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TYROSINAEMIA TYPE I AND II

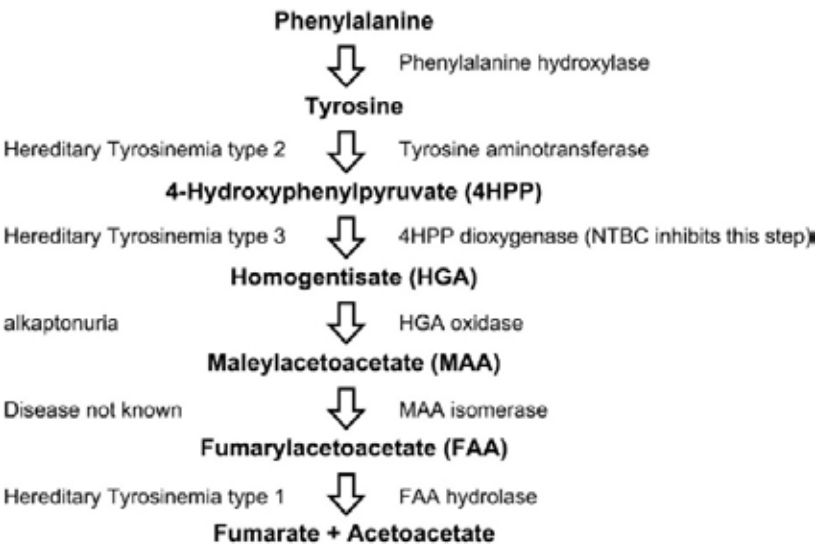
Tyrosinaemias are a group of inborn errors of metabolism and for optimum adult functioning and outcome, lifelong treatment is needed[1] with a low protein diet, amino acid supplements and regular monitoring of nutritional status.

Tyrosine is a conditionally essential amino acid derived from dietary protein intake and the hydroxylation of phenylalanine. Tyrosine is either incorporated into proteins in the body, or it is degraded into fumarate (Krebs Cycle compound) and acetoacetate (ketone body). There is a five-step process to this[2] which happens in liver cells and also the kidneys (Figure 1).

Tyrosinaemia Type I:

- Worldwide incidence of about 1 in 100,000 with a higher incidence in Norway and Canada and specifically in a region of Quebec where the frequency is as high as 1 in 700.[2]
- Originally the most severe type with high child mortality rate unless liver transplants were performed.
- Also known as hepatorenal tyrosinaemia.
- Results from a defective enzyme fumarylacetoacetate hydrolase (FAH).
- The toxic metabolite which accumulates and causes damage in liver and kidneys is succinylacetone.
- Tyrosine levels are typically only moderately raised, at around 250-500umol/l in untreated disease.[3]
- Drug treatment with Nitisinone (NBTC) has greatly improved outcomes[4] by effectively suppressing production of succinylacetone, although there is also an increase in serum tyrosine, making dietary treatment also an essential treatment.[5]
- Low protein diet with tyrosine and pheny-lalanine free amino acid supplements needed.

Figure 1: Catabolic pathway for phenylalanine and tyrosine



For full article references please email info@networkhealthgroup.co.uk

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Table 1: Recommended blood levels

Cohort	Recommended tyrosine (µmol/l)	Recommended Phenylalanine (µmol/l)
Unaffected Adult	30-120[6]	
Tyr Type I	200-400[5]	>40[6,8]
Tyr Type II	200-500[1]	>50[1]

Tyrosinaemia Type II:

- Incidence of about 1 in 250,000
- Also known as oculocutaneous tyrosinaemia or Richner-Hanhart syndrome.
- Less severe than Type I although there is no drug treatment available.
- Results from a defect in the enzyme tyrosine aminotransferase (TAT).
- Tyrosine levels are typically >1,200umol/L.[6]
- The symptoms develop from an accumulation of tyrosine itself, crystallizing in the cornea and skin.
- Neurological development can be affected with the potential for poor intellectual attainment.[7]
- Low protein diet, with phenylalanine- and tyrosine-free amino acid supplements needed

METABOLIC AND NUTRITIONAL GOALS OF TREATMENT

The aims of treatment are to achieve blood tyrosine levels within the ranges shown in Table 1, whilst optimising nutritional status.

WHAT ARE THE COMPONENTS OF THE DIET?

Protein substitutes

A phenylalanine- and tyrosine-free amino acid supplement is important to avoid protein deficiency and prevent muscle catabolism. There is a small range of products available in ready-to-drink form and in powders which can be flavoured. The supplements should be taken throughout the day to optimise metabolic control, achieving the most stable blood tyrosine levels.

Amino acid consumption is reported by people with IMD as the most difficult aspect of the diet.[9] Amino acids are bitter and acidic tasting; they can cause gastrointestinal symptoms and bad breath and the prescribed amount is usually a significant volume: 400mls/day in adults if taking a ready-to-drink version. The amount or volume of amino acids prescribed needs to account for inefficiencies in amino acid and protein metabolism and as much as 140% of the RNI for protein may be needed in total.[6]

Micronutrients are needed as per the relevant dietary reference values (reference nutrient intake) for age, gender and life stage. A highly restricted protein intake results in low intakes of vitamin B12, long chain polyunsaturated fatty acids (LCPUFAs) and essential fatty acids, as well as minerals such as iron, calcium and zinc. Micronutrients are present in the protein substitute products, although LCPUFAs may not be, making compliance with these products even more important.

Low protein foods

Naturally occurring low protein foods, such as fruit and vegetables and fats and sugars, should form the bulk of the diet. Low protein foods which are available on prescription (e.g. milk substitute, flour, bread, pasta, crackers and biscuits) are a good way to make the diet palatable, varied and energy balanced. Consistent energy intake is important, as catabolism could cause muscle breakdown and raise blood tyrosine levels.

Protein exchanges

People with tyrosinaemia need to restrict high protein foods (meat, fish, eggs, cheese, nuts, beans, soya and dairy) and follow a tailored diet with a specific number of protein exchanges.

One exchange = 1g protein, or an assumed 50mg tyrosine.

Natural protein, (i.e. phenylalanine and tyrosine) tolerance varies with age, severity of the disorder and size of the individual, as well as their life stage, gender and general health.

A certain amount of both tyrosine and phenylalanine will be needed to keep blood concentrations within range and prevent muscle breakdown. The balance between natural protein and

Table 2: Amount of food providing 1 tyrosine exchange or 1g of protein - a small sample[6]

Food	Amount for 1 exchange	Food	Amount for 1 exchange
Cows' milk	30mL	Jacket or boiled potatoes	50g
Single cream	30mL	Roast potatoes	35g
Double cream	60mL	Chips	25g
Yoghurt	20g	Broad beans	12g
Rice - boiled	45g	Peas (fresh, frozen and tinned)	15g
Rice - raw	15g	Spring greens (boiled)	55g

amino acids to meet overall nitrogen requirements is individualised and also may need adjustments over time to allow for growth, development and changes in health status, such as pregnancy.

MONITORING

Monitoring is encouraged to ensure both metabolic and nutritional goals are met. Home-based monitoring and clinic monitoring is done, thus people with tyrosinaemia may need encouragement to comply with treatment and testing.

Monitoring in adults with tyrosinaemia includes the following:

- Monthly dried blood spots for plasma tyrosine and phenylalanine.
- Annual or twice yearly nutritional bloods in clinic:
  - Plasma Amino Acid profile
  - Full blood count including haematocrit
  - Haematinics including serum ferritin, serum folate and serum B12
  - Adjusted calcium and, if available, zinc, selenium and copper

The nutritional deficiencies which are possible in IMDs are wide ranging and are more likely if someone follows a low protein diet, but is poorly compliant with their protein substitute. The nutritional deficiencies which may arise include protein deficiency, as well as vitamin, mineral and trace element deficiencies, such as anaemia and poor bone mineral density.

PHENYLALANINE SUPPLEMENTATION

On routine blood monitoring, patients with both Type I (NBTC treated) and Type II tyrosinaemia have been found to have low blood phenylalanine concentrations and needed supplementation.[10] Phenylalanine is an essential amino acid and deficiency can cause anorexia, skin rashes and, in the longer term, changes to skin and nails, lethargy, mental retardation, seizures and death. Phenylalanine monitoring is an essential part of treatment. If phenylalanine intake is insufficient then this amino acid will be rate limiting in bodily protein synthesis, potentially causing catabolism and thus raising tyrosine levels.

Recently published data from a group of children with Type I tyrosinaemia[11] suggests that morning blood phenylalanine levels are very different to afternoons; only 2% of fasting morning levels were under the treatment range, but in the same children 83% of non-fasting afternoon blood samples were below target range. Thus the timing of biochemical monitoring must be considered when interpreting data and making decisions about dietary control. The main concern raised is that, potentially, children or adults with tyrosinaemia may have periods of the day when phenylalanine levels are too low and this compromises growth, development or neurocognitive functioning. (The tyrosine levels were stable through morning and afternoon). The threshold to supplement with additional phenylalanine may need to be considered at a higher level in light of these findings.

TREATING POOR METABOLIC CONTROL

Raised tyrosine levels, due to low phenylalanine levels, can be addressed by supplementing with phenylalanine. However, increased tyrosine levels due to inadequate energy intake are usually addressed by increasing calories, specifically with carbohydrates, such as a sugary or glucose polymer drink. Raised tyrosine levels in the absence of catabolism may be addressed by reducing protein exchanges, but in all of the above scenarios, attention should also be given to compliance with taking the tyrosine and phenylalanine-free protein substitute.

PREGNANCY IN TYROSINAEMIA

There has been a small number of encouraging reports of successful pregnancies in tyrosinaemia and these include pregnancy whilst taking NTBC. In Type II tyrosinaemia in particular, blood tyrosine control needed to be stricter than usual for a successful outcome (100-200umol/L).[1] In practice, this means returning to a strict exchange system for counting natural protein and decreasing the number of permitted protein exchanges for the first and possibly second trimester.

By mid-gestation, the foetus needs more protein for growth and protein tolerance, and permitted protein exchanges may be more than double the original number at the start of pregnancy. Protein tolerance continues to increase throughout the third trimester.

Untreated tyrosinaemia in pregnancy can, but not always, result in poor outcomes[12] for the offspring.

Pregnancy and post-delivery triggers for metabolic imbalance include:

- the first trimester when energy intake may be difficult to maintain (if there is morning sickness);
- post-partum (involution of the uterus and a large release of endogenous protein);
- breastfeeding which imposes metabolic demands - however breastfeeding is strongly encouraged for people (mothers and babies) with metabolic disorders.

CASE STUDY - JANE: TYPE II TYROSINAEMIA

Jane has Type II tyrosinaemia which was diagnosed at age 7. She previously had a gastrostomy tube inserted for receiving her amino acid supplement. She is 32 years old, married, without children and works as a care assistant. Jane's medical history includes epilepsy, a cataract, dietary zinc deficiency, osteopaenia, low mood, miscarriages and, this year, she suffered from a fractured wrist.

Jane's diet

- Low protein diet (about 15-20g/day, she doesn't accurately count exchanges)
- Prescribed three times daily protein substitute - with poor compliance
- Tyrosine levels are rarely <700umol/L and often>1,000umol/L

Issues

- Jane moved house and changed GP which resulted in an incorrect prescription for her protein substitute and non-compliance for 12 months.
- There was an 18-month loss of contact with the patient by her metabolic clinic.
- Jane's diet became nutritionally inadequate since she was still following a low protein diet without taking her protein substitute.
- Jane's eyes became intermittently itchy, but it did prompt her to seek help from her GP.

The role of the dietitian

The role of the dietitian is collaboration with the patient to motivate and provide practical ways to follow the diet for tyrosinaemia. Another significant role is to ensure that all healthcare providers, especially prescribers, completely understand the disease, the treatment and the products involved.

Outcome for Jane

Jane is trying to increase her intake of her protein substitute and manages the full prescribed amount on working days, but less so on weekend days. She continues with her low protein diet. Jane's nutritional monitoring has increased in frequency, including monitoring of her bone health.

Conclusion

Tyrosinaemia Types I and II are conditions with low incidence; however, people with these conditions need careful consideration in their dietetic treatment. The evidence base is small for these conditions, but it is clear that for good outcomes, compliance with diet and monitoring is vital. For best functioning in adults, lifelong dietary treatment is needed.