NETWORK HEALTH DIGEST

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THE LOW-PROTEIN DIET IN PKU: ITS EFFECTS ON GUT HEALTH

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This article looks at how the low-protein diet for life in PKU affects the gut microbiome and gut health of patients.

Phenylketonuria (PKU) is treated with a very low-protein diet, necessitating specialist low-protein products to provide energy and variety. A protein substitute providing amino acids without the phenylalanine (Phe) which is neurotoxic to people with PKU is an essential requirement.[1] Currently in the UK, there is no pharmaceutical treatment available for individuals with PKU. The European guidelines for diagnosis and management of PKU, published in *The Lancet* in 2017, state that strict blood Phe control should be lifelong, based on a significant body of evidence describing poor neurological outcomes if treatment is stopped.[2]

A low-Phe diet consists of four main principles:

- Exclusion of high-protein/high-Phe foods, eg, meat, fish, eggs, cheese, bread, flour, pasta, nuts, seeds and aspartame.
- Measured amounts of Phe according to individual tolerance from food sources such as potatoes and peas (exchange foods).
- Replacement of most of the natural protein with a synthetic protein (protein substitute or medical food), usually with added vitamins and minerals.
- Use of very low-protein foods (exchange free) from fruits, some vegetables, butter, oil, sugar and manufactured low-protein special foods. All the foods for special medical purposes (FSMPs) are prescribed by the NHS and approved by the Advisory Committee for Borderline Substances. (The same applies to protein substitutes.)

The National Society for Phenylketonuria (NSPKU) undertook a survey of UK adults and children with PKU and half of all respondents (631 in total) were taking less than 10 Phe exchanges daily – equivalent to 10g protein per day.[3]

NON-STARCH POLYSACCHARIDES (NSP)

A comprehensive review of nutritional aspects of low-protein foods was undertaken recently (with comparisons to alternative or corresponding supermarket foods).[4] Some of the low-protein foods contained natural fibre sources such as apple flakes, but the main fibre sources added to low-protein bread and pasta were hydrocolloids: methylcellulose, guar-gum, hydroxypropyl-methylcellulose, inulin and locust bean gum. These hydrocolloids are common additives in food manufacturing, as they add texture and viscosity in food products. It is unclear about the physiological benefits of hydrocolloids in the intestine and their contribution to the gut biome and wider gut health.

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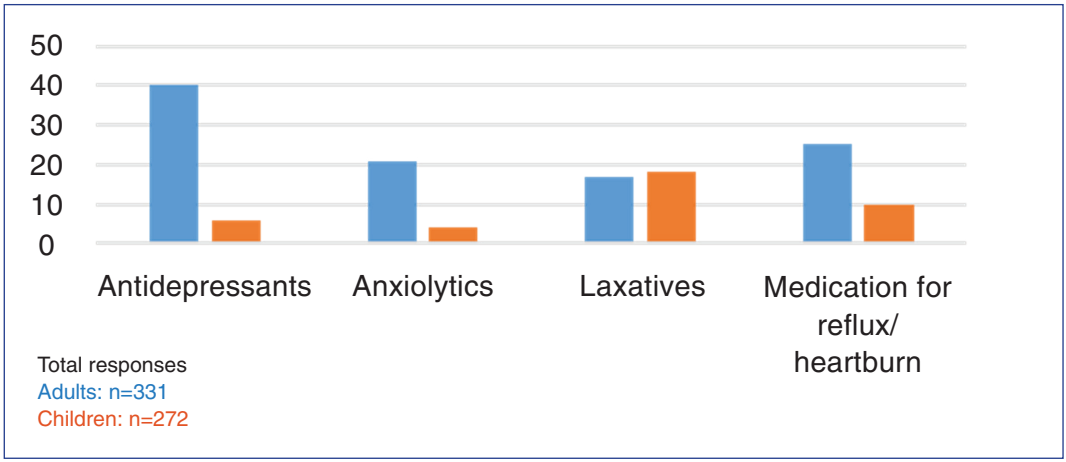
Figure 1: Medications in adults and children with PKU, as reported in the NSPKU survey on Living with PKU



Daly et al recently reported the results of in-depth dietary analyses from 48 children with PKU over the course of a three-year prospective longitudinal study.[5] Each child/carer contributed between nine and 12 semiquantitative dietary assessments or food frequency questionnaires. The subjects' fibre intake met 83% of the Scientific Advisory Committee on Nutrition's (SACN) reference value, with 50% contributed by the low-protein foods and their added gums and colloids.

The overall daily fruit intake of the children was low: the 11-year-olds and younger ate two portions a day (1200g/week) and the 12-year-olds and older ate only one portion daily (700g/week). Similarly, vegetable intake decreased over the time of the study period. At the start of the study period, the younger subject group averaged 660g vegetables a week and this decreased to 560g, whilst the older subject group of 12-year-olds and over started the study eating 900g vegetables a week, which reduced to 700g per week. In summary, most of the subjects were averaging one portion of fruit and one portion of vegetables each per day during the study period – clearly less than the government's recommended five a day. Thus, the variety of NSPs contributed by fruits and vegetables could be deemed limited in both range of NSPs and total volume of NSPs. There is no similar data published about adults following a low-Phe diet.

GASTROINTESTINAL PATHOLOGY

A literature review about PKU and ageing found no scientific literature on any direct link between PKU and gastrointestinal pathology,[6] but did state that a number of aspects of the PKU diet suggested a link, such as:

- inadequate fibre intake with potential link to constipation, and
- the acidity and osmolarity of some of the protein substitutes,[7] which may cause dyspepsia.

It may be speculated that in the long-term there could be additional consequences, as increasing dietary fibre can reduce risk of bowel cancer and diverticular disease.

Reports of gastrointestinal symptoms from the NSPKU survey of 631 patients and caregivers are in support of the above hypotheses.[3] Gastrointestinal symptoms were reported in 34% of children and adults, with 24% of adults taking medication for reflux symptoms and over 14% using laxatives (see Figure 1). This is higher than the prevalence of reflux in the general population of 22%,[8] as well as the prevalence of self-medicating for gastrointestinal reflux of 14% and constipation with laxatives of 10%.[9] Similarly, Burton et al reported higher prevalence of gastritis and oesophagitis in people with PKU compared with controls.[10]

MICROBIOME AND THE PKU DIET

Verduci and colleagues have recently published an in-depth review of the potential

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significance of the gut microbiome for IMD patients, many of whom are on a highly artificial diet and many of whom experience brain function disruption.[11]

The mechanisms of action of the gut microbiome alterations and their effects on the host's wider physiology are both still quite unclear. The diet contents, specifically NSPs, act as prebiotics, and these can be augmented by ingestion of pre-fermented foods known as probiotics. Changes in the gut microbiome have impacts more widely than just on the gut, as metabolites released by gut microbial metabolism appear to enter the host bloodstream, exerting positive and negative effects. De Oliveira and Verduci have both shown in primary research that the gut microbial populations of children with PKU are less diverse than healthy controls.[12,13] This could have significance, as many long-term conditions (non-inherited) have been linked to gut microbial populations. For instance, as well as risks of obesity, diabetes and cardiovascular disease (as cited in [11]) being likely to be influenced by the gut microbiome, there is research implicating gut microbes in brain function and mood.

The communications along the gut–brain axis are altered by gut microbiota. So far, evidence is not strong; for instance in murine models, or extremely low small study numbers. However, certainly one small study was elegantly designed and although it was in healthy volunteers, there may be some relevance to the PKU patient population. It took the form of a triple-blinded placebo-controlled randomised study of 40 subjects without mood disorder. Twenty received probiotics for four weeks and results showed that negative thoughts and sad mood were reduced compared with 20 subjects receiving placebo.[14]

NSPKU, PHE ANALYSIS AND RESEARCH INTO FRUIT AND VEG

Currently, metabolic dietitians in the UK agree that fruit or vegetables <75mg of Phe per 100g can be eaten without counting, those >75mgs/100g must be eaten in measured amounts (a Phe exchange is 50mg Phe). In this way, the UK-based patients with PKU are encouraged towards a diet featuring five portions of fruit and vegetables a day, without having to compromise their metabolic control.[15]

The NSPKU regularly undertakes costly Phe analysis of fruit and veg, to ascertain the exact role that 'new' vegetables may have in the PKU diet. For instance, ruby chard, kalettes, pea shoots and watercress have been looked at and, surprisingly, savoy cabbage had not been analysed before in the UK, so this was included.

If the diet of patients with PKU can be expanded in the range of vegetables permitted without counting, then this may contribute towards gut health in the PKU population. The NSPKU has contributed towards funding of a vegetable study currently underway in Birmingham, whereby children's metabolic control is compared when adding either vegetable or cereal/dairy protein exchanges.

CONCLUSIONS AND NEED FOR FURTHER RESEARCH

Firstly, after agreeing if a different or more varied gut microbiome in PKU patients is a desirable aim, we should ask, how can this be achieved? One way would be if low-protein

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food manufacturers invested in well-designed products that have the optimal content of NSPs. The consumers of low-protein foods will be using these products for their whole lives and the body of research suggests that a range of fibre sources is best.

Secondly, there is a little more work to do in Phe analysis of vegetables and other foods. Traditionally, fermented foods in the UK have been dairy based and contain significant protein, thus unlikely to feature in the PKU diet. However, a popularity for fermented vegetables such as sauerkraut, kimchi and similar products, might be compatible with the PKU diet – Phe analysis of these products is required to ensure this.

Thirdly, as the overall microbiome knowledge base builds, in the future it will be worthwhile to consider whether the knowledge of specific microbiome patterns of the PKU patient populations can also be built. Further work is needed.

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Questions relating to: *The low-protein diet in PKU: it's effects on gut health* *Type your answers below, download and save or print for your records, or print and complete by hand.*	
Q.1	Describe the aetiology of phenylketonuria (PKU).
A	
Q.2	Explain the treatment for life for PKU patients.
A	
Q.3	What are the main principles of a low-Phe diet?
A	
Q.4	Outline the issues surrounding the diet for life and gastrointestinal pathology.
A	
Q.5	What impact does the low-Phe diet have on fibre (NSP) intake.
A	
Q.6	Explain the possible link between the PKU diet and health via the gut microbiome.
A	
Q.7	What is the current thinking around fruit and veg intake for PKU patients?
A	
Q.8	Summarise the three areas of research required for a better understanding of the impact of a low-protein diet.

Please type additional notes here . . .

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