment.

To conclude, life-long adherence to the tyrosine and phenylalanine restricted diet is necessary to prevent tyrosine concentrations to increase. Regular follow-up of growth, development and metabolic control needs to be done to ensure sufficient intake of all amino acids, especially including phenylalanine. Adherence to the dietary treatment is however a great challenge when the patient gets older. This, in combination with other issues associated with the disease, makes multidisciplinary treatment necessary. A multiprofessional team with expertise in the treatment of HT1 patients including paediatricians/physicans, dieticians, psychologists and social workers is an asset for the care of patients with HT1. To this aim Centers of Expertise are being formed throughout Europe to guarantee optimal care. These Centers of Expertise are members of a specific European Reference Network.

Supplementary Data

Supplementary data 1: Expected natural protein tolerance in HT1

	Protein	Protein
Age years	g/d	g/kg/d
<2	2–6	0.4–0.5
2–9	5–10	0.2–0.5
10–14	9–20	0.3–0.4
>15	11–25	0.2–0.4

Around 70–90% from total protein must be covered by the amino acid mixture

Notice: natural protein tolerance individually to be defined. Intake of tyrosine/natural protein is altered according to plasma tyrosine concentrations (influenced by residual enzyme activity, growth velocity

Supplementary data 2: Contact information for manufacturers of tyrosine- and phenylalanine-free medical foods

Manufacturer and website address	Contact details
Abbott Nutrition	3300 Stelzer Road, Columbus, OH 43219
www.abbottnutrition.com	Office Phone: 614–624-4416, Toll Free: 800–986-8755
	Cell: 614–264-4388, Fax: 614–727-4416
Vitaflo	Distributed by Vitaflo USA
www.vitaflousa.com	211 N. Union St. Suite 100, Alexandria, VA 22314
	Phone: 1–888-VITAFLO (1–888–848-2356), Fax: 1–631–693-2002
	Email: vitaflo@vitaflousa.com
Vitaflo Europe	Vitaflo International Ltd
www.vitaflo.co.uk	Suite 1.11, South Harrington Building, 182 Sefton Street Brunswick Business Park
	Liverpool L3 4BQ UNITED KINGDOM
	Metabolic product queries: +44 (0)151702 4938
	Email: vitaflo@vitaflo.co.uk
Mead Johnson (Enfamil)	Phone: 1–812–429-6399
www.meadjohnson.com/pediatrics/us-en/product-information/products	Email: mjmedicalaffairs@mjn.com
Cambrooke	4 Copeland Drive, Ayer, MA 01432
www.cambrooke.com	Phone: 866,456 9776, Fax: 978,443 1318
	Mail: info@cambrooke.com
Nutricia-NA USA	Phone: 301–795-2300 or 1–800–365-7354
www.medicalfood.com	Fax: 301–795-2301
Nutricia-NA Canada	Phone: 877–636-2283
www.Nutricia-NA.com	Fax: 514–745-6625
Nutricia	Nutricia Advanced Medical Nutrition
http://www.nutricia.com	Danone Place Schiphol, Tower E, World Trade Centre
	1118BG Schiphol, The Netherlands.
	Phone: +31 20,456 9000
	Email: medicalnutrition@nutricia.com
Dr Schär	In various countries with various phone and
http://drschaer.com	e-mail contacts around the world as in UK,
	Germany, Italy, Spain and with a translated
	website in various languages.
MetaX	Email: info@metax-gmbh.de
www.metax.org/EN/Products/Metabolics.aspx	
Nutricia GmbH	Email: info-metabolc@nutricia.com
www.nutricia-metabolics.info	Phone: 00800–74773799

Supplementary data 3: Monitoring the diet

Age		Frequency
0–6	Months	Fortnightly
6–12	Months	Fortnightly to monthly
1–2	Years	Quarterly
		(when applicable monthly Tyr-Phe in bloodspot)
> 3	Years	Every 3–6 months
		(when applicable monthly Tyr-Phe in bloodspot)

As soon as nutritional support is well established for the patient, the prescription should be routinely and frequently fine-tuned to growth and lab results. Changes in intake take time to be reflected in lab results. The time needed to evaluate effects increases with age

Monitoring of Nutritional Status

- Plasma amino acids
- Nutrient intake
- Growth (linear and weight)
- Condition of hair and skin
- Biochemistry

can verify the adequacy of intake.

Introduction of Solids: Follow General Advice When Possible

- At about 4–5 months of age
- Developmental readiness
- Important source of unidentified nutrients such as fiber
- Contributing to a child's acceptance of a variety of tastes and textures
- Development of jaw muscles important for speech

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