Adults with PKU and brain damage

Composition and management of a protein restricted diet

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Hovedoppgave

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"Much has happened during the last eight or nine years. Some changes came promptly, like in her skin and hair, and eye contact when brushing her teeth. But we waited long before noticing any reactions when we talked to her. But lately she has been escalating, repeating words and asking for things. Before the diet everything about her was negative, now she smiles and appreciates company. We can take her along on trips and to concerts." (Caregiver)

Acknowledgements

This study is the result of many years work on PKU. My interest for PKU started as a dietitian at the Department for Paediatrics at Rikshospitalet, and developed further in my present position as a consultant at The Centre for Rare Disorders.

The adults with PKU and brain damage are special to me. I have come to admire the individuals, the relatives and professional caregivers who manage this strict diet, motivated by the positive effects they experience.

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Summary

Phenylketonuria (PKU) is an inborn error of metabolism, due to a defective liver enzyme the conversion of the amino acid phenylalanine (phe) to tyrosine is not functioning. PKU was first described in 1934 by the Norwegian doctor and scientist Asbjørn Følling. Without treatment persons with PKU suffer permanent neurological damage and mental retardation. Today newborn screening programmes result in early diagnosis. Dietary treatment is started shortly after birth to prevent brain damage. The intake of phe is restricted by allowing only small amounts of protein in the diet. Requirements are met by taking a protein substitute containing amino acids, vitamins and minerals. Special low protein food secure energy requirement. For a person with brain damage due to late diagnosed PKU, dietary treatment may ease neurological and behavioural signs. Positive effects are reported for a majority of late diagnosed patients after treatment start. Literature on how these persons and their caregivers translate the advice and prescriptions from doctors and dietitians into an everyday diet is lacking.

The objective of the present study was to analyse the composition of dietary intake and describe how adults with PKU and brain damage manage the diet.

Methods:

An observational cross-sectional study was performed on 21 subjects with brain damage and adhering to a PKU diet: 8 men, 13 women; 26 – 66 years of age. Seven mildly retarded subjects living independently constituted group A. Group B consisted of fourteen severely retarded subjects needing continuous support and living in group homes. Data were collected by a four-day weighed food registration, a semistructured interview, blood samples and hospital charts. Descriptive statistics were used in analysing.

Results:

Serum phe was lowered by the diet to a median 472µmol/L. Median intake of selected nutrient: 1.02 g/kg protein (substitute and natural protein), 26 E% from fat, 15 E% from added sugar and 1.7 g/MJ of dietary fibre. The median intake of fruit and vegetables was 370g/d, comparable to the Norwegian mean intake. Fortification resulted in excessive intakes of micronutrients and high blood concentrations of folate and vitamin B_{12}. Other blood parameters as iron, zinc or magnesium, did not show the same effect despite high intakes. The intake was above estimated upper limit for a few nutrients, as iron.

Discussion and conclusion:

The study showed that adults with PKU and brain damage could manage a diet according to nutritional recommendations. However, this required great efforts and special considerations regarding food choice. The fortification of micronutrients is excessive and the doses and compounds used need evaluation in order to compose an optimal diet. The subjects in group A faced great challenges in adhering to the diet. Practical support was needed to maintain low serum phe levels and compose a varied diet. Managing the diet in group B depended on mutual agreement and a basic knowledge of PKU among the group home staff, this improved cooperation and supported the responsible caregivers. Caregivers in group B requested information and knowledge, whereas the psychological and emotional aspects of adhering were more important for subjects in group A.

This study has provided new knowledge that can prove important in regard to giving dietary advice and in organising follow-up of persons with PKU and brain damage. It may also stimulate an improved cooperation between local and central systems for treatment and support. The results of the present study also show that further investigation into the nutritional impact of a semi-synthetic diet is required.

Sammendrag på norsk

Fenylketonuri (PKU) er en medfødt stoffskiftesykdom. Årsaken er et ødelagt leverenzym omdannes ikke aminosyren fenylalanin (phe) til tyrosin som vanlig. PKU ble først beskrevet I 1934 av den norske legen og vitenskapsmannen Asbjørn Følling. Uten behandling vil personer med PKU utvikle varig nevrologisk skade og utviklingshemning. I dag fører screening program for nyfødte til tidlig diagnose. Diettbehandlingen starter kort tid etter fødselen for å forhindre hjerneskade. Inntaket av phe begrenses ved å tillate svært lite naturlig protein i dietten. Proteinbehovet blir dekket gjennom en proteinerstatning med aminosyrer, vitaminer og mineraler. Spesialprodusert lavproteinmat brukes for å sikre energibehovet. For personer med utviklingshemning på grunn av sen PKU-diagnose kan behandlingen lette nevrologiske og adferdsmessige tegn. Dietten kan ikke endre hjerneskader som alt er oppstått, men positiv effekt er rapportert for de flest personer som starter behandling sent. Det er mangel på litteratur om hvordan disse menneskene og deres hjelpere oversetter råd fra leger og kliniske ernæringsfysiologer til et daglig kosthold.

Formålet med studien var å analysere sammensetningen av kostholdet og beskrive hvordan voksne med PKU og hjerneskade mestret dietten.

Metoder:

En observasjonsstudie ble foretatt på 21 deltakere med utviklingshemning og PKU-diett: 8 menn og 13 kvinner, alder 26 – 66 år. Sju personer, med mild utviklingshemning, utgjorde gruppe A. Gruppe B besto av fjorten alvorlig utviklingshemmede personer med heldøgns hjelp i omsorgsboliger. Data ble samlet gjennom en firedagers veid kostregistrering, semistrukturert intevju, blodprøver og journaler. Deskriptive statistiske metoder ble brukt i analyse av data.

Resultater:

Medianen for serum-phe nivået var 472 µmol/L. Inntak av visse næringsstoffer viste en median på: 1,02 g/kg fra protein (erstatning og naturlig protein), 26 E% fra fett, 15 E% fra tilsatt sukker og 1,7 g/MJ kostfiber. Medianinntak av frukt og grønnsaker var 370 g/d, omtrent som norsk gjennomsnittsinntak. Forsterkninger ga svært høyt inntak av mikronæringsstoffer og høye konsentrasjoner i blod for folat og vitamin B_{12}. Denne effekten var ikke tilstede i blodprøvesvar for jern, sink eller magnesium, på tross av høye inntak. Inntaket av visse næringsstoffer, som jern, var over anbefalt øvre grense.

Diskusjon og konklusjon:

Studien viste at voksne med hjeneskade og PKU klarte å holde en diett som tilsvarte ernæringsmessige anbefalinger. Men dette var krevende og trengte spesiell omtanke i matvarevalg. Forsterkningen med mikronæringstoffer ga overdrevent høye doser, mengde og typer må vurderes videre for at dietten skal bli mer optimal. Deltakerne i gruppe A opplevde store utfordringer i å holde dietten. De hadde behov for praktisk hjelp for å holde serum-phe lavt og for å sette sammen et variert kosthold. For å holde dietten i gruppe B krevdes samforståelse og basiskunnskap om PKU blant ansatte i boligen, dette bedret samarbeidet og ga støtte til ansatte med hovedansvar. Omsorgsarbeidere i gruppe B ønsket informasjon og kunnskap, mens de psykologiske og følelsesmessige aspektene ved å følge dietten var viktigst i gruppe A.

Studien har bidratt med ny kunnskap som kan være viktig i diettrådgivning og i organisering av oppfølgingen av personer med PKU og hjerneskade. Den kan også stimulere samarbeidet mellom lokale og sentrale systemer for behandling og støttetiltak.

Resultatene viser også behov for videre forskning på ernæringsmessige følger av å leve på en slik delvis kunstig sammensatt diett.

Abbreviations and terminology

AA	Arachidonic acid, essential long chain polyunsaturated fatty acid, synthesised by elongation of linoleic acid.
Adherence	The extent to which a person's behaviour corresponds with agreed recommendations from a health care provider.
Alertness	Emotional state of attention and responsiveness, being aware of and interested in the surroundings.
BH4	Tetrahydrobiopterine, coenzyme for PAH.
BMI	Body mass index, kg/m^2.
BMR	Basal metabolic rate.
DHA	Docosahexaenoic acid, essential long chain polyunsaturated fatty acid, synthesised by elongation of α-linolenic acid.
Group home	Community based residence for disabled persons needing support. Group homes for mentally retarded persons with different diagnoses have replaced larger institutions. Staff members on duty have responsibility for one or more residents at the time. Four to six residents live in separate apartments constituting one group home.
ICD 10	International statistical classification of diseases administered and updated by the World Health Organisation (WHO).
Inborn error of metabolism	A genetic failure in cellular metabolism, often due to malfunction of specific enzymes. PKU is an inborn error of protein (amino acid) metabolism
LCPUFA	Long chain polyunsaturated fatty acids, from food or synthesised in the body by elongation of linoleic acid and α-linolenic acid.
LNAA	Long neutral amino acids, essential amino acids.
Mental retardation	Limitations or halt in childhood development resulting in general learning disabilities and intelligence quotients (IQ) below 70 (coded as F70-F79 in ICD10).
MUFA	Monounsaturated fatty acids.
Natural foods	Food and food products for general consumption, not specially produced or intended for protein reduced diets, containing normal amounts of protein.
Neurotransmitter	Chemical compounds transmitting signals between neurons.

Newborn screening	Pre-symptomatic blood test taken one of the first days of life, in order to detect and treat rare disorders like PKU.
PAH	Phenylalanine hydroxylase.
PAL	Physical activity level. The ratio of total energy expenditure divided by BMR, used for quantifying and comparing energy expenditure.
Phe	Phenylalanine.
Phenylalanine hydroxylase	Enzyme converting phenylalanine to tyrosine (genetically defined in the database Online Mendelian Inheritance in Man OMIM 261600).
Phenylalanine	Essential amino acid, not normally metabolized in PKU.
Phenylketonuria	An inborn error of metabolism caused by a deficiency of human phenylalanine hydroxylase. (coded as E70.0 in ICD 10).
PKU	Phenylketonuria
Protein reduced food	Special food products produced with little or no protein,intended as substitute for natural foods with higher protein content in protein reduced diets. Also called low protein food.
Protein substitute	Mixture of amino acids used in treatment of inborn errors of protein metabolism. For treatment of PKU, the protein substitutes are devoid of phe and often supplemented with minerals and vitamins.
PUFA	Polyunsaturated fatty acids, essential fatty acids.
Self-mutilation	Inflicting harm or injury on oneself, can be a symptom of mental or emotional disturbances. Often seen in untreated PKU.
Serum phe	Serum phenylalanine concentration, unit of measurement is µmol/L.
SFA	Saturated fatty acids.
Tyrosine	Amino acid. Tyrosine becomes an essential amino acid in PKU because the conversion of phenyalanine to tyrosine by PAH is impaired.

Contents

"Being on diet is like becoming a new person. You are happier, more energetic, more awake, - but you sleep better at night." (Subject)

1. Introduction

Phenylketonuria (PKU) is an inborn error of protein metabolism. The disorder is due to a defect in phenylalanine hydroxylase (PAH); a liver enzyme catalysing the conversion of the amino acid phenylalanine (phe) to tyrosine (1-4). High levels of serum phenylalanine and low serum levels of tyrosine are diagnostic hallmarks for this inborn error. These findings are associated with permanent damage to the central nervous system. A diet, containing only small amounts of natural protein restricts the intake of phenylalanine and can prevent mental retardation and physical damage from PKU. Presymptomatic diagnosis is verified in the national newborn screening programme allowing dietary treatment to be started within days or a few weeks after a child with PKU is born. This is preventing brain damage in persons with PKU (1-4).

1.1 Phenylketonuria, symptoms and development

PKU is an autosomal recessive disorder. Children, homozygotic, or compound heterozygotic, for a mutant PAH-gene are born symptom free, but develop symptoms if intake of dietary phenylalanine (phe) is over their individual tolerance. On a normal diet serum phenylalanine becomes elevated to toxic levels within a few days after birth (1). When the level of phenylalanine in serum is persistently over 400 μmol/L, treatment is started. Normal levels are below 100 μmol/L. If left untreated, the high phe levels are associated with permanent brain damage and neuropsychological problems (1).

The brain damage develops progressively if blood phenylalanine is high over time, and treatment should be started within the first two to four weeks of life to avoid permanent damage (1;3;5). The mechanisms of damage and at what concentration levels phenylalanine starts to be neurotoxic, are not fully understood. Phenylalanine competes with other large neutral amino acids (LNAA's) for the same carrier to pass

the blood-brain barrier. When PKU is untreated, there will be an imbalance of brain amino acids due to the high concentration of phenylalanine in serum (6;7). The resulting high concentration of phenylalanine in the brain is neurotoxic, leading to defects in neuronal growth and myelination. There will be a relative deficiency of tyrosine and tryptophane, leading to deficient production of the neurotransmitters dopamine, noradrenaline and serotonine (6-8).

Parents of untreated or late treated patients report that developmental deficiencies started to be obvious after a few months of life (personal communications from mothers to older patients with late treatment start). High blood concentrations of phenylalanine lead to formation of phenylketones, giving urine and sweat an unpleasant, musty odour. The tyrosine deficiency results in light pigmentation of the skin and hair, and eczema like skin lesions, due to lack of melanine production (1-4). Treatment will result in normalisation of body odour and pigmentation. If diet is started in infancy or early childhood, before the brain damage is fully developed, further aggravation may be halted. Even if treatment is started late in childhood or in the adult years neurological and behavioural signs may be eased (9;10).

Late start of dietary treatment will not alter the structural brain damage already present, but the biochemical changes, which occur in persons with PKU as a result of dietary intervention do have positive effects on the majority (7;9;11).

1.1.1 History of PKU

Phenylketonuria was first described in 1934 by the Norwegian doctor and scientist Asbjørn Følling. He found phenylketones in the urine of some mentally retarded children. He hypothesised that the symptoms were due to an inherited disease involving the metabolism of phenylalanine (2;12). This proved to be correct, and twenty years later Horst Bickel presented the first dietetic study from England, showing that a phenylalanine reduced diet lowered blood phenylalanine and relieved symptoms in PKU (13).

With treatment of PKU now available, it became important to screen babies for elevated phenylalanine (4). The first screening tools tested the babies' urine for phenylketones at about three months of age. During the 1960's blood screening became available. In Norway, newborn blood screening has been nationally available since 1975. Only one baby is known to have missed screening after this (2). During the last few decades mental retardation due to phenylketonuria has been almost eliminated in countries with well-running national screening programmes. Children are screened for PKU within a few days after birth, and if serum phenylalanine is above 400 µmol/L, dietary treatment is immediately started (1;2).

1.1.2 The PKU diet

The principles of the PKU diet are the same today as they were 50 years ago. The intake of phenylalanine is restricted to requirements for growth and individual tolerance (1;5). In keeping phe levels within therapeutic levels, the diet will be so restricted that the intake of protein, vitamins and minerals will be below human requirements if not otherwise substituted. According to Scriver & Kaufman the treatment is defined as a semi-synthetic diet, low in phenylalanine content and presumed to be adequate in other nutrients (1).

To secure nutritional needs a protein substitute, devoid of phe, is given. The substitute is usually enriched with vitamins and minerals, and is taken with meals, at least three times a day (14). The intake of phe, or natural protein, is measured in milligrams (5). In order to maintain serum phe levels within the therapeutic range, most adults with PKU tolerate 500 – 1200 mg Phe per day (equivalent to 10 to 25 grams of protein). The variation is mainly due to an individual degree of impaired phenylalanine hydroxylase activity (PAH) (1).

In a mixed Western diet, where protein consumed derives from a mixture of animal, cereal and vegetable sources, about 5% of the total protein weight will be phenylalanine (5). In fruits and vegetables the phenylalanine content is lower than in cereal or animal protein; usually between 3 and 4 % of the protein weight is

phenylalanine (15). Therefore fruits and vegetables are preferred sources for natural protein in the diet. Products consisting mainly of fat, starch and sugar are used to meet energy requirements, together with special protein reduced products. The available special products are flour or baking mixes, bread, pasta, cereals and milk substitutes. The diet requires special preparation. Lists on phenylalanine content food and special recipes are used in calculating phe intake and preparing meals (16;17).

1.1.3 PKU treatment

The annual incidence of PKU is 1 in 12–13000 live births in Norway. On average this means about five new patients annually. In Europe the average incidence is about 1 in 10000, varying from about 1 in 3000 in Turkey and 1 in 5000 in Ireland to less than 1 in 100 000 in Finland (1;2).

In Norway diagnosis and treatment of PKU is centralised to Rikshospitalet (2;18). Blood samples from about 58 000 newborns, in addition to routine blood tests from about 150 PKU patients on diet, are analysed every year for phenylalanine concentration. The diet is supervised by metabolic dietitians at Rikshospitalet. All patients with PKU born after 1970 in Norway are registered at the hospital. Patients born prior to 1970 are usually only registered if they are on diet or have followed dietary treatment at an earlier age. Of a total of about 160 patients older than 18 years of age, 70 were born in 1970 or before (personal communication from metabolic dietitian Åse Andresen Bradley at Rikshospitalet).

Adult patients on diet have annual or biannual ambulatory consultations at the Medical Outpatient Department at Rikshospitalet, irrespective if treatment started after newborn screening or later. For the severely retarded patients treatment and follow-up is performed in cooperation with local practitioners and group home staff, without visits to the hospital.

There is no exact cut-off level for when phenylalanine starts to be toxic, and treatment limits tend to differ somewhat between countries and metabolic centres

throughout the world. In addition it has been found that phe levels in the brain can be both higher or lower than the level measured in blood (1;6;7). Treatment levels for phenylalanine in serum are therefore mainly based on experience. The treatment levels have become more strict over time, especially for younger children and pregnant women with PKU. Consensus on optimal treatment levels is lacking, and in the United Kingdom and Germany the upper limits are graded according to age. In Norway the treatment recommendations for serum phe are uniform at all ages, the range is 120 – 400 µmol/L (18). This is about 2-6 times the normal non-PKU level. Individual consideration is taken in follow-up of adolescents and adults, and many adults on diet choose to have mean serum phenylalanine higher levels than 400 µmol/L. Up until the 1980'ies dietary treatment was usually stopped or relaxed in late childhood or adolescence. The current advice, in most Western countries and in Norway, is that dietary treatment should be lifelong (19-21). After childhood, as growth and building of body protein stores have come to a halt, the tolerance of dietary phenylalanine per kg bodyweight is reduced to maintenance levels.

Measuring the blood phe level is the only practical biological marker for treatment adherence.

1.1.4 Late treatment of PKU

That late diet start could relieve symptoms in PKU, was first described by Bickel in the early 1950'ies (13). The first treatment of PKU was on a two year old girl, who showed striking behavioural and neurological response as phenylalanine in the blood was reduced to about 800 µmol/L. A blind provocation with phenylalanine resulted in return of head banging, restlessness and loss of eye contact.

Results from this first trial and fifty years of clinical experience have proven the effects of dietary treatment. Dietary treatment for PKU in children diagnosed after newborn screening was never tried in a randomised controlled study, and today a randomised study would be judged as unethical (14).
Randomised studies on late treatment of older children or adults are also lacking.

There was, however, a study in Norway during the 1980'ies, using an A-B-A design. The two subjects in this study acted as their own controls. After months on diet, period A, the subjects underwent a blind provocation, period B. Caretakers were blinded in relation to the addition of phenylalanine to the previously phenylalanine free protein substitute. Period B lasted until symptoms of self-mutilation reappeared after five months, after wich dietary treatment was resumed for another 3 months of observation, the second period A. This trial showed that positive effects were apparent during treatment, and disappeared when normal protein intake was resumed. A report was published for one of the patients in 1994 (22). Details of the diet were documented by Motzfeldt, but never published (23). Both subjects have since been on permanent diet.

Later Fitzgerald et al planned a similar study on several patients in England (24). However, treatment effects were so positive for most subjects that provocation was deemed unethical. It was decided that treatment should be continued on a permanent basis for four out of five subjects, even if this weakened the scientific value of the study. Most other studies on adults with late treatment have been case studies, also without provocation (9;25;26).

1.2 Background for this study

Today most people with PKU, in the Western world, are treated from the newborn period, and PKU no longer leads to mental retardation (1;11). Of those who are retarded today, the majority are adults, born before newborn screening programmes were available. A few younger subjects may have been lost to screening or are born in countries where screening and dietary treatment are unavailable. Therefore dietary treatment of adults in need of special support will continue to be necessary.

Several trials and case studies have showed the effect of implementation of a low-phenylalanine diet in adult life on neurological and behavioural abnormalities (9;10;24-29). The improvements are often obvious both to the patient and caregivers.

The most important findings are reduction in self-mutilation, screaming and aggressive behaviour. Alertness and communication skills may be enhanced, and the musty odour will disappear. Most studies on late treated patients describe the neurological or neuropsychological changes while the nutritional or dietary aspects of the treatment are not discussed, apart from reporting that the dietary principles are important (9;24;25). The intention of this study is to focus on the nutritional or dietary aspects.

Literature on how patients with PKU and their caregivers translate the advice and prescriptions from doctors and dietitians into an everyday diet is lacking. The principles of how the diet should be composed to lower toxic phenylalanine levels are known (5). Most available studies report dietary effects on serum phe, without giving details on how the diet is composed. A few studies on diet and nutrition are available, mainly for children and adolescents treated after newborn screening (30-33). Most studies look at single nutrients such as protein (34-36), iron (37) or fat (38;39) in the PKU diet. There are studies postulating special nutrient metabolism in PKU and deficiencies or shortcomings of the diet (40-43). Most studies do not relate their findings to the food products chosen or total nutrient intake. This makes it more difficult to evaluate the need for changes in the composition of the diet, and what special advice patients need in order to manage the treatment.

In the present study the diet of one small subgroup of PKU, mentally retarded adults, is described. Perhaps the results reported can give further knowledge which will improve the diet and lead to better follow-up for people who need this special and restricted diet in order to achieve a better quality of life.

> *"It has been hard, and I am still not used to it. But it is fun to manage the diet and notice that it is helping me." (Subject)*

2. Aims and hypotheses

The objective of this study was to analyse the composition of the dietary intake and describe how the restricted diet is managed by adults with PKU and brain damage due to late diagnosis.

The study aims may be expressed more specifically with the following questions.

- Can adults on a PKU diet follow the same nutritional recommendations as the general population, and are persons with mild to moderate mental retardation able to manage the diet?
- Does the diet result in satisfactory nutritional status for a subgroup of adults with late diagnosis of PKU?
- Is the diet effective in reducing serum phenylalanine and is it associated with improvements of symptoms and clinical signs of PKU?
- How did patients and caregivers describe the strains of adhering to the diet?
- Is it possible to point out or define a minimum of prerequisites necessary for managing the diet of adults with mental retardation and PKU?

In order to answer these questions the following hypotheses will be tested.

1. Adults with brain damage due to late diagnosis of PKU will:
    a. have a nutrient intake in compliance with the Nordic Nutrition Recommendations 2004 (44);
    b. have a satisfactory nutritional status, measured by BMI and standard biochemical markers;
    c. have a mean serum phenylalanine complying to Norwegian treatment standards.
2. The degree of mental retardation or need for support will have no influence on dietary intake, markers for nutritional status, average phenylalanine levels or dietary adherence.

3. Ethical considerations

The majority of the subjects in this study were unable to give consent according to the Declaration of Helsinki (45). In accordance with international ethical standards and Norwegian legislation, medical research studies implying blood samples or other major interventions in the daily lives of people unable to give informed consent, have to be considered necessary for promoting health in order to be recommended. Recommendations for evaluation studies or descriptive studies on people or groups of people without full ability to understand and give consent are in principle more difficult to obtain than studies involving testing of drug therapy (46-48;48). Close relatives, caregivers or legal guardians can only give advice and not consent on behalf of their wards (48). This study was designed to meet the Norwegian ethical and legal standards (48-50). To minimise the burden on persons without the ability to consent, the blood tests taken in this study were restricted to those regularly taken at clinical controls for follow-up of PKU treatment.

All invited participants had some degree of learning disability or mental retardation; hence information and the form for consent had to be both easily read and reasonably short (Appendix 4 and 5). The instructions and information had to fulfil the standards of the Declaration of Helsinki (45). Thus two sets of information were distributed, one for the participants who could give consent themselves, and one for the caregivers, relatives and/or legal guardians who needed information and would be involved in the study (Appendix 5 and 6).

3.1 Approvals and recommendations

The study was recommended by the Regional Committee for Medical Research Ethics on the 14th of March 2006 (Appendix 1). Approval was granted provided that it would interfere minimally with the everyday life of subjects unable to give informed consent (14 of 21 participants).

In order to use blood samples for research purposes from these patients, it was necessary to apply for a bio-bank consent according to the Norwegian Bio-bank Act (49). This authorisation was given 3rd of April 2006 (Appendix 2).

As the author and the main tutor are both employed at Rikshospitalet, the study was reported to the commissioner for privacy protection (personvernombudet) at the hospital. Approval was given on the 8th of March 2006 (Appendix 3).

> *"He has had bad periods with aggressive behaviour also when on diet, especially during holidays. Some improvement has come because we're better in managing the diet, other changes are due to better routines in the group home." (Caregiver)*

4. Subjects and methods

4.1 The sample

In this study all adult PKU patients in Norway, born prior to 1988, known to have mental retardation and following a diet for PKU were invited to participate.

- Criteria for inclusion: People with PKU over 18 years of age, having mild to profound mental retardation, and adhering to PKU treatment according to the definition beneath.

- Criteria for exclusion: People with PKU over 18 years of age, without mental retardation, or not adhering to PKU treatment according to the definition beneath.

For inclusion in this study adherence to treatment had to be defined. People were defined as adherent if they claimed to be following a PKU diet and if Rikshospitalet received blood samples for routine control of serum phenylalanine at least 2-4 times a year. In addition, all participants should have been in contact with the Centre for Rare Disorders to receive advice or information on living with PKU.

The total sample consisted of 27 persons; 26 were diagnosed late (age at diagnosis was 1 to 30 years of age). One subject with mild mental retardation of unknown origin was also invited. This person was diagnosed with PKU and treated after neonatal screening. Of the 27 invitations distributed, 21 positive answers were returned, resulting in a response rate of 78%. Table 1 shows the response rate in the different groups of eligible participants.

The participants in the present study had been on diet for at least one year. Treatment had been judged as beneficial and was maintained on a permanent basis at the time of the study. For one patient, however, evaluation of one years treatment showed both

positive and negative behavioural effects. Decision on further dietary treatment on a permanent basis was scheduled to take place a couple of months after this study.

Table 1: Description of participants

	Group A		Group B		Total
	Men	Women	Men	Women	
Eligible	3	8	9	7	27
Participants	1	6	7	7	21

4.1.1 Subgrouping of sample

The participants were divided into two groups, according to everyday function, see table 1.

- Group A: Subjects managed most skills needed for independent and everyday self-care, all had adequate communication skills. The subjects received limited support from parents and/or community. They lived alone, with their spouse or with parents. The degree of mental retardation in group A corresponded to mild or moderate mental retardation in the International Classification of Diseases (ICD10) by The World Health Organisation (51). Persons belonging to this group were able to give informed consent (45). A total of eleven were invited, and seven consented to participate.

- Group B: Subjects lived in staffed community group homes and needed continuous support. Some had simple verbal skills. The degree of mental retardation in subjects in group B corresponds to severe or profound mental retardation in the ICD10 classification (51). Nobody in this group was able to give informed consent. In group B fourteen out of sixteen participated. Two group homes had each two residents with PKU, giving a total of twelve group homes represented in the study.

4.2 Study design

The study was an observational cross-sectional study on adult patients with PKU.

Together with the invitation and form for consenting to participation (Appendix 4), the subjects received two information letters, one aimed at the participants themselves and one for relatives or caregivers, group home staff or legal guardians (Appendix 5 and 6). Additional information regarding the study was given on request by telephone. A reminder was sent after 10 days to those who had not responded. Nine group homes were contacted by telephone to secure that the information had been considered by responsible staff.

Data were collected by a semistructured interview, a four-day weighed food recording, blood samples and hospital patient records.

Seven subjects were interviewed in connection with ambulatory consultation at Rikshospitalet. They received information on food registration and took blood samples at the same visit. For the additional 14 subjects, the author visited the group homes for interviewing, information on food registration and blood sampling.

4.2.1 Semistructured interview

The interview was a semistructured survey, prepared and administered by the author (Appendix 7). It was designed with an interview guide based on the model of Monica Dalen (52). Prior to the study the interview was tested on colleagues for determination of specificity, comprehension and time required.

Survey topics were socioeconomic background, history of diagnosis, organisation of the diet work, phe-tolerance and treatment effects.

All subjects in group A were interviewed personally, and for subjects in group B caretakers were interviewed. Relatives, mostly mothers, gave additional information related to eight subjects, four from each group.

The semistructured interview functioned mainly as a qualitative method in order to gain better insight and understanding of the subject's personal experiences (52;53). In this study, interview was used as a supplement to quantitative methods. It was known that some participants in the study might have difficulties in reading and answering written surveys. The interview process gave the subjects the possibility of answering in their own words and also to have questions reformulated and explained in different ways.

Interpretation and analysis of the interviews were done in two different ways. Questions with fixed answers were quantified and could be used in statistical analyses. Other questions were open, and some were categorized and ordered into qualitative groups and used in frequency distributions.

Reports on clinical effect or changes related to dietary treatment were collected retrospectively by means of interview or hospital patient records.

4.2.2 Registration of food intake for four days

Intake of food and drink was registered in four subsequent days, within two weeks after the interview. Verbal and written information was given on how to measure and document food intake (Appendix 8). Intake was recorded in a booklet designed especially for this study (Appendix 9). This method was chosen because the participants and their helpers already were accustomed to weighing and measuring food. Taking a dietary history or 24-hour recall was deemed more complicated as the subjects in group B usually had at least two different caregivers responsible for preparing and serving meals during the day. Caregivers were responsible for all recordings in group B. Four subjects in group A received extra support from family or community workers in recording their food intake. The remaining three subjects had contact with the author at least once a day during the recording period. All participants were contacted by telephone at least once during the registration, and the author could be reached by telephone at any time.

Food was weighed on digital scales, with 1 gram increments. Drinks were weighed or measured in decilitres. All but two subjects were used to weighing food, either for measuring prescribed amounts of natural foods and protein substitute, or as a method in cooking and baking. The registration booklets were returned by mail, in pre-stamped envelopes.

Food and drink registration was recorded and calculated in a Norwegian nutrient calculation software "Mat på data 4a" (54). This programme uses the official Norwegian food composition tables from 2001 (55). The food composition tables were supplied with data on special dietary products, information having been collected from producers. Phenylalanine content was calculated according to Norwegian PKU lists (16). The lists are based on the average amino acid distribution of protein in food products and official analyses from different countries and they are adjusted for the protein content of Norwegian food products (55).

One subject used an unfortified protein substitute and had to take additional supplements of vitamins and minerals. These supplements were calculated as part of the protein substitute. Vitamin B_{12} content in food was not included in the program "Mat på data", thus only vitamin B_{12} contribution from protein substitutes were calculated.

Intake of fruit and vegetables was calculated as the total intake of juice, fruit, berries and vegetables. Potatoes, potato products and dried legumes were not included, as they contain more protein and are used in a different way in the diet (16;17). This is in contrast to the general Norwegian dietary recommendations where potatoes are included in the recommendation of at least five portions or 750 g/d fruit and vegetable intake (56).

4.2.3 Blood sampling and analyses

Eight subjects had blood samples taken at the laboratory at Rikshospitalet. The eleven others had blood samples taken at a local hospital or laboratory. For these subjects

information on blood sampling was distributed at visits to the group homes. This consisted of an information letter for the local practitioners and/or laboratory staff, two requisition forms and an instruction on handling the blood samples (Appendix 10-12). The information was prepared in cooperation with senior consultant Per Mathisen, MD, responsible for follow-up of adult PKU patients at the Medical Outpatient Department, and senior consultant Berit Woldseth, MD, Department of Medical Biochemistry, both Rikshospitalet.

All blood samples were taken as a part of the clinical follow-up program for the subjects. Requisitions were signed by doctor Per Mathisen, and copies of the answers were forwarded to the author. As the majority of subjects could not give consent, secondary blood samples could only be taken if deemed medically necessary at the time. As a result some blood samples were lost, due to improper procedures or because they were unsuccessfully analysed. For two subjects, venous drawing of blood could only be done in anaesthesia, and this was only done when requested for medical reasons and dental care.

Missing data from blood analyses are due to these limitations.

Amino acids

Amino acids in blood were analysed at the Department of Medical Biochemistry at Rikshospitalet. The blood was drawn into heparin glasses after overnight fasting. It was then centrifuged and frozen within thirty minutes. Amino acids were analysed by ion exchange chromatography with ninhydrine colouring on an Amino Acid Analyser Biochrom 30, from Biochrom Ltd, Cambridge, United Kingdom (personal communication from Berit Woldseth).

Other blood samples

Blood samples for the amino acid test, iron status, blood lipids, renal function, albumin, prealbumin, magnesium, zinc, vitamin B_{12} and folic acid were drawn simultaneously. All samples were planned to be analysed at the Department of

Medical Biochemistry at Rikshospitalet; however for two subjects the blood samples, apart from the amino acid analyses, were analysed at local hospitals. Analyses were done according to standard procedures at the laboratory, described in The Laboratory Handbook (57). For most analyses in this study the laboratory used accredited methods.

Routine phenylalanine tests

Routine tests for serum phenylalanine in capillary blood, obtained by finger pricking, were analysed by the Neonatal Screening Laboratory at Rikshospitalet. After overnight fasting sampling was done by the parents, nurses in group homes or by local laboratory staff. Microtainers with 0.5 ml blood were sent by mail to the Screening Laboratory. Phenylalanine in the serum was determined fluorimetrically after enhancement of the fluorescence by a phenylalanine-ninhydrin reaction in the presence of a peptide, leucylalanine. This is a specific and sensitive method, first described by M. W. McCaman in 1962 (58)

4.2.4 Data on treatment history

Retrospective data on blood phenylalanine levels and treatment history were found in hospital charts, or communicated via the interviews.

4.2.5 Statistics

Descriptive statistics were done on socioeconomic background, diagnosis, anthropometrics and treatment history.

Statistical analyses were done on parameters from interview, blood tests and food intake and the following methods were used.

For categorical data: frequency distributions and cross-tabulations.

For continuous data: descriptive statistics (median, quartiles of the median, range, mean and standard deviation), Mann-Whitney U-test, Spearman's rho rank correlation.

The study was done on a small number of participants, and there was great variability between subjects. Therefore the median and the inter-quartile range were chosen rather than the mean to describe variability in the total sample and when group A and B were described as separate entities (59;60).

Statistical calculations and analyses were performed on Statistical Package for the Social Sciences (SPSS), version 13.0 for Windows.

4.2.6 Economy

All mail to or from participants was paid by the Centre for Rare Disorders at Rikshospitalet. The visits from the author to group homes were followed by meetings with the staff, and these were also financed by the Centre for Rare Disorders.

As the study was organised in connection with ordinary outpatient follow-up, blood tests and analyses were paid through the Norwegian social security system.

4.2.7 Feed-back to participants

After the food registrations were calculated and evaluated, the subjects or their caregivers received individual feed-back and dietary advice from the author. Subjects in need of sustained dietary changes were referred to metabolic dietitian for further advice.

Treatment changes indicated by blood test results were handled by dr. Per Mathisen or the local general practitioner.

5. Results

5.1 Subject characteristics

All subjects in group A (n=7) managed everyday meals, Table 2. Most of them had difficulties in reading recipes; all had difficulties in planning and organising their diet. Three received daily dietary support for controlling amounts, preparation or planning of meals and for acquisition of special food products and protein substitute. Two lived in the same house as their parents, but in separate apartments. Three were married, but the spouses did not have sufficient resources to give substantial support in the dietary work.

Table 2: Background data on participants

	Group A n=7	**Group B** n=14
Ability to consent	Yes	No
Function in everyday life	Independent living. Limited support from family or society.	Living in staffed group homes. Continuous support.

In group B (n=14) everyone was dependent on the staff for preparation and serving of meals, Table 2. Eight subjects needed soft textured food, due to teeth and denture problems or an inability to chew. Two subjects were unable to eat or drink without help, and another four needed some assistance during meals. Four subjects used wheelchairs; four more had restricted walking function.

Some could make restricted choices related to meals, for example in choosing between two alternatives like: coffee or tea, PKU-milk or juice. Most subjects in group B were unable to differentiate their own food from food belonging to others, and “stealing” or snatching accessible food was a problem in some group homes. Two subjects had very selective food preferences, making variation and presentation of new food difficult. Seven persons took initiative to obtain food or drink (mainly

coffee) without being encouraged in advance, and four had some verbal communication skills.

Table 3: Treatment history

		Group A	Group B	Total	P
Age, years	N	7	14	21	
	Mean (SD)	39.3 (9.4)	50.1 (7.5)	46.5 (9.5)	
	Median (Q1-Q3)	42 (28 – 48)	49 (45 – 53.5)	48 (42 – 51.5)	0.02
	Min-max	26 – 51	36 – 66	26 – 66	
Age at diagnosis, years	N	7	12	19	
	Mean (SD)	2.4 (1.2)	6.6 (8.3)	5.1 (6.8)	
	Median (Q1-Q3)	2.5 (2 – 3)	4 (1.6 – 9.8)	2.5 (2 – 5)	0.43
	Min-max	0.1 – 4	1 – 30	0.1 – 30	
Age at first treatment, years	N	7	14	21	
	Mean (SD)	8.5 (17)	27.9 (17.2)	21.4 (19.2)	
	Median (Q1-Q3)	2.5 (2 – 3)	36 (3.8 – 41.8)	26 (2.5 – 41.5)	0.07
	Min-max	0.1 – 47	1.5 – 45	0.1 – 47	
Current diet period lasted, years	N	7	14	21	
	Mean (SD)	20.8 (13.5)	15.7 (11.7)	17.4 (12.2)	
	Median (Q1-Q3)	25 (2.5 – 31)	10 (9 – 22)	18 (9 – 26)	0.32
	Min-max	1 – 35	1.5 – 41	1 – 41	
s-phe prior to treatment, µmol/L	N	7	14	21	
	Mean (SD)	1772 (423)	1669 (320)	1704 (350)	
	Median (Q1-Q3)	1540(1500-2376)	1591(1521-1885)	1591(1497-1882)	0.91
	Min-max	1471 – 2400	1131 – 2468	1131 – 2468	
Mean s-phe one year prior to study, µmol/L	N	7	14	21	
	Mean (SD)	642 (254)	489 (122)	540 (186)	
	Median (Q1-Q3)	596 (456 – 795)	432 (382 – 633)	472 (417 – 625)	0.08
	Min-max	432 – 1143	352 – 717	352 – 1143	
s-phe at study, µmol/L	N	7	14	21	
	Mean (SD)	665 (336)	474 (158)	538 (242)	
	Median (Q1-Q3)	600 (389 – 853)	505 (336 – 621)	542 (373 – 635)	0.17
	Min-max	293 – 1310	146-731	146-1310	

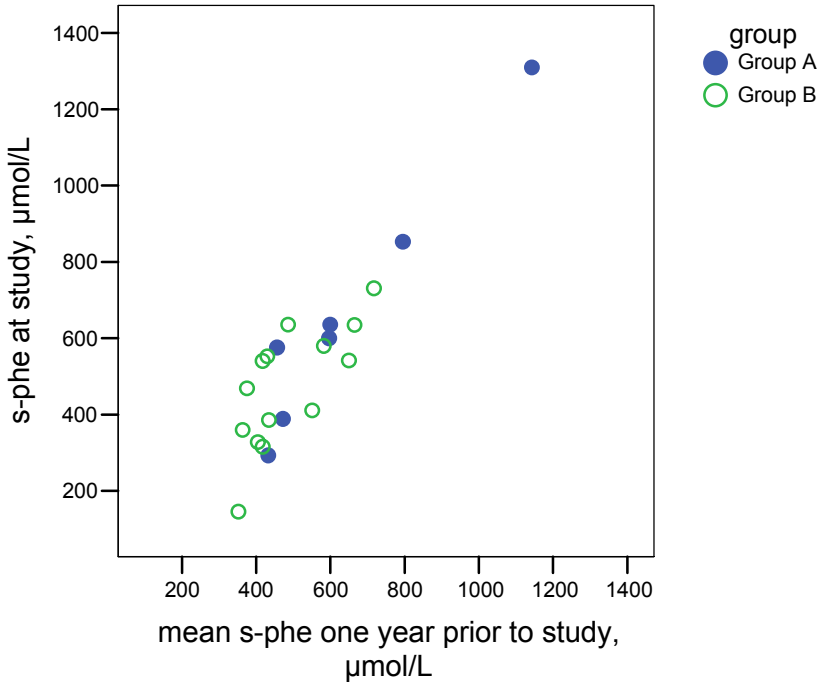
The Mann-Whitney U-test is used for differences between group A and B
P = p-value for difference between group medians
Q1 = first quartile or 25th percentile, Q3 = third quartile or 75th percentile

Subjects in group A were significantly younger than subjects in group B, Table 3. The age at diagnosis or first treatment, serum phenylalanine at diagnosis or one year prior to the study, did not differ significantly between the groups.

Each individual tended to have fairly stable values of serum phenylalanine; single tests could, however, be higher or lower than the personal average. Rank correlation

for mean serum phe one year prior to study and serum phe at the study (just before or after the food recording) gave a Spearman's rho correlation of 0.83 ($p<0.01$), Figure 1. The subjects maintained the same mean serum phe levels also over a longer period, with a Spearman's rho correlation of 0.82 ($p<0.01$) between serum phe levels one year prior to study and two years prior to the study.

Figure 1: Association between serum phe at the study and mean serum phe level one year prior to the study



5.1.1 Socioeconomic background

All subjects received social security benefits for the disabled. All but one received extra welfare money for diet expenses.

Six in group A and one in group B had part time work, all received some supervision. Three of these were employed in sheltered workshops. Ten subjects in group B attended day-care units for the mentally retarded. In workshops and day-care units, dietary needs were taken into consideration at mealtimes.

Ten persons, three in group A and seven in group B, took part in afternoon leisure activities at least once a week. In group A three subjects had no regular or organised leisure activities.

5.2 Effect of treatment

Reports on changes in selected symptoms and signs related to diet and reduction of s-phe levels were collected retrospectively from the interviews. The frequencies of the most common variables for clinical effect in late treated patients with PKU are listed in Table 4. In addition improvement in neurological signs like better balance and gait, reduced tremor or spasticity were reported for ten (47.7%) in the total sample; or three (42.9%) in Group A and seven (50%) in group B.

Table 4: Reported effects after starting dietary treatment

	A (n=7)	B (n=14)	Total (n=21)
Self-mutilation[a]	1 (14.3%)	10 (71.4%)	11 (52.4%)
Agitation[b]	2 (28.6%)	12 (85.7%)	14 (66.7%)
Alertness[c]	6 (85.7%)	8 (57.1%)	14 (66.7%)
Hair[d]	3 (42.9%)	11 (78.6%)	14 (66.7%)
Odour[e]	3 (42.9%)	11 (78.6%)	14 (66.7%)

[a] reduction in self-mutilation and self stimulating behaviour
[b] reduced pacing, screaming and hitting others
[c] improved awareness of surroundings, attention and concentration
[d] darkening of hair
[e] musty body odour disappeared

Other treatment effects were better skills in communication, defined here as own speech or understanding, verbal and non-verbal response to instructions or signs of recognition/differentiation between people. Treatment effects resulting in increased social participation and appreciation of contact with others were also reported. Communication skills and social participation are counted together as the terms seemed closely related when reported from informants. Positive effects were reported for fourteen (66.7%) subjects; five (71.4%) in group A and nine (64.3%) in group B.

Increased initiative, defined as starting activities or making requests without prompting from others, or uttering signs of likes and dislikes, were reported for six (85.7%) in group A and 7 (50%) in group B, or for 13 (61.9%) in the total sample.

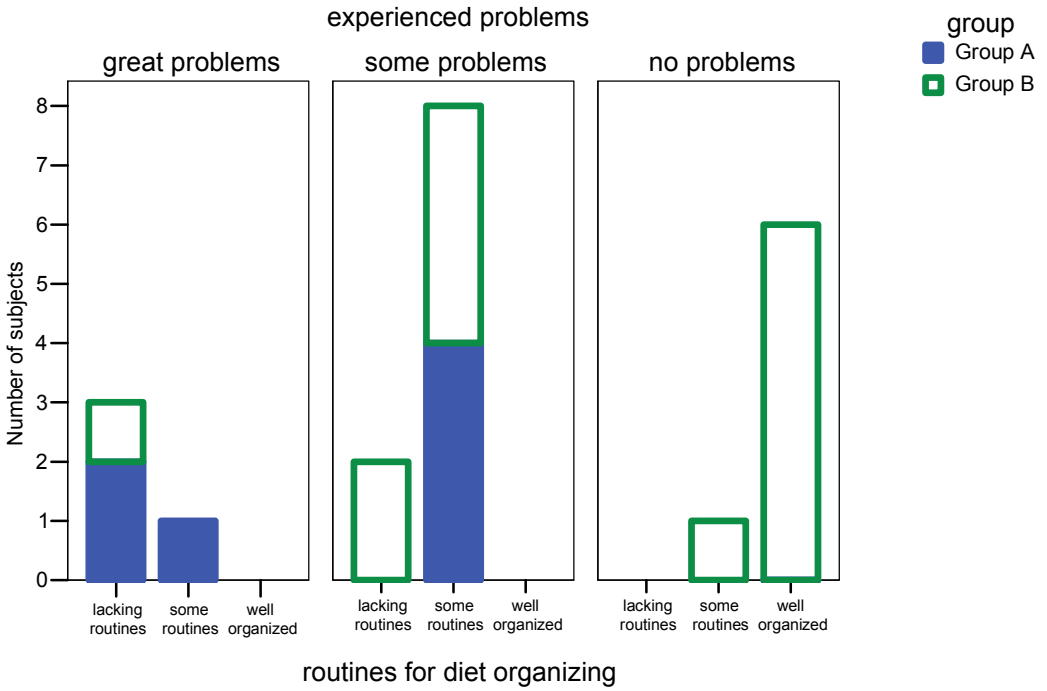
Subjects in group A reported personal experiences after having started or resumed treatment as adults. Subjective effects of treatment were reported as better sleep at night by five persons (71.4%) and the same number meant that adherence increased their self-confidence or mastering abilities. Three (42.9%) reported that they had less anxiety and psychiatric problems when on diet.

5.3 Support and diet organisation

Information about support, effectiveness of everyday routines and the experience of problems in adherence were categorized from the interviews. The subjects in group A who did not receive regular assistance from community or parents, had fewer working routines for food preparation and for acquisition of special foods and protein substitute. The subjects in group A expressed practical and emotional problems in adhering to the diet. Three subjects in group B lacked effective routines or because written procedures and menu lists were lacking not followed, Figure 2. No subject in group A felt that following the diet was problem free, and nobody managed to keep routines as stringent as those living in group homes.

The effectiveness of dietary routines and the degree of experienced difficulties in adhering to diet was associated with the subject's individual average serum phe levels. Figure 3 shows that subjects with serum phe below the median for the total group, tended to have more effective routines and experienced fewer problems than subjects with average serum phe over the median.

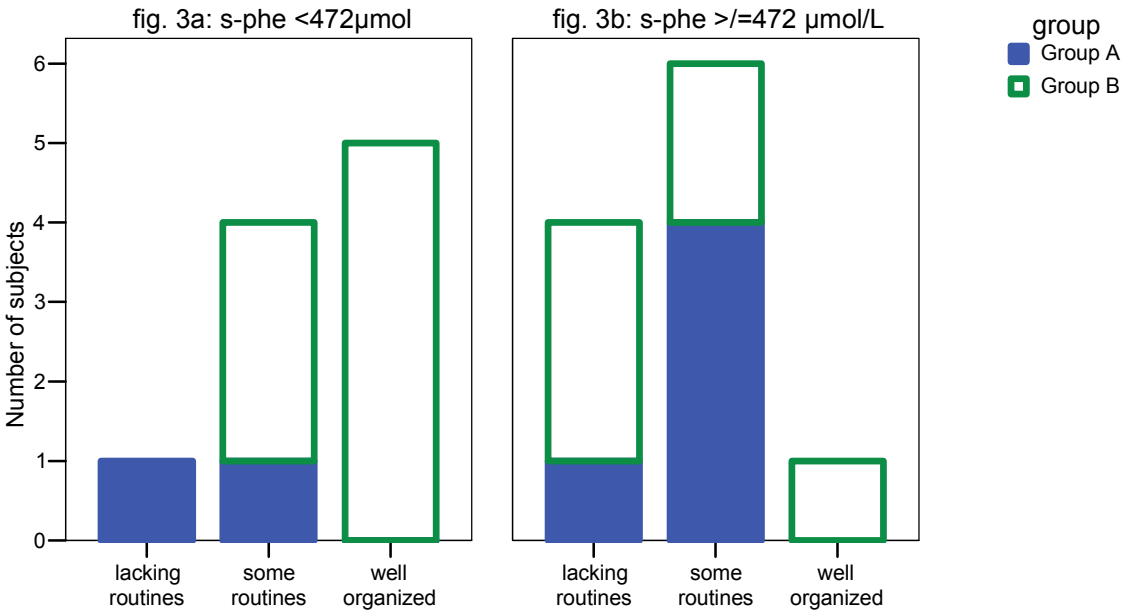
Figure 2:Co-variance of routines and experience of problems in adherence to the diet



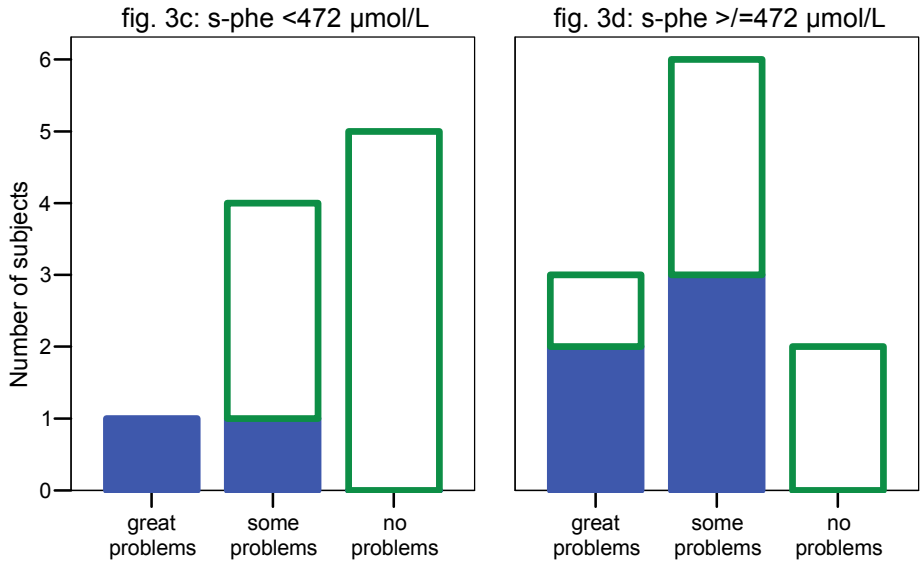
"I wished there was another person on diet close to where I live, you need to talk to somebody." (Subject)

Figure 3: Association between phe level and routines and experience of problems in adherence to the diet

Routines for diet organisation



Experience of problems



Serum phe <472µmol/L: n=10
Serum phe ?472Mmol/L: n=11

5.4 Blood samples

Blood tests were collected from 17 subjects. Amino acids in serum were analysed for 15 subjects. Results from amino acid analyses are shown in Appendix table 1.

As anticipated, all subjects had high phenylalanine. Apart from this only small discrepancies were observed, mostly due to mistakes in handling: in some samples the time before centrifugation or freezing might have been too long and for two subjects serum was used instead of heparin blood.

A high glycine value was seen in two subjects, but valine was normal for all 15 subjects.

Tyrosine was in the normal range (28 to 76 µmol/L) for all but one who had 100 µmol/L. This person took a protein substitute based only on essential or large neutral amino acids (LNAA). This substitute contained higher amounts of tyrosine and tryptophan than other substitutes.

Results from other blood tests analyses are shown in Appendix table 2.

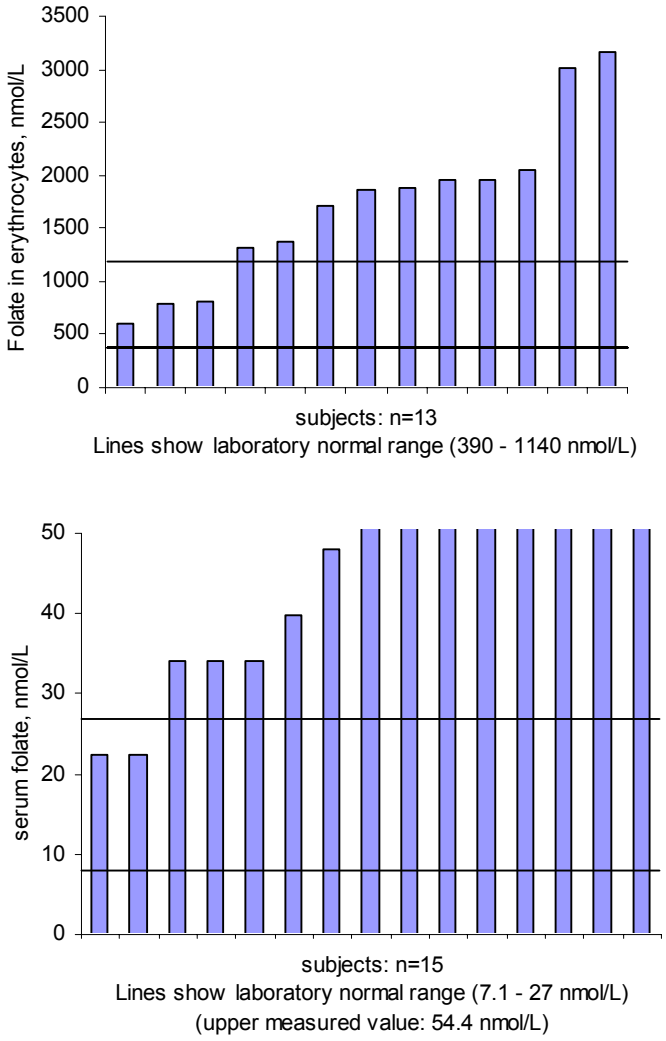
Apart from folate, most results were within normal limits for age and sex. Folate in erythrocytes was beyond upper normal limit for the laboratory (1140 nmol/L) for 10 of 13 subjects. For serum folate 13 of 15 analyses were beyond the upper normal limit (27 nmol/L). Eight had values over the highest measurable value (54.4 nmol/L), Figure 4. Folate in serum correlated significantly to folate intake; Spearman's rho correlation 0.59 ($p=0.02$).

Vitamin B_{12} levels were generally high, five out of 17 exceeding the upper normal limit (10 pmol/L). One person had low serum vitamin B_{12} (110 pmol/L).

Iron, ferritin, transferrin and transferrin saturation in plasma were generally in the low normal range. All subjects had normal levels of haemoglobin. One person had signs of iron deficiency: ferritin 9 µg/L (WHO cut-off value <15µg/L), iron 7 µmol/L

(normal range 9-34 µmol/L) (44). Another subject had a low ferritin 11 µg/L (WHO cut-off value <15µg/L), but other parameters were in the lower normal range.

Figure 4: Folate in erythrocytes and serum



Albumin was normal for everyone, but prealbumin was just below the normal limit for four subjects, and unsuccessfully analysed for one. One female had a low prealbumin of 0.16 g/L (normal range 0.23 – 0.39 g/L).

Median total cholesterol for the total sample was 4.6 mmol/L. In group A, one person had a total cholesterol over 5 mmol/L (6.5 mmol/L), this person also had high serum

triglycerides. In group B three subjects had a total cholesterol over 5 mmol/L (5.5, 7.8 and 5.7 mmol/L), one also had high triglycerides.

5.5 Intake of energy and nutrients

The food registrations were done for 19 subjects. Two subjects in group B did not take part in the registrations due to lacking staff resources. The registrations were marked by the subjects or their helpers as reflecting habitual intake on days with usual activities. One person in group A took part in a social gathering in the recording period; all food was recorded and was included in the calculations. In group B one subject became ill during the recording period and one day of food registration was subsequently omitted from calculations for this subject.

There were no significant differences between group A and B in median daily intake of energy, macronutrients, dietary fibre or fruit and vegetables, Table 5. Neither were there any significant differences between group A and B when intake was expressed as energy density, energy % (E%), Table 6.

5.5.1 Energy intake and expenditure

The subjects had a median energy intake of 8.8 MJ/day, ranging from 6.4 MJ to 13.7 MJ. Goldberg's cut-off limits to identify under-recording of energy intake were used to validate the food registrations (61). Estimations of basal metabolic rate (BMR), based on height, weight, gender and age, were done in order to calculate the physical activity levels (PAL) from reported energy intake. The equations of Schofield and World Health Organisation were used to estimate BMR (62). The mean PAL value for the 19 registrations in this study was 1.39, just above the cut-off limit of 1.37 for groups of twenty subjects given by Goldberg (61). The median PAL was also 1.39 with an interquartile range (Q1-Q3) of 1.27 – 1.47, and a total range of 1.17 – 1.75.

Table 5: Intake of main nutrients, added sugar, dietary fibre, fruit and vegetables

		Group A	Group B	Total	P
	N	7	12	19	
Energy, MJ/d	Mean (SD)	8.6 (0.7)	9.8 (2.3)	9.4 (1.9)	
	Median (Q1-Q3)	8.2 (8.0 – 9.1)	9.3 (8.0 – 12.2)	8.8 (8.0 – 10.1)	0.43
	Min-max	7.9 – 10	6.4 – 13.7	6.4 – 13.7	
Protein, g/d	Mean (SD)	67.1 (18.6)	79.9 (11.4)	75.2 (15.4)	
	Median (Q1-Q3)	72 (54 – 81)	79 (70 – 87)	77 (68 – 85)	0.17
	Min-max	33 – 87	65 – 106	33 – 106	
Fat, g/d	Mean (SD)	58.0 (13.8)	71.0 (20.3)	66.2 (18.9)	
	Median (Q1-Q3)	65 (47 – 68)	73 (52 – 85)	65 (48 – 78)	0.20
	Min-max	37 – 76	42 – 102	37 – 102	
SFA, g/d	Mean (SD)	20.7 (8.1)	25.1 (8.8)	23.5 (8.6)	
	Median (Q1-Q3)	21 (14 – 23)	26 (18 – 31)	22 (17 – 30)	0.26
	Min-max	12 – 36	12 – 39	12 – 39	
MUFA, g/d	Mean (SD)	12.3 (3.7)	15.9 (6.7)	14.5 (5.9)	
	Median (Q1-Q3)	12 (10 – 16)	17 (10 – 21)	14(10 – 18)	0.34
	Min-max	6 – 17	7 – 28	6 – 28	
PUFA, g/d	Mean (SD)	15.6 (6.9)	19.9 (5.9)	18.3 (6.5)	
	Median (Q1-Q3)	15 (11 – 21)	20 (15 – 25)	20 (13 – 25)	0.20
	Min-max	5 – 25.3	8 – 28	5 – 28	
Carbo-hydrates, g/d	Mean (SD)	314.8 (51.7)	341.8 (90.1)	331.8 (77.6)	
	Median (Q1-Q3)	320 (275 – 333)	321 (271 – 414)	320 (275 – 411)	0.65
	Min-max	247 – 411	212 – 494	212 – 494	
Added sugar, g/d	Mean (SD)	85.3 (57.8)	84.4 (42.3)	84.7 (47.0)	
	Median (Q1-Q3)	73 (34 – 132)	90 (41 – 121)	73 (38 – 123)	0.26
	Min-max	9 -179	23 – 144	9 – 179	
Fibre, g/d	Mean (SD)	14.7 (6.8)	18.3 (8.4)	17.0 (7.9)	
	Median (Q1-Q3)	12 (10 – 21)	16 (13 – 23)	16 (11 – 21)	1.00
	Min-max	9 – 27	8 – 38	8 – 38	
Fruit & vegetables, g/d	Mean (SD)	382.1(338.9)	551.8 (420.5)	489.3 (39.7)	
	Median (Q1-Q3)	339 (137 – 575)	435 (195 – 848)	369 (147 – 706)	0.30
	Min-max	71 – 1042	120 – 1361	71 – 1361	

The Mann-Whitney U-test is used for differences between group A and B
P = p-values for difference between group medians
Q1 = first quartile or 25th percentile, Q3 = third quartile or 75th percentile
Fruit and vegetables = fruit, berries, juice and vegetables.

The seven men had registered a median intake of 11.9 MJ/d (Q1-Q3: 8.8 – 12.4 MJ/d). The twelve women had a median intake of 8.4 MJ/d (Q1-Q3: 7.9 – 9 MJ/d). This gave a significant difference on Mann-Whitney test for energy intake between the sexes ($p = 0.01$). Also the difference in energy % from added sugar was significant between genders, with a median intake for men of 15 E%, and 12.5 E%

for women (p = 0.03). Differences between the sexes in intake of energy, fat or fruit and vegetables were not significant.

Table 6: Intake, as percent of energy

		Group A	Group B	Total	
N		**7**	**12**	**19**	**P**
Energy % from protein	Mean (SD)	13.6 (4.2)	14.3 (2.8)	14.1 (3.3)	
	Median (Q1-Q3)	14 (12 – 17)	15 (11.8 – 15.8)	14 (12 – 16)	0.84
	Min-max	6 – 19	10 – 20	6 – 20	
Energy % from fat	Mean (SD)	24.7 (6.1)	26.7 (4.1)	26 (4.8)	
	Median (Q1-Q3)	24 (20 – 28)	27 (23.3 – 30.3)	26 (21 – 28)	0.38
	Min-max	17 – 35	21 – 33	17 – 35	
Energy % SFA	Mean (SD)	8.7 (3.9)	9.3 (2.4)	9.1 (3.0)	
	Median (Q1-Q3)	8 (6 – 9)	9 (8 – 10)	9 (7 – 10)	0.30
	Min-max	5 – 17	5 – 14	5 – 17	
Energy % MUFA	Mean (SD)	5.3 (1.6)	6.0 (2.0)	5.7 (1.9)	
	Median (Q1-Q3)	5 (4 – 6)	7 (4.3 – 7.8)	6 (4 – 7)	0.43
	Min-max	3 – 8	3 – 9	3 – 9	
Energy % PUFA	Mean (SD)	6.6 (2.9)	7.4 (1.8)	7.1 (2.2)	
	Median (Q1-Q3)	6 (5 – 9)	8 (6 – 8.8)	7 (6 – 9)	0.43
	Min-max	2 – 11	4 – 10	2 – 11	
Energy %, carbo-hydrate	Mean (SD)	61.7 (6.0)	59.0 (4.1)	60 (4.9)	
	Median (Q1-Q3)	64 (55 – 65)	59 (56.3 – 62)	59 (56 – 65)	0.34
	Min-max	53 – 70	53 – 66	53 – 70	
Energy % added sugar	Mean (SD)	16.3 (9.9)	14.2 (5.9)	15 (7.4)	
	Median (Q1-Q3)	15 (7 – 25)	15 (8.8 – 19.5)	15 (15 – 25)	0.59
	Min-max	2 – 31	5 – 24	2 – 31	
Fiber g/MJ	Mean (SD)	1.7 (0.9)	1.9 (0.7)	1.8 (0.7)	
	Median (Q1-Q3)	1.4 (1.0 – 2.7)	1.7 (1.3 – 2.3)	1.7 (1.3 – 2.4)	0.48
	Min-max	0.9 – 3.2	1 – 3.4	0.9 – 3.4	

The Mann-Whitney U-test is used for differences between group A and B
P = p-values for difference between group medians
Q1 = first quartile or 25th percentile, Q3 = third quartile or 75th percentile

All participants led a sedentary life; only two male subjects had some regular physical activity by walking. Most subjects (16 of 21), had BMI>25, and could be defined as overweight, Table 7. Five were obese with BMI>30. None were underweight, the lowest BMI was 20.2. There was no significant association between BMI and sex, age, intake of nutrients or between group A and B.

Table 7: Subjects' Body mass index (BMI)

		Group A	Group B	Total	P
	N	7	14	21	
BMI, kg/m^2	Mean (SD)	28.0 (6.4)	27.3 (4.1)	27.5 (4.8)	
	Median (Q1-Q3)	28.0 (20.9-33.1)	27.5 (24.6-30.2)	28.0 (24.1-30.4)	0.91
	Min-max	20.4 – 38.5	20.2 – 34	20.2 – 38.5	

The Mann-Whitney U-test is used for differences between group A and B
P = p-values for difference between group medians
Q1 = first quartile or 25th percentile, Q3 = third quartile or 75th percentile

5.5.2 Protein and phenylalanine intake

The median total protein intake (from natural foods and substitute) was 1.02 g/kg for group A and 1.00 g/kg for group B, see Table 8. All subjects but one had a protein intake above the FAO/WHO recommendations of 0.75 g/kg (44).

The proportion of natural protein to total protein intake was low, about 25% for the total sample. Subjects in group A obtained 25 % of their total protein intake from natural food protein, compared to 27% in group B. This corresponded to a median phenylalainin intake of 746 mg/d in Group A and 808 mg/d in group B, Table 8.

The main sources of natural protein in the diet were potato, fruits and vegetables. In addition small amounts of cheese and meat and fish products were used in maincourse dishes and as spreads on low protein bread.

There was no significant association between serum phe levels and intake of natural protein or phenylalanine for the group as a whole. The total intake of phenylalanine from natural food was significantly higher among men than women (p=0.02), but the difference disappeared when looking at the phenylalanine intake in mg/kg bodyweight.

Protein substitute

Protein substitutes were the main source of protein for all subjects, Table 8. All substitutes were devoid of phenylalanine; 17 of 19 subjects used substitutes in the

form of powder containing a balanced mixture of essential and non-essential amino acids, fortified with minerals and vitamins. The daily dose was approximately 140 g/d of the traditional powder, and about 100 g/d of more modern types. Two subjects used substitutes in the form of tablets. The dose was 105 tablets per day of the product containing both amino acids and vitamins and minerals, the other containing only essential amino acids. The product with only essential LNAA was taken as 30 tablets per day.

Information sheets on protein substitutes used in the study can be found in Appendix 13.

Table 8: Intake of protein and phenylalanine, from substitutes and food

		Group A	Group B	Total	P
N		**7**	**12**	**19**	
Protein from substitute, g/d	Mean (SD)	50 (19)	58 (8)	55.2 (13.1)	
	Median (Q1-Q3)	59 (43 – 60)	57 (13.8 – 31.2)	59 (51 – 71)	0.38
	Min-max	13 – 71	47 – 75	13 – 75	
Natural protein from food, g/d	Mean (SD)	17 (4)	22 (8)	20.1 (7)	
	Median (Q1-Q3)	18 (14 - 20)	21 (14 - 31)	19 (14 - 22)	0.26
	Min-max	11 – 21	13 – 33	11 – 33	
Phe intake, mg/d	Mean (SD)	681 (176)	856 (340)	791.4(297.4)	
	Median (Q1-Q3)	746 (561 - 824)	808 (495 - 1191)	746 (499 – 952)	0.43
	Min-max	370 – 841	462 – 1370	370 – 1370	
Protein, g/kg	Mean (SD)	0.95 (0.33)	1.06 (0.2)	1.02 (0.25)	
	Median (Q1-Q3)	1.03 (0.80-1.22)	1.0 (0.89 – 1.31)	1.02 (0.85 -1.22)	0.54
	Min-max	0.32 – 1.26	0.84 – 1.36	0.31 – 1.36	
Phe, mg/kg	Mean (SD)	9.3 (2.6)	11.4 (5.0)	10.6 (4.3)	
	Median (Q1-Q3)	8.8 (7.1 – 11.5)	10.4 (6.8 – 14.3)	10.2 (7.1 – 13.0)	0.54
	Min-max	6.2 – 13.1	5.6 – 21.3	5.6 – 21.3	

The Mann-Whitney U-test is used for differences between group A and B
P = p-values for difference between group medians
Q1 = first quartile or 25th percentile, Q3 = third quartile or 75th percentile

"Without the diet, nobody wants to be with me." (Subject)

5.5.3 Fat intake

The median intake of fat constituted 26% of the energy, Table 6. There was no significant difference between the groups. More than half of the subjects had a fat intake according to the recommendations of 25 – 35 E%, no one had a fat intake over 35 E% (44). A total of eight had a fat intake below 25 E% (17 – 24 E%). All participants had an intake of saturated fatty acids (SFA) below the recommended maximum of 10 E% (44).

The Norwegian food tables do not list the individual poly-unsaturated fatty acids (55), thus the proportion of omega-3 fatty acids of the total PUFA was not calculated. However, all subjects but one had an intake over the estimated minimum requirements of 3 E% of polyunsaturated fatty acids (PUFA), Table 6. Only three (16%) subjects had an intake of polyunsaturated fat (PUFA) below the Norwegian mean intake of 5.4% of energy (E%) (63). Seventeen (89%) subjects met the Nordic recommendations of at least 5% of the energy from PUFA (44). Supplements of omega-3 fatty acids were taken by 14 subjects, either in the form of cod liver oil (n=10), or fish oil concentrates (n=4).

5.5.4 Carbohydrate intake

The mean carbohydrate intake was 59 E% for the total sample, ranging from 53 E% to 70E%, Table 6.

Most carbohydrates in the diet came from refined sugar and purified starch products such as protein-reduced bread, baking mixtures and pasta. Apart from this, carbohydrate sources were natural foods like potato, fruit and vegetables. The most commonly used protein substitutes also contained a substantial amount of starch/polysaccharides, added to enhance texture and taste. Fibre was usually low, as low protein bread and cereal products contain little or no fibre.

Added sugar

The median intake of added sugar constituted 15% of the energy for the total sample, with large interpersonal variation, Table 6. Only five subjects managed to have a sugar intake under the recommended maximum of 10 E% (44). Subjects with a low sugar intake tended to have s-phe under the median for the total sample, Table 9.

Table 9: Association between intake of added sugar and high or low mean serum phenylalanine

	Mean serum phe one year prior to study		
Sugar intake	**=472 µmol/L**	**< 472 µmol/L**	**Total**
> 11 E%	8	6	14
= 10E%	1	4	5
Total	9	10	19

Dietary fibre

Fibre sources in the diet were fruit, vegetables and potato; some subjects obtained additional fibre from purified fibre products added to low protein bread. The median intake was 1.7 g fibre/MJ, much lower than the recommended 3 g/MJ (44). Only two persons, both with an intake of more than 1000 g of fruit and vegetables a day, managed to reach the recommendations of 25 – 35 g/d or about 3 g/MJ dietary fibre (44). Subjects with la ow fibre intake tended to have a higher sugar intake, Figure 5. Rank correlation between dietary fibre in g/MJ and energy % from added sugar gave a Spearman's rho correlation of -0.75 ($p<0.001$).

5.5.5 Intake of fruit and vegetables

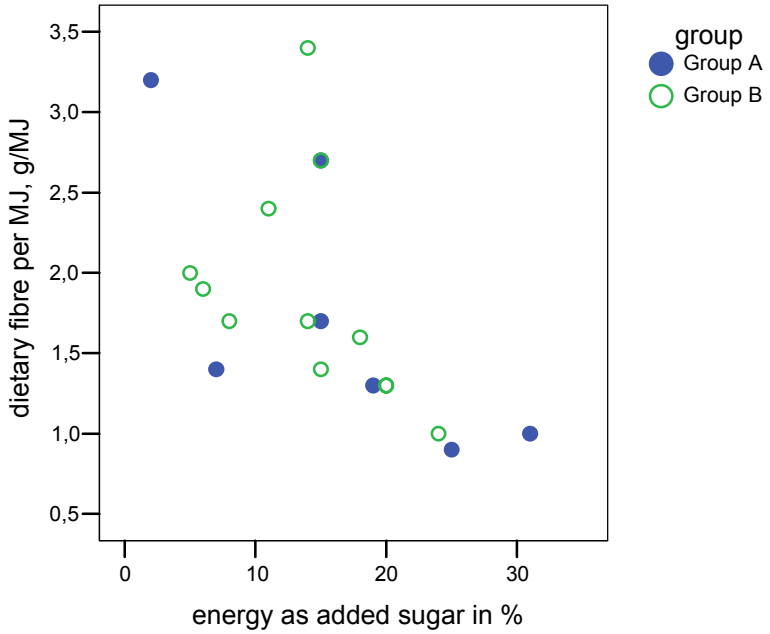
In the PKU diet, patients are advised to eat most of their natural protein as fruit and vegetables, see page 5 (16;17).

The median intake of fruit and vegetables was 369 g per day (339 g in group A, and 435 g in group B), Table 5. This amount is about the same as the mean Norwegian intake found in Norkost (mean 357 g/d) (63). The variation between subjects was

large, without any significant differences between the two groups or between males and females. There was a positive Spearman's rho correlation of 0.49 ($p<0.03$) between intake of fruit and vegetables and dietary fibre in the diet.

In addition to the intake of fruit and vegetables, the subjects had a median potato intake of 87 g/d. Mean potato intake in the Norwegian population is 135 g/d (63).

Figure 5: Association between intake of added sugar and fibre in the diet



5.5.6 Non-energy nutrients in the diet

When the prescribed amount of substitute was taken, the intake of micronutrients was above the recommended daily intakes for essential non-energy nutrients (44). In addition to fortification of protein substitutes, low protein bread and baking mixes were often fortified with vitamin B and iron. Total intake of nutrients is listed in Appendix Table3. The intake of vitamins and minerals was higher for most subjects than the average Norwegian intake (63).

Table 10: Intake of micronutrients according to recommended daily intake

Micronutrient	Total diet		Protein substitute			
	Median intake	% of recommended intake	Median intake	% of recommended intake	Upper level (UL)	Number of subjects over UL
Calcium	1196 mg	150%	972 mg	122%	2500 mg	0
Magnesium	549 mg	157%	399 mg	114%	-	-
Iron	40 mg	444%	31.7 mg	352%	25 mg	18
Zinc	22 mg	244%	19 mg	211%	25 mg	3
Selenium	84 µg	168%	73 µg	146%	300 µg	0
Vitamin A [a]	2002 µg	222%	1001 µg	111%	1500 µg	4
Vitamin D	18.4 µg	245%	11.3 µg	151%	50 µg	0
Vitamin E	22 mg	220%	7.8 mg	78%	300 mg	0
Vitamin C	222 mg	296%	122 mg	163%	1000 mg	0
Thiamin	2.9 mg	207%	1.96 mg	140%	-	-
Riboflavin	2.9 mg	171%	1.96 mg	115%	-	-
Niacin [b]	54 mg	284%	39.7 mg	209%	910 mg	0
Vitamin B_6	4.0 mg	250%	2.9 mg	181%	25 mg	0
Folate [c]	866 µg	289%	678 µg	226%	1000 µg	3
Vitamin B_{12} [d]	-	-	5.4 µg	338%	-	-

[a] Vitamin A: Upper level refers to retinol for postmenopausal women, due to risk of osteoporosis – only women >50 years of age counted
[b] Niacin: Upper level refers amount in fortification
[c] Folate: Upper level refers amount in fortification
[d] Vitamin B_{12} was only calculated for protein substitutes

The two subjects who used tablet substitutes had the lowest intakes for all micronutrients. The tablet substitutes gave intakes of vitamins and minerals below the Norwegian recommendations for magnesium, vitamin C, vitamin D, folate and B_{12}. One contained less than the recommended amount of calcium, and the other one had less vitamin A. But when intake from food and substitutes were calculated together the recommendations were met for all nutrients, possibly excluding B_{12}, as the diet had few sources of this vitamin (44).

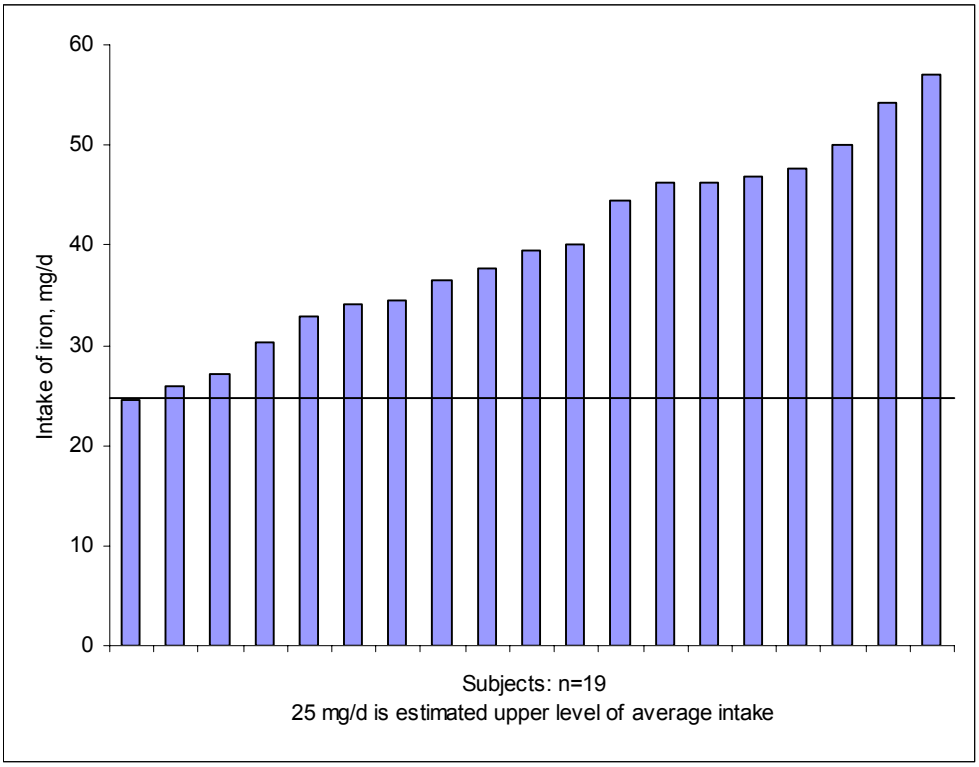
By listing both the intake from substitutes and the total diet, the amount of fortification becomes evident, Table 10. Intakes from substitute alone gave median intakes over recommendations for all micronutrients apart from vitamin E. For vitamins A, C and E food intake constituted about half the total intake. For other vitamins and minerals, the proportion from substitutes varied from ca 60% to almost

90% of the total intake. For iron the upper level was exceeded from the intake of protein substitute alone. Also the intakes of zinc and folic acid were high, and three individuals had intakes above the estimated upper level for zinc, and thre for folate (44). The four female subjects over 50 years of age all had intakes of vitamin A above the estimated upper level given for postmenopausal women. Seven women younger than 50 years of age also had intakes over 1500 µg/d.

The two persons using tablet substitutes ingested 0.9 and 1.0 µg/d vitamin B_{12} from substitutes, one had B_{12} deficiency. For the remaining 17 subjects B_{12} intake from substitutes ranged from 4.3 to 11.8 µg/d.

Daily doses of powdered protein substitute resulted in intakes of 500 – 900 µg/d of folate. Food intake gave about 200 µg/d, ranging from 110 – 320 µg/d. All subjects had folate intakes over the Norwegian mean of 240 µg/d and the Nordic recommendations of 300 µg/d (44;63).

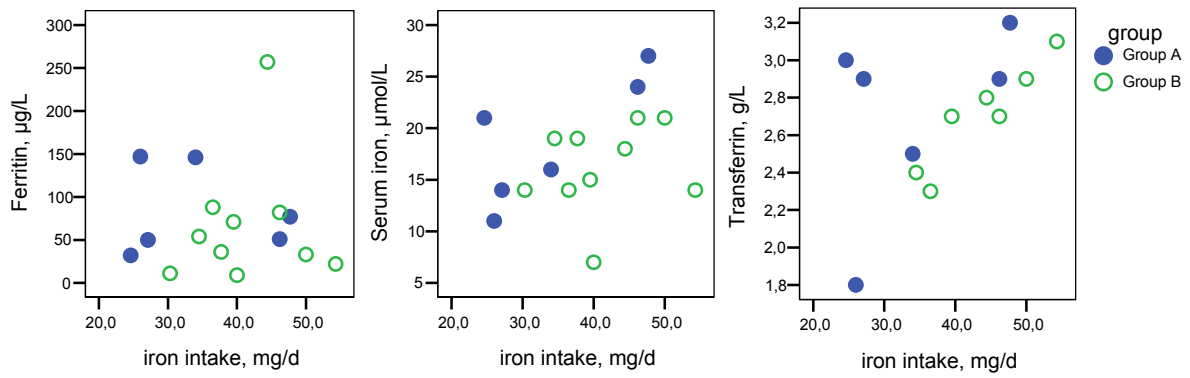
Figure 6: Distribution of iron intake



The participants had a median

iron intake of 40 mg/d, ranging from 24.6 to 57 mg/d, Figure 6. The estimated upper level for intake is 25 mg/d and 18 of 19 subjects had intake of iron above this level (44).

Figure 7: Iron intake in association to blood iron parameters



The protein substitute alone gave a median iron intake of 31.7 mg/d (range 12.3 – 40 mg/d). The fortification of low protein bread and baking mixes gave a median of 6.6 mg/d (range 1.9 – 15.4 mg/d). Iron intake from other natural food sources had a median of 3.7 mg/d (range 1.6 – 7.2 mg/d), with only 0.6 mg/d (range 0.0 – 1.8 mg/d) from products containing meat or fish. The high intake was not reflected in high levels of iron status in blood, Figure 7. The blood tests did not reveal signs of iron overload despite the high iron intake.

"Sometimes it's crap! Having PKU and fixing the diet." (Subject)

6. Discussion

There is ample documentation that late dietary treatment is effective in reducing behavioural and neurological signs in PKU. At least half of the patients who start dietary treatment as adults display benefit (9;27). It is also stated that these effects persist providing serum phe levels are low (10;22;25).

The dietary composition and nutritional results will be discussed after the phe levels in serum. Thereafter will themes related to adherence and living on a PKU diet be discussed.

6.1 Phenylalanine in serum

Blood phenylalanine for all subjects in this study was efficiently lowered by the diet. However, all subjects in group A had mean phe levels above Norwegian treatment recommendations. Subjects in group B had levels closer to the standards, but only three managed to keep a mean level below 400 µmol/L. As recommendations on serum phe levels are lacking for adults with late commencement of treatment, finding the optimal individual level for adults will always be a compromise between treatment effects and a practical and manageable everyday diet. This is also reflected through other studies on late treatment where some aim at phe levels below 600 µmol/L, others are satisfied if serum phe falls below 1000 µmol/L (9;24;27).

Adults will have fairly stable blood phe levels when the diet supplies sufficient energy, sufficient protein substitute and natural protein to meet individual requirements of phenylalanine. In absence of illness or changes in bodyweight, fluctuations in the blood phenylalanine are caused by dietary variations. In the present study this was demonstrated by the correlation between the serum phe taken at the time of food recording and mean phe prior to the study, see Table 3 and Figure 1.

From the data it may be concluded that the Norwegian upper limit for serum phenylalanine is impracticably low and not manageable for adult patients with brain damage. It seems easier to keep low levels for patients living in group homes with full support, than for adults living independently. However, the two groups had few participants and the difference in phenylalanine levels between groups was not significant.

6.2 Composition of the diet

6.2.1 Do the weighed food registrations give valid results?

The assumption that the registrations reflected habitual intake was supported by the subjects' dietary routines, with fixed amounts of natural protein and protein substitute from day to day (5). Usually subjects in group B followed detailed lists or menus, stating food types and amounts of phenylalanine to be taken at each meal. Also the subjects in group A had lists for help in determining amounts of protein rich foods, but their routines and meals were not as closely planned as in group B. The blood phenylalanine levels during the study were closely correlated to individual phe levels in the past, indicating that the intake of natural protein was fairly stable.

Further support was found in the food registrations. The energy intake recorded gave an estimated physical activity level (PAL) above Goldberg's cut-off limit for healthy sedentary adults (61). PAL was however, lower for subjects in group A than in group B. This can be due to gender differences, as group A consisted mainly of women who tend to have lower PAL than men. Another reason may be that people tend to eat less when recording their own intake (61;64).

Underreporting is more common when people report their own intake, than if reporting is done by "neutral observers" as reported by Westerterp and Goris (65). However, caregivers, especially parents of disabled children, tend to overreport

intake (65). This tendency must be considered when studying profoundly retarded adults as subjects in group B. But as all subjects in this study had BMI>20, and no-one had eating problems resulting in insufficient energy intake over time, the tendency to overreport seems less probable.

A tendency to underreport, as seen among obese or overweight people seems less probable in this study as most subjects did not reflect on their own body appearance (61;64;65). Neither did subjects with high BMI have lower PAL values than subjects with BMI in the normal range. In addition intake of low protein snacks and sweets were reported, often in ample amounts, both by subjects with normal and high BMI.

It may be concluded that the food registrations are reliable and give valid results. There were no significant differences in intake between the two groups, but each group was small in number and varied in distribution of sex, age and activity levels.

6.2.2 Bodyweight and energy intake

The prevalence of overweight among the participants (Table 7) was above the Norwegian mean BMI=26.5 for men and 25.2 for women (66). Several studies from Western countries have shown a higher prevalence of overweight and obesity among people with mental retardation than among the general population (67-69). This corresponds to the present study where 75 % had BMI>25 and the subjects in group A had median BMI of 28.

There was no significant difference in distribution of BMI between the two groups. This differs from the Norwegian study by Hove, who reported a higher prevalence of overweight and obesity among persons with mild mental retardation and living independently, than in the normal population or mentally retarded residents in group homes (69).

Hove also reported that underweight was more common than overweight among severely retarded people; probably due to a high prevalence of feeding problems,

food refusal and lack of independent choice (69). This tendency was not observed in the present study. Some case studies of late treatment for PKU describe normalisation of bodyweight and reduction of eating problems after institution of dietary treatment (24;25). This is in accordance with information given in the interviews and from hospital charts; five subjects in group B suffered from eating refusal and low body weight prior to treatment, but developed better appetite and gained weight whilst on diet. Apart from case reports, information on bodyweight in adults with PKU is lacking.

The relative high BMI in this study might be due to substantial amount of "hidden" energy from the protein substitutes. Both subjects and caregivers tended to define the substitute as a medicine instead of food, and therefore the energy contents were often not appreciated. Accordingly, the portions of food allowed without restriction might increase, and this could result in an excess energy intake. In addition, the intake of added sugar was high, partly because drinks and sweets were predominantly chosen in variants containing sugar. Artificial sweeteners were usually avoided because aspartame contains phenylalanine.

6.2.3 Protein intake

No controlled studies have concluded that PKU patients have requirements for protein that vary from those of the normal population (70-72). In the present study all subjects but one had protein intake in accordance to recommendations (44). For babies and young children however some treatment centres recommend higher intakes (5;70;71). The sum of protein substitute and natural protein should, according to a Cochrane review from 2005, provide recommended amounts of total protein, adjusted for age (70). All subjects seemed to receive an appropriate amount and quality of protein over time when the data were considered together. One subject had an intake of protein of only 0.37 g/kg. This was not associated with subnormal blood analyses, so this subject probably used to eat more natural food with protein.

The intake of phenylalanine varied according to individual tolerance. For subjects with similar serum phe levels the intake of phe from food in mg/kg could vary as as much as 100%. This was due to individual differences in the impairment of the PAH-activity, in food absorption, age, weight and variation in the metabolic turnover of phenylalanine (1;11). If an individual subject wished to obtain lower serum phe levels, he or she would have to ingest less dietary phenylalanine than before. This would mean greater restrictions in natural protein, and a diet more problematic to follow.

All subjects in the present study took their protein substitute every day, even though the taste and smell of the powder substitutes are extremely unpleasant to most people. Information from the interviews showed that single doses of substitute could be forgotten, especially in group A. In group A some subjects also had changed to a different substitute because of the taste and smell. Problems in taking the substitute were surprisingly few among subjects in group B. According to information given in the interviews most subjects in group B accepted and even liked, the protein substitute. Even so, some subjects needed persuasion or extra praise to drink the substitute. One subject took a very long time, and took less than prescribed several times a week. The fact that retarded patients easily accept the substitute is also reported by Fitzgerald et al (24); other reports mention that the substitutes were a smaller problem than expected by caregivers and dietitians (9;10;25;27).

The unpleasant flavour is, however, a reason for non-adherence to the diet in well functioning and early treated adolescents and adults according to literature (73;74), this complies with the experiences from group A.

In this study recommendations for protein or nitrogen intake were met when the prescribed amounts of natural protein and protein substitute were taken (44). Differences in amounts or types of protein varied according to phe tolerance and body weight and not to the degree of mental retardation. One person in group A had a low intake of protein during the registration period. The amount of natural protein eaten was similar from day to day, indicating that this subject was not able to understand or follow the dietary advice provided. This shows that patients with

milder disabilities might need help and supervision by people who are familiar with the dietary principles.

6.2.4 Fat intake

Without conscious use, the energy from fat in the PKU diet will not reach the recommended 25-35 % of energy intake (44). In this study almost half of the subjects had a fat intake below the recommendations and a risk of deficiency in essential fatty acids was present.

Fatty food products in a normal Norwegian diet usually contain protein. These products were used in small amounts, and portions of food like cheese, meat and chocolate varied from 2 to 20 g/d. The negative correlation normally seen between energy from fat and sugar is therefore less apparent in a PKU diet, and did not reach significance in the present study. The main sources of fat were vegetable margarines, vegetable oils and mayonnaise dressings, all rich in unsaturated fatty acids. Sources for saturated fat (SFA) were cream and a special low protein milk. Some subjects, mainly in group A, also received saturated fat from low protein biscuits, chips and butter.

Low concentrations of the long chain polyunsaturated fatty acids (LCPUFA) arachidonic acid (AA) and docosahexaenoic acid (DHA) have been reported in blood from children and adults with PKU (38;39;41;75). Some reports find AA and DHA more compromised than their precursors, linoleic and α-linolenic acid. According to Infante and Huszagh this may be due to inhibitory effects on endogenous synthesis of AA and DHA by elevated phenylalanine or its metabolites (42). Supplemention with essential fat, either as linoleic and α-linolenic acid or as LCPUFA, has shown to improve fatty acid balance in children's plasma and erythrocytes (38;39;75). Moseley et al. found low levels of LCPUFA also in adults, but these were less severe than those formerly reported in children (41). They also reported higher DHA values when serum phe was below 600 μmol/L.

The fat sources registered in the present study showed that intake of linoleic acid, and thus probably arachidonic acid, were met in the diet when fat of vegetable origin was used. All subjects had been advised by the dietitian to take supplements of fish oil concentrate or cod liver oil to ensure a minimum intake of DHA. As fat had to be chosen specially to obtain sufficient DHA , the intake may have been suboptimal for some individuals. Fish oil supplements were used in very small doses by some and not all by seven.

The present data support the hypothesis that patients with PKU involving brain damage can obtain sufficient amounts of fat and LCPUFA through the diet. However, advising patients to supplement the diet with fish oil seems reasonable in order to secure intake of DHA. The majority of subjects in this study, 16 out of 21 (five in group A and 11 in group B), had a mean serum phe below 600 μmol/L, thus the risk of inhibitory effects from phenylalanine upon DHA and AA synthesis seemed low (41).

It seems important to give repeated advice on the preferred types of fats in the diet, in order to secure intake of essential fat, and reduce the risk of replacing unsaturated fat sources with saturated fat.

The degree of mental retardation or need of support did not seem to interfere with the total intake of fat. But subjects in group B ingested more essential fat even though the difference between groups did not reach significance.

6.2.5 Carbohydrate intake

A high energy percent of sugar will usually have adverse effects on the intake of micronutrients from food. In the PKU-diet however, sugar intake influences the total nutrient intake only to a small extent, as the majority of micronutrients are supplied in the protein substitute. Most subjects in group A reported to use sweets and protein-reduced biscuits or cakes for snacks, when eating away from home and at social occasions. Sweets and soft drinks are easily available and many types can be enjoyed

in unrestricted amounts. This reduced the need for planning, cooking and bringing along special food, but it also reduced the overall quality of the diet.

According to Nordic recommendations less than 10% of the total energy should be refined or added sugar (44). This is far less than most subjects in group A used. Also in group B subjects used more added sugar than recommended, mostly from soft drinks or conserves; often taken in spoonfuls with medicine. Sweets were regularly used as treats, for instant after taking the protein substitute.

Subjects with a low intake of added sugar tended to have s-phe under the median for the total sample, Table 9. The food registrations showed that subjects with low a E% from sugar used smaller portions of soft drinks, snacks and sweet spreads on bread. However, the number of food products, total amount of fruit and vegetables or fat did not vary according to sugar consumption. Subjects with a low intake of added sugar also adhered better to dietary prescriptions when evaluated by serum phe levels. Perhaps they also were more meticulous with food containing natural protein.

The intake of dietary fibre was compromised when products abundant in sugar replaced other kinds of natural low protein food, Figure 5. The seven subjects with more than 15 E% from added sugar had very low intakes of fibre (ca 1 g/MJ).

The low fibre intake may also have increased the risk of constipation, a problem reported from several subjects in the interviews. To increase fibre intake, some subjects, mainly in group B, used small amounts of purified fibre products in the low protein bread, and some used oats or whole grain wheat in porridge. A positive change in the diet would be to add fibre to low protein bread and baking mixes. This should preferably be done at production level, as all procedures which complicate food preparation are negative in such a demanding diet, specially for subjects in group A who receive little or no practical support.

Data showed that it was difficult for adults with brain damage to manage a diet in compliance with recommendations regarding amounts of added sugar and dietary

fibre. However, a couple of the subjects showed that it was possible. The difficulties seemed similar in both groups, and not related to the degree of mental retardation.

6.2.6 Micronutrients

Fortification of protein substitutes resulted in excessive intakes of micronutrients for all subjects taking the powder substitutes, Table 10. The high intake resulted in abnormally high concentrations of folate and vitamin B_{12} in the blood. However, this effect was not seen in other blood parameters such as iron, zinc or magnesium. Due to the high intakes of protein substitute in order to maintain low serum phenylalanine levels patients with low tolerance for dietary phenylalanine will have the highest intake of micronutrients.

These data demonstrate the problem of optimal fortification. Clearly, semi-synthetic diets for metabolic diseases like PKU need fortification to secure a sufficient intake. However, the necessity for large doses should be documented. There are available studies describing the balance and metabolism of several micronutrients in patients on a PKU diet (37;43;76-78). The majority refer to concentrations in blood without reporting the correspondent intake and the studies are usually related to children. Study controls are often siblings or healthy children, who obtain their micronutrients from natural food in much smaller amounts than subjects with PKU.

Documentation is needed, both on the effects and side effects of excessive intakes. Documentation is important in dietary follow-up both for clinical reasons and for better adherence. Smaller doses of micronutrients could perhaps enhance the taste of substitutes and reduce the osmolality for these highly concentrated mixtures. In the present study some subjects reported abdominal discomfort after taking the substitutes, possibly due to the high concentration or to the large volumes.

From a nutritional point of view the bioavailability of the compounds used in fortification should be the best possible. They should also interfere minimally with solubility or taste of the finally prepared substitute.

Fortification of the protein substitute is the common way to give micronutrients in PKU as it reduces the necessity for additional supplements. This makes the diet less complicated and increases adherence (74). The powder substitutes used in this study were recommended both for children over eight years of age and for adults. However, it is impossible to obtain the correct balance of protein and micronutrients from the same product for a child of 30 kg and a man of 90 kg (44).

Folate and B_{12}

Serum folate is strongly correlated to the recent intake of folic acid or folate. Folate levels in erythrocytes reflect tissue stores. The high levels indicated a high folate intake over a longer time, showing that the subjects did take their protein substitute, see Figure 4.

Robinson et al (79) believed that the high erythrocyte folate levels in PKU were a result of a high vegetable intake, but without reporting the dietary intake. Also Colomé et al (80) reported high serum folate in treated PKU subjects, without reporting folate intake. In the present study the majority of folate was folic acid from fortification, as levels from food intake were below the recommended amounts, Table 10 (44). Even if vegetable intake had been doubled, fortification would constitute most of the total folate intake.

There are indications of interaction between folate and biopterine in PKU. Tetrahydrobiopterine (BH4) is a coenzyme for PAH in the conversion of phenylalanine to tyrosine (1). Lucock et al studied folate metabolism in PKU (43), and reported higher concentrations of certain stable folate metabolites in erythrocytes in PKU patients than in controls. This was found in subjects both on and off diet. The significance of this altered folate metabolism remains unknown. Smith et al discussed whether the blood levels unmetabolised folic acid seen after fortification may be harmful or possibly interfere with the folate metabolism (81). They were also concerned about the unknown consequences of high intracellular concentrations and concluded that fortification with folic acid needs further investigation.

None of the reports give evidence for higher requirements for folate in PKU, and it remains unclear if the high erythrocyte folate is beneficial for PKU patients. Whether the high folate in blood tests is influenced by an altered metabolism in addition to an increased intake cannot be concluded from this descriptive study.

The high intakes of vitamin B_{12} were also reflected in the blood samples, Table 10. Several reports show that PKU adults not adhering to the diet have a risk of developing B_{12} deficiency because the patients stop taking the substitute without managing to eat a "normal" healthy diet (77;79;82). In this study the deficiency seemed rather due to insufficient fortification of the protein substitute used. In contrast to the tablet substitutes, the powders supplied abundant B_{12} , resulting in blood levels above the upper limits for normal concentration. To reduce risk of masking a vitamin B_{12} deficiency it is important that the fortification with folic acid is balanced with high amounts of vitamin B_{12} (81)

Iron

There was no correlation between the high iron intake and iron status. Similar absence of correlation between intake and iron status is reported in children by Acosta et al and by Arnold et al (37;83). The high amounts of dietary iron did not seem to have beneficial effects on the subjects' iron status.

The iron sources in the diet had poor bioavailability as the amounts of haeme iron and the enhancing factors for iron absorption in meat, fish and poultry were negligible. The intake of iron from natural food varied from 1 to 6 mg/d and was below the estimated lower level of intake, and showed that supplementation was needed (44). Dietary iron is generally poorly absorbed and the iron salts used for fortification have an even lower bioavailability (44). The substitutes used in this study were fortified with iron sulphate, iron gluconate and iron fumarate. In addition the most common baking mix was fortified with elemental iron (ferrum reductum).

Some essential micronutrients in the protein substitutes are known inhibitors of iron absorption. For example will doses of more than 165 mg calcium in a single meal

cause a 50% reduction in iron uptake (44). In the PKU diet this inhibition will take place at all meals containing protein substitutes and may result in high amounts of intestinal iron. Local intestinal toxicity is reported as a side effect of iron intakes beyond 50-60 mg/d (44). Only two subjects had intakes this high, but six more had intakes above 40 mg/d. It is, however, reasonable to suggest that the high iron intake in combination with the low fibre intake aggravates intestinal problems such as constipation.

The substitutes also contain enhancers for iron absorption, such as vitamin C (44). The enhancers evidently did not counteract the inhibitors sufficiently enough to improve iron absorption. It seems relevant to ask if fortification with haeme iron in lower concentration can better iron status, and reduce the excessive fortification.

According to the nutrient intake and the blood analyses available substitutes did not seem to be optimal for treatment of adult patients. Intakes of most minerals and vitamins were above recommendations when protein substitute was taken in the amounts required. The excessive amounts resulted in intakes close to or above estimated upper levels for some nutrients.

Possible harmful effects from excessive fortification need further investigation.

6.2.7 Fruit and vegetables

Fruits and vegetables can to a great extent be used without restrictions in the PKU diet as reported by MacDonald et al (32). Despite this, intake in the present study was only a little higher than the mean Norwegian intake reported by Johansson and Solvoll (63). The amounts and types used varied greatly between individuals. Subjects with a fruit and vegetable intake over the median had a larger diversity of natural food products in their diet than subjects who ate little fruit and vegetables. The total intake of natural protein or phenylalanine from food was not influenced by the amounts of fruit and vegetables in the diet.

Only two subjects in Group A had an intake of fruit and vegetables above the median for the total group. One of them received extensive support from parents, and the other suffered from diabetes mellitus and put great effort into organising meals according to the lists from the dietitian. Three subjects in group A had very low intakes; two of them received no support in dietary matters. Support in cooking and everyday organisation of the diet seemed important in helping subjects in group A to include a wider use of fruit and vegetables in their diet.

Intake of fruit and vegetables in Norway has traditionally been low (84), and the subjects in group A had learned cooking and household skills in a period when fruit and vegetables were used in smaller amounts. Advice from the dietitian had not changed their perception of fruit and vegetables as supplementary food instead of a main ingredient in their diet. The fact that they had learning disabilities and problems in acquiring new knowledge and skills, may also contribute to a greater reluctance to change habits and experiment with food products and tastes.

In group B the interviews revealed that intake of fruit and vegetables was dependent on knowledge, cooking skills and opinions on healthy food amongst the staff. For eight subjects, lists and scales were used for all foods containing protein, including fruit and vegetables. The others used fruit and vegetables in free amounts. This difference in organisation did not result in any differences in subjects' intake.

Caregivers were more prone to serve fruit and vegetables if these products were explicitly mentioned in menus or diet plans. If the plans only listed the amount of phenylalanine to be used, often small amounts of protein rich food was used instead. In order to reach the national goals of "five a day", dietitians must recommend fruit and vegetables as an option at each meal. In this way the total volume of normal food products in the diet will increase. Trained staff members, with adequate knowledge of the diet, reported that they were more liberal with fruit and vegetables than staff members with less knowledge and routine. Some reported they had started to serve fruit and berries to all residents, replacing some of the cakes and biscuits for afternoon coffee.

The data show that the recommendation "five a day" is compliable with a PKU diet, but it requires special consideration and a new perception of which food products should constitute the basic diet. It is known that an increased use of fruit and vegetables is easier to obtain when subjects have health risks known to be influenced by diet (85;86). However, the subjects in the present study had already carried out changes according to health needs. It appeared problematic for them to alter eating habits even more, despite the fact that more fruit and vegetables would result in a greater variation in the diet. Increased use of fruit and vegetables would also enhance the intake of naturally occurring components as dietary fibre and antioxidants.

> *"People want to be kind, and she appreciates fruit. If you give her other things, may be she'll be happy at the moment, but the next day she'll feel poorly." (Caregiver)*

6.3 Living on a PKU diet

Information from the interviews showed that having PKU and adhering to the diet was experienced as problematic by all subjects in group A. However, they still wished to follow the diet and managed to do so most of the time. A discussion on quality of life among people with brain damage due to PKU is beyond the scope of this study, but aspects related to management and adherence will be discussed. This section is based mainly on qualitative methods and data from the interviews (52;53). Adherence is defined as the extent to which a person's behaviour corresponds with and agrees with recommendations from health care providers (87). Hopefully, the discussion can point out some factors important for better adherence among patients with brain damage due to PKU.

Studies show that adhering to dietary treatment is challenging even when necessary for health and wellbeing. Sherman et al report that adherence to a dietary regime is

influenced by both individual and social barriers and is more challenging than adhering to pharmacological treatment (88). One aspect is that medical diets are not easily adapted to meet the social, cultural or religious properties of food. This can lead to a feeling of deprivation and of being socially excluded. Additional barriers are lack of availability and cost of special food products as pointed out by MacDonald et al (74).

In group A barriers to adherence were elucidated in behaviour related to eating away from home or at special social occasions. Most subjects preferred to take normal food products; based on sugar or as small amounts of other food, in stead of bringing along special products or asking to be served special dishes. In this way the subjects also reduced the need for planning and cooking. In using the same food as others the feeling of deprivation or being different became less prominent. The subjects reported that the diet was emotionally challenging because of the small amounts of natural food, the taste and smell of the substitute and a feeling of being different. Ievers-Landis et al reported similar findings in children and adolescents (73). These feelings seemed to be a part of having PKU and adhering to the diet, and were independent of serum phe levels and how well the diet was managed.

Perception of these problems was not always noticeable among caretakers, who did not drink the substitute or face temptations themselves. Caretakers' problems were expressed as related to cooperation among staff, available time for planning and cooking, and in challenges of composing a varied diet . Some caretakers expressed a need for more support and knowledge. This was not available locally because of PKU being so rare. Most patients are diagnosed early, after newborn screening, and knowledge and skills in self-management can be transmitted gradually. For adults with brain damage due to PKU, the need for information and knowledge from the central treatment centre has to be renewed when new caretakers are employed. This need for support must be understood and acknowledged by the national PKU-team and The Centre for Rare Disorders at Rikshospitalet.

In contrast to the request for knowledge by the employed caregivers, psychological and emotional aspects are described as more important than knowledge for maintaining dietary procedures by the patients with PKU and their parents (86;88-90). Bekhof et al found that knowledge is necessary only to the extent of making the diet feasible and practical (91). Being convinced that treatment results in a better life and less symptoms is more important for adherence. Waisbren et al used the method "Theory of planned behaviour" to describe necessary factors for individual adherence (92;93). The factors are 1) "subjective norms"; or feedback and support from important others, 2) "attitudes"; or personal beliefs and experiences that diet is causing a decrease in symptoms, 3) "manageability"; or a perception of the diet as manageable.

The "important others" include relatives, friends and supportive professionals. In this study the PKU-team at Rikshospitalet acted as "important others", both to subjects in group A and to the group home staff who administered the diet in group B. In accordance with Sherman, sensitive and personally adapted feedback was reported as important incentives for adherence (88). To build stronger "subjective norms", people need to have support available on a day to day basis and closer than the national PKU-team at Rikshospitalet can render. The need for practical and emotional support was clearly voiced by subjects in group A. Some need daily help and supervision, for others support on a weekly basis might be sufficient.

Reports from both groups stated that the diet was laborious and impractical, but the overall impression was that it was effective and important for subjects' wellbeing. Thus the "attitudes" seemed firmly anchored (92). However, in some group homes primary caregivers reported disagreement on attitudes. Some members of the staff, often with little knowledge of PKU and the subject, were opposed to the treatment and felt that the restriction of the resident's personal choice was an ethical problem (24). This problem was most apparent in newly employed staff members or if immediate behavioural effects of phenylalanine elevations were difficult to observe. In these homes documentation on treatment effects or fluctuations in serum phe levels

were unavailable to staff members. The relation between diet, serum phe and behaviour could be difficult to discover or document as caregivers worked at different times during the day. For some subjects negative behaviour and depressive moods were clearly related to high levels of serum phe, but others could have similar behaviour problems as reactions to stress or illness, independent of serum phe. Available documentation on diet and serum phenylalanine history seemed to be helpful for sustained adherence in group homes; providing caregivers had learned to understand them. In order to learn whether behaviour problems were related to dietary changes or varying serum phe, caregivers needed feed back the metabolic dietitians. General information on PKU and competence in dietary skills for all staff members working with the subject with PKU seemed important for adherence in group B.

In group A the "manageability" was inadequate for some subjects, and this had resulted in periods of non-adherence in the past. Subjects receiving practical support from parents or community services managed to maintain lower mean serum phe and had better everyday routines. This is an important argument for organising local help and supervision. The parents acknowledged these problems, but reported difficulties regarding the local welfare authorities and their understanding the need for support.

Manageability in group homes seemed to depend on good organisation and routines as well as mutual agreement on treatment. All homes had one or two staff members responsible for the diet, and in some homes the whole staff had a basic knowledge of PKU and the diet. The latter seemed to improve staff cooperation, and was supportive for the caregivers with main responsibility. Agreement on treatment and the significance of maintaining a strict diet seemed as important as written routines and procedures. In this way the factors of attitude and manageability seemed intertwined.

A main prerequisite for dietary adherence and management for adults with brain damage who are treated for PKU and living independently is a need for support from their local community. The amount of support necessary will vary according to individual needs, but will be needed for organising, ordering special products and

cooking. Individuals who render assistance or support require knowledge of PKU and should have some basic skills in preparing low protein food.

Support should be organised on a permanent basis and secure follow-up of the caretakers as well as the patients. Cooperation between local welfare authorities and the central follow-up system at Rikshospitalet is required. The Centre for Rare Disorders supplies support and information to persons with PKU, their relatives and professionals working with the diagnosis in local communities. This study illustrates that there is still much to do and that information needs to be rendered on a more systematic basis.

> *"I wish she had more support. In order for her to manage somebody has to know, she won't have me for ever." (Parent)*

7. Conclusions

The objective of this study was to describe the composition and management of a protein restricted diet for PKU. Questions were raised in respect to whether nutritional recommendations were met and to prerequisites for adherence. Two hypotheses were formulated and tested in order to answer these questions, see page 17???.

The subjects formed a subgroup within the PKU population. Age, mental function and requirements of support varied between the 21 subjects who were divided into two groups according to mental functioning. The study was designed in order to minimise the impact on the brain damaged subjects, limiting the number of blood tests taken and the obtainable analyses. Despite a high participation rate, the participants were few and this made it difficult to demonstrate statistical significance between the two groups, and thus made it more difficult to generalise the results.

However, the PKU diet leaves little room for variation regarding the amounts of protein and micronutrients in the diet. This conformity makes it possible to generalise certain results from the food registrations to other adults adhering to a PKU diet.

The food registrations showed that adults with brain damage due to late diagnosis of PKU, as hypothesised, could manage a diet in accordance with the Nordic Nutrition Recommendations. However, this required great effort and special considerations regarding food choice. The intake of protein from the substitute and natural protein was sufficient, however, the first part of hypothesis one could not be confirmed due to the following reservations:

- The intake of fat was below recommendations for many subjects, and special caution had to be taken to secure intake of essential fatty acids.
- The subjects had high intakes of added sugar, the median intake was 15 E%. The intake of fibre was low, especially in individuals with a high sugar intake.
- If precautions were not taken to choose more natural protein as fruit and vegetables, the recommendations for fibre and five portions of fruit and vegetables a day were not met.

Even when the diet fulfils the nutritional recommendations, biomarkers for nutritional status showed suboptimal or deviant results for individual subjects. For micronutrients this was due to the composition of the protein substitutes and could not be controlled by the subjects or caregivers.

- This shows that the second part of the first hypothesis was not confirmed due to the following reservations:
- All subjects had high intakes of micronutrients, and the majority used protein substitutes fortified with excessive amounts of vitamins and minerals.
- The high intake of folic acid and vitamin B_{12} was reflected in high blood levels.
- The iron status in blood was not elevated although intakes were above the estimated upper level of intake.
- Fortification of the diet is necessary, but the amounts and types of compounds used to fortify the substitutes need to be evaluated and further investigated.
- The proportion of overweight was higher in this study than in the general Norwegian population. This could be due to low physical activity and mental retardation as well as the energy content of the protein substitutes or the widespread use of food products rich in sugar.

The third part of the hypothesis was not confirmed as the subjects did not manage to maintain serum phenylalanine according to Norwegian treatment recommendations.

- The upper recommended level for serum phe (<400µmol/L) was not manageable for the majority of subjects. All subjects had lowered their serum phenylalanine substantially, but very few managed to maintain serum phe levels according to the recommendations.

The statement in the second hypothesis was partly confirmed. Despite few significant differences between the two groups, however, the degree of mental retardation appeared to have impact on how the diet was managed:

- The subjects with mild mental retardation, who lived independently, faced greater challenges in following the diet than subjects in group homes. This difference was related to the degree of support the subjects received. Subjects with practical support from parents or the community managed to maintain

lower serum phe levels and had better everyday routines than the subjects without regular support.

- Manageability in group homes depended on mutual agreement on the importance of treatment and a basic knowledge of PKU among the staff to improve cooperation and support caregivers with main responsibility.
- Adults with brain damage due to PKU, and their caregivers, need sufficient support from their local community. Help must be taylor-made to cater for individual needs.

Better knowledge of how patients with PKU and their caregivers translate the advice and prescriptions into an everyday diet may improve the dietary treatment. This study has provided new knowledge that can prove important in regard to giving dietary advice and in organising follow-up of persons with PKU and brain damage

The results show that further investigation into the nutritional impact of this semi-synthetic diet is required.

The results from the present study can be used to stimulate the cooperation between local and national treatment and support systems.

> *"It is kind of lonely, the colleagues ask me, but I have nobody to talk to. I wish that persons working with PKU residents could get into contact. I wish there were more frequent courses and follow-up for the group homes." (Caregiver)*

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List of appendixes

Appendix table 1: Amino acids in serum

(other blood parameters in Appendix table 2)

		Group A	Group B	Total	Comments[1]
	N	7	8	15	
Taurine, µmol/L	**Mean (SD)**	57.7 (14.4)	85.5 (42.0)	72.5 (34.3)	
	Median (range)	58 (36-82)	68.5 (45-150)	60 (36-150)	
	Normal range			30-80	
Phosfoetanol-amine, µmol/L	**Mean (SD)**	0.3 (0.8)	0	0.2 (0.6)	
	Median (range)	0 (0-2)	0	0(0-2)	
	Normal range			0-4	
Aspartic acid, µmol/L	**Mean (SD)**	3.6 (1.0)	14.6 (4.0)	9.1 (14.6)	2 improperly
	Median (range)	4 (2-5)	3.5 (3-51)	4 (2-51)	prepared,
	Normal range			0-4	
Hydroxyproline µmol/L[2]	**Mean (SD)**	-	-	-	
	Median (range)	4 (trace-8)	4 (trace-9)	4 (trace-9)	
	Normal range			0-47	
Threonine, µmol/L	**Mean (SD)**	120 (26.9)	113.6 (19.6)	116.6 (22.6)	
	Median (range)	115 (90-161)	118 (90-146)	115 (90-161)	
	Normal range			84-196	
Serine, µmol/L	**Mean (SD)**	92 (19.1)	112.5 (37.4)	102.9 (31.1)	2 improperly
	Median (range)	86 (67-123)	96 (61-172)	95 (61-172)	prepared,
	Normal range			54-158	
Asparagine, µmol/L	**Mean (SD)**	46.9 (8.4)	53.8 (15.5)	50.5 (12.8)	
	Median (range)	47 (33-58)	53 (33-78)	51 (33-78)	
	Normal range			36-80	
Glutamic acid, µmol/L	**Mean (SD)**	33.7 (12.9)	86.9 (76.0)	62.1 (60.9)	
	Median (range)	30 (16-57)	54 (21-253)	43 (16-253)	
	Normal range			0-44	
Glutamine, µmol/L	**Mean (SD)**	560.4 (50.4)	497.6 (76.8)	526.9 (71.3)	
	Median (range)	552 (472-627)	487.5 (381-610)	540 (381-627)	
	Normal range			426-802	
Proline, µmol/L	**Mean (SD)**	142.1 (37.3)	156.5 (51.2)	149.8 (45.5)	
	Median (range)	124 (110-194)	155 (94-238)	141 (94-238)	
	Normal range			58-294	
Glycine, µmol/L	**Mean (SD)**	263.4 (79.8)	314.6 (63.6)	290.7 (73.8)	5 high
	Median (range)	258 (164-414)	323 (228-329)	282 (164-414)	
	Normal range			111-327	
Alanine, µmol/L	**Mean (SD)**	320.6 (64.0)	323.4 (39.4)	322.1 (50.3)	
	Median (range)	300 (250-426)	330.5 (251-383)	311 (250-426)	
	Normal range			186-522	
Citrulline, µmol/L	**Mean (SD)**	26.6 (6.9)	29.1 (7.5)	27.9 (7.1)	
	Median (range)	24 (17-38)	27.5 (22-46)	26 (17-46)	
	Normal range			17-49	

App.table 1: continued

		Group A	Group B	Total	Comments[1]
	N	7	8	15	
α-aminobutyric acid, µmol/L	Mean (SD)	14.9 (3.0)	11.8 (1.3)	13.2 (2.7)	
	Median (range)	15 (9-18)	12 (10-13)	13 (9-18)	
	Normal range			8-36	
Valine, µmol/L	Mean (SD)	220.6 (42.7)	212.6 (27.0)	216.3 (34.1)	
	Median (range)	235 (160-266)	215 (175-258)	218 (160-266)	
	Normal range			145-313	
Cystine, µmol/L	Mean (SD)	22.3 (10.3)	21.8 (17.0)	22.0 (13.8)	8 low
	Median (range)	22 (6-40)	29.5 (1-39)	24 (1-40)	
	Normal range			30-62	
Methionine, µmol/L	Mean (SD)	20.4 (4.4)	19.5 (3.6)	20.0 (4.0)	
	Median (range)	20 (14-26)	18.5 (16-26)	19 (14-26)	
	Normal range			14-30	
Isoleucine, µmol/L	Mean (SD)	52.4 (9.6)	49.3 (6.5)	50.7 (8.0)	
	Median (range)	48 (41-67)	47 (41-62)	47 (41-67)	
	Normal range			35-83	
Leucine, µmol/L	Mean (SD)	95.6 (12.1)	98.9 (17.3)	97.3 (14.8)	
	Median (range)	95 (74-112)	101 (79-129)	95 (74-129)	
	Normal range			69-161	
Tyrosine, µmol/L	Mean (SD)	57 (20.7)	47.4 (15.0)	51.9 (17.9)	No-one low
	Median (range)	53 (39-100)	39 (35-73)	52 (35-100)	1high
	Normal range			28-76	
Phenylalanine, µmol/L	Mean (SD)	618.4 (374.3)	379.8 (180.0)	491.1 (302.3)	All high!
	Median (range)	505 (187-1315)	325 (115-660)	401 (115-1315)	
	Normal range			32-68	
Homocystine free, µmol/L	Mean (SD)	0	0	0	
	Median (range)	0	0	0	
	Normal range			0	
Histidine, µmol/L	Mean (SD)	71.3 (6.0)	69.3 (7.0)	70.2 (6.4)	
	Median (range)	73 (61-80)	68.5 (58-81)	69 (58-81)	
	Normal range			64-116	
3-metyl-histidine µmol/L[2]	Mean (SD)	-	-	-	
	Median (range)	2 (trace-5)	2 (trace-4)	2 (trace-5)	
	Normal range			1-5	
1-metyl-histidine µmol/L[2]	Mean (SD)	-	-	-	
	Median (range)	3 (trace-20)	3.5 (2-23)	3 (trace-23)	
	Normal range			0-20	
Tryptophane, µmol/L	Mean (SD)	34.9 (11.4)	36.9 (11.1)	35.9 (10.9)	
	Median (range)	31 (27-60)	34 (20-56	33 (20-60)	
	Normal range			19-59	

App.table 1: continued

		Group A	Group B	Total	Comments[1]
	N	**7**	**8**	**15**	
Ornithine, µmol/L	**Mean (SD)**	62.7 (20.0)	65.4 (20.1)	64.1 (19.3)	2 high, both
	Median (range)	62 (38-102)	59 (40-99)	62 (38-102)	improperly
	Normal range			24-84	prepared
Lysine, µmol/L	**Mean (SD)**	171.9 (19.2)	193.3 (26.7)	183.3 (25.2)	
	Median (range)	169 (135-192)	188.5 (162-230)	176 (135-230)	
	Normal range			128-248	
Arginine, µmol/L	**Mean (SD)**	54.7 (9.2)	87.4 (29.9)	72.1 (27.7)	2 improperly
	Median (range)	53 (44-65)	92.5 (50-137)	64 (44-137)	prepared,
	Normal range			40-128	

[1] The terms low and high refer to results lower or higher than the laboratory's normal range.
[2] For the amino acids hydroxyproline, 3-metylhistidine and 1-metylhistidine some results were given as trace instead of definite values; mean and standard deviation could thus not be calculated.

- All **phenylalanine** analyses were high, as expected.
- **Tyrosine** will fall to subnormal levels in PKU if protein substitute is not taken, therefore the substitute is fortified with extra tyrosine. One subject was taking a substitute with larger amount of tyrosine than the other participants, resulting in a high tyrosine level.
- **Glutamic acid** easily transforms into **glutamine**, analyzed results are therefore often added and seen as one, the result should be <846 µmol/L. The results over are all in the normal range, when adding glutamine and glutamic acid.
- In a catabolic state **glycine** will rise and **valine** will fall to subnormal lavels. Five blood tests had elevated glycine, one >400 µmol/L, but valine was normal for all. Elevated glycine can be a sign of a beginning catabolic state, may be due to a long overnight fast.
- Low **valine** would implicate a catabolic state and that protein substitute was not taken as prescribed. No subject had low valine in this study.
- **Ornithine** will rise if the test is not properly prepared within a short time; simultaneously **arginine** and **cystine** will tend to fall, the high ornithine observations in the study could be explained due to improper preparation leading to these reactions.
- For two subjects, analyses were done from serum instead of heparine plasma, resulting in false high answers for aspartic acid, serine and arginine

Interpretation of amino acid analyses were done in cooperation with senior consultant Berit Woldseth, MD, Department of Medical Biochemistry at Rikshospitalet.

Appendix table 2: Blood analyses

(Amino acids in appendix table 1)

		Group A	Group B	Total	Comments[1]
B-Haemo-globin g/dl	**N**	7	6	13	All normal
	Mean (SD)	13.9 (0.8)	13.8 (0.8)	13.8 (0.76)	
	Median (range)	13.5 (13.2-15.2)	13.6 (12.9-15.2)	13.5 (12.9-15.2)	
	Normal range			F: 11.7-17 M: 13.4-17	
B-Hemato-crite, %	**N**	7	5	12	Most in low
	Mean (SD)	41.3 (1.6)	41.2 (4.7)	41.3 (3.1)	normal range
	Median (range)	41 (39-44)	39 (38-49)	41 (38-49)	
	Normal range			F: 35-46 M:40-50	
P-Iron, µmol/L	**N**	6	10	16	1 low
	Mean (SD)	18.8 (6.2)	16.2 (4.3)	17.2 (5.1)	Most in low
	Median (range)	18.5 (11-27)	16.5 (7-21)	17 (7-27)	normal range
	Normal range			F & M: 9-34	
P-Transferrin, g/L	**N**	6	7	13	Most in low
	Mean (SD)	2.7 (0.5)	2.7 (0.3)	2.7 (0.4)	normal range
	Median (range)	2.9 (1.8-3.2)	2.7 (2.3-3.1)	2.8 (1.8-3.2)	
	Normal range			F & M: 2.2-3.9	
P-Transferrin saturation	**N**	6	7	13	Most in low
	Mean (SD)	0.27 (0.06)	0.26 (0.05)	0.27 (0.05)	normal range
	Median (range)	0.27 (0.19-0.34)	0.26 (0.18-0.32)	0.26 (0.18-0.34)	
	Normal range			F: .1-.5 M:.15-.57	
P- Ferritin, µg/L	**N**	6	10	16	1 low
	Mean (SD)	83.8 (50.6)	66.3 (72.7)	72.9 (64.1)	
	Median (range)	64 (32-147)	45 (9-257)	52.5 (9-257)	
	Normal range			F:10-167 M: 29-383	
S-Carnitine free, µmol/L	**N**	6	8	14	
	Mean (SD)	31.8 (8.9)	37.6 (4.9)	35.1 (7.2)	
	Median (range)	30 (22-44)	38 (28-43)	37 (22-44)	
	Normal range			F: 19-50 M: 28-50	
S-Carnitine total, µmol/L	**N**	6	8	14	
	Mean (SD)	39.5 (9.9)	45.6 (6.8)	43 (8.5)	
	Median (range)	39 (26-51)	45.5 (35-54)	43.5 (26-54)	
	Normal range			F: 20-58 M: 34-59	
S-Urea, Mmol/L	**N**	7	9	16	
	Mean (SD)	3.6 (0.7)	4.2 (0.6)	3.9 (0.7)	
	Median (range)	3.5 (2.6-4.7)	4.1 (3.4-5.0)	3.8 (2.6-5.0)	
	Normal range			F: 2.6-6.4 M: 3.2-8.1	

App.table 2:continued

		Group A	Group B	Total	Comments[1]
S-Creatinine, µmol/L[2]	**N**	7	10	17	
	Mean (SD)	66.1 (12.8)	63.5 (10.7)	64.6 (11.3)	
	Median (range)	62 (52-82)	63.5 (46-83)	62 (46-83)	
	Normal range			F: 50-90 M: 60-105	
S-Magnesium mmol/L	**N**	6	10	16	
	Mean (SD)	0.82 (0.03)	0.91 (0.09)	0.87 (0.08)	
	Median (range)	0.83 (0.76-0.85)	0.89 (0.82-1.07)	0.85 (0.76-1.07)	
	Normal range			F&M: 0.71-0.94	
S- Vitamin B12, pmol/L	**N**	7	10	17	1 low
	Mean (SD)	464.3 (258.7)	666.4 (188.1)	583.2 (235.6)	5 high
	Median (range)	490 (110-915)	672.5 (440-1030)	580 (110-1030)	
	Normal range			F&M: 160-710	
ER-Folate, nmol/L	**N**	7	6	13	10 high
	Mean (SD)	1846.4 (1006.7)	1601.3 (447.1)	1733.3 (778.6)	
	Median (range)	1950 (605-3165)	1790 (793-1963)	1870 (605-3165)	
	Normal range			F&M: 390-1140	
S- Folate[3], nmol/L	**N**	7	8	15	13 high
	Mean (SD)	-	-	-	
	Median (range)	>54.4 (22.3-54.4)	50.5 (34->54.4)	53 (22.3->54.4)	
	Normal range			F&M:7.1-27	
S-Zinc, µmol/L	**N**	7	7	14	
	Mean (SD)	12.1 (1.1)	14.1 (1.7)	13.1 (1.7)	
	Median (range)	12 (11-14)	14 (12-17)	13 (11-17)	
	Normal range			F&M: 10-16	
P-Cholesterol mmol/L	**N**	7	10	17	4 >5.0
	Mean (SD)	4.3 (1.2)	5.0 (1.2)	4.7 (1.2)	no known heart
	Median (range)	3.9 (3.2-6.5)	4.8 (3.9-7.8)	4.6 (3.2-7.8)	disease
	Normal range			30-49 y: 3.3-6.9	
P- HDL-Cholesterol mmol/L	**N**	7	10	17	
	Mean (SD)	1.4 (0.6)	1.3 (0.3)	1.3 (0.4)	
	Median (range)	1.1 (0.9-2.3)	1.3 (0.9-1.8)	1.2 (0.9-2.3)	
	Normal range			F: 1.0-2.7 M: 0.8-2.1	
P- LDL Cholesterol mmol/L	**N**	6	10	16	6 >3.0,
	Mean (SD)	2.6 (0.6)	3.2 (1.0)	3.0 (0.9)	no known heart
	Median (range)	2.5 (1.9-3.8)	3.0 (2.4-5.8)	2.8 (1.9-5.8)	disease
	Normal range			30-49 y: 1.9-4.8	
P-Triglyceride mmol/L	**N**	7	10	17	2 high
	Mean (SD)	1.8 (1.7)	1.8 (1.2)	1.8 (1.4)	
	Median (range)	1.0 (0.7-5.6)	1.6 (0.8-4.8)	1.4 (0.7-5.6)	
	Normal range			F&M 0:.5-2.6	

App.table 2: continued

		Group A	Group B	Total	Comments[1]
P- Albumin, g/L	**N**	7	10	17	
	Mean (SD)	45.6 (3.6)	42.7 (2.1)	43.9(3.1)	
	Median (range)	47 (39-50)	42.5 (39-45)	44 (39-50)	
	Normal range			F: 36-45 M: 36-48	
S- Prealbumin, g/L	**N**	7	8	15	1 low
	Mean (SD)	0.30 (0.07)	0.25 (0.04)	0.27 (0.06)	
	Median (range)	0.31 (0.16-0.37)	0.25 (0.19-0.33)	0.27 (0.16-0.37)	
	Normal range			F: 0.23-0.39 M: 0.26-0.45	
S- Cerulo-plasmin, g/L	**N**	6	9	15	
	Mean (SD)	0.33 (0.09)	0.28 (0.06)	0.30 (0.07)	
	Median (range)	0.31 (0.25-0.47)	0.27 (0.22-0.38)	0.29 (0.22-0.47)	
	Normal range			F: 0.24-0.55 M: 0.22-0.38	

B = blood
S = serum
P = plasma

F: female
M: male
When normal range varies according to age, only mid-adult values are given.

[1] The terms low and high refer to results lower or higher than the laboratory's normal range.
[2] Estimated glomerular filtration rate (GFR) was normal >60 ml/min/1.73 m^2 for all subject with analyzed creatinine
[3] Folate in serum: 7 results were given as values >54.4 nmol/L. Geometric mean and standard deviation could thus not be calculated.

For information on analytical methods see Laboratoriehåndbok from Rikshospitalet (57)

Interpretation of the blood analyses were done in cooperation with senior consultant Per Mathisen, MD, Medical Outpatient Department at Rikshospitalet.

Appendix table 3: Intake of non-energy nutrients

		Group A	Group B	Total	NNR[1]	Nor-kost[2]
	N	7	12	19		
Cholesterol, mg/d	**Mean (SD)**	54 (36)	59 (40)	57 (38)		291
	Median (Q1-Q3)	52 (31 – 60)	44 (33 – 100)	46 (31 – 89)		
	Min-max	17 – 128	0 – 133	0 – 133		
Calcium, mg/d	**Mean (SD)**	1157 (285)	1246 (206)	1213 (235)	800	900
	Median (Q1-Q3)	1124 (942 – 1450)	1201 (1095 – 1336)	1196 (1029 – 1355)		
	Min-max	765 – 1509	1028 – 1746	765 – 1746		
Sodium, mg/d	**Mean (SD)**	2190 (619)	2453 (654)	2356 (637)		
	Median (Q1-Q3)	2466 (1782 – 2574)	2409 (1987 – 3010)	2466 (1984 – 2644)		
	Min-max	941 – 2626	1310 – 3446	941 – 3446		
Potassium, mg/d	**Mean (SD)**	2677 (822)	3381 (735)	3122 (823)		
	Median (Q1-Q3)	2663 (1963 – 3078)	3368 (2839 – 4145)	3078 (2632 – 3552)		
	Min-max	1721 – 4214	2185 – 4530	1721 – 4530		
Phosphorus mg/d	**Mean (SD)**	1200 (412)	1486 (262)	1380 (344)		
	Median (Q1-Q3)	1309 (988 – 1493)	1455 (1291 – 1589)	1410 (1215 – 1581)		
	Min-max	431 – 1719	1147 – 2147	431 – 2147		
Magnesium, mg/d	**Mean (SD)**	482 (140)	586 (84)	548 (116)	280/350	
	Median (Q1-Q3)	511 (436 – 583)	567 (529 – 640)	549 (502 – 626)		
	Min-max	209 – 640	458 – 758	209 – 758		
Iron, mg/d	**Mean (SD)**	34 (10)	43 (8)	40 (10)	15/9	10.8
	Median (Q1-Q3)	33 (26 – 46.2)	42 (36.8 – 49.2)	40 (32.9 – 46.8)		
	Min-max	25 – 48	30 – 57	25 – 57		
Zinc, mg/d	**Mean (SD)**	20 (4)	24 (3)	22 (4)	7/9	
	Median (Q1-Q3)	19 (16 – 23.1)	23 (21.4 – 24.1)	22 (19.3 – 24)		
	Min-max	14 – 25	19 – 32	14 – 32		
Selenium, µg/d	**Mean (SD)**	76 (20)	86 (15)	82 (17)	40/50	
	Median (Q1-Q3)	79 (57 – 95)	85 (79 – 91)	84 (73 – 92)		
	Min-max	43 – 100	65 – 124	43 – 124		
Vitamin A[3], µg/d	**Mean (SD)**	1680 (365)	2443 (627)	2162 (654)	700/900	1500
	Median (Q1-Q3)	1840 (1239 – 1966)	2286 (1969 – 3008)	2002 (1719 – 2598)		
	Min-max	1093 – 2002	1658 – 3507	1093 – 3507		
Vitamin D[4], µg/d	**Mean (SD)**	17.2 (6)	18.7 (5.5)	18.1 (5.6)	7.5	4.8
	Median (Q1-Q3)	18.4 (12.4 – 21.1)	18.4 (14.6 – 20.0)	18.4 (14.3 – 20.1)		
	Min-max	9.1 – 26.9	10.5 – 31.8	9.1 – 31.8		

App.table 3: continued

		Group A	Group B	Total	NNR[1]	Nor-kost[2]
	N	7	12	19		
Vitamin E[5], mg/d	**Mean (SD)**	20 (6)	22 (9)	21 (8)	8/10	
	Median (Q1-Q3)	21 (16.3 – 24.1)	23 (14.3 – 29.8)	22 (14.7 – 25.0)		
	Min-max	11 – 28	8 – 38	8 – 38		
Thiamin, mg/d	**Mean (SD)**	2.6 (0.4)	3 (0.5)	2.9 (0.5)	1.1/1.4	1.4
	Median (Q1-Q3)	2.6 (2.2 – 3.0)	3.0 (2.6 – 3.5)	2.9 (2.5 – 3.1)		
	Min-max	2.2 – 3.1	2.2 – 3.6	2.2 – 3.6		
Riboflavin, mg/d	**Mean (SD)**	2.8 (0.5)	3.2 (0.5)	3.0 (0.5)	1.3/1.7	1.7
	Median (Q1-Q3)	2.7 (2.3 – 3.4)	3.1 (2.8 – 3.6)	2.9 (2.6 – 3.5)		
	Min-max	2.2 – 3.5	2.4 – 3.9	2.2 – 3.9		
Niacin[6], mg/d	**Mean (SD)**	46 (13)	54 (9)	51 (11)	15/19	17
	Median (Q1-Q3)	46 (33 – 57)	55 (47 – 61)	54 (46 – 58)		
	Min-max	29 – 64	36 – 66	29 – 66		
Vitamin B_6[7], mg/d	**Mean (SD)**	3.6 (0.6)	4.2 (0.6)	4.0 (0.7)	1.2/1.6	
	Median (Q1-Q3)	3.3 (3.0 – 4.1)	4.1 (3.8 – 4.7)	4.0 (3.4 – 4.5)		
	Min-max	2.9 – 4.5	3.4 – 5.4	2.9 – 5.4		
Folate[8], µg/d	**Mean (SD)**	715 (273)	888 (142)	824 (211)	300	
	Median (Q1-Q3)	706 (381 – 922)	870 (792 – 969)	866 (706 – 964)		
	Min-max	342 – 1065	656 – 1174	342 – 1174		
Vitamin C[9], mg/d	**Mean (SD)**	211 (79)	281 (144)	255 (126)	75	120
	Median (Q1-Q3)	203 (161 – 266)	239 (203 – 298)	222 (183 – 266)		
	Min-max	97 – 346	178 – 696	97 – 696		
Energy from protein substitute, MJ/d	**Mean (SD)**	1.3 (0.6)	1.8 (0.3)	1.6 (0.4)		
	Median (Q1-Q3)	1.4 (0.7 – 1.9)	1.7 (1.6 – 1.9)	1.7 (1.4 – 1.9)		
	Min-max	0.4 – 1.9	1.3 - 2.1	0.4 – 2.1		

[1] NNR: Nordic Nutrition Recommendations 2004 (44)
Only adult recommendations are noted
Gender differences noted as female/male.
[2] Norkost: Johansson & Solvoll (63)

[3] Vitamin A: Retinol equivalents = retinol + 1/6 β-carotene
[4] Vitamin D: Cholecalciferol (D_3) + ergocalciferol (D_2)
[5] Vitamin E: α-tocoferol
[6] Niacin: Nicotinic acid + nicotinamid
[7] Vitamin B_6: Pyridoxin + pyridoxal + pyridoxamine
[8] Folate: Folic acid + derivatives
[9] Vitamin C: Ascorbic acid + dehydroascorbic acid

Food intake was calculated on Mat på Data 4.a (54)
Norwegian food composition table from 2001 (55)

Appendixes

Appendix 1

UNIVERSITETET I OSLO
DET MEDISINSKE FAKULTET

Avdelingsleder dr med Bengt Frode Kase
Senter for sjeldne sykdommer og syndromer
Rikshospitalet
Rikshospitalet-Radiumhospitalet HF

Regional komité for medisinsk forskningsetikk
Sør- Norge (REK Sør)
Postboks 1130 Blindern
NO-0318 Oslo

Telefon: 228 44 666
Telefaks: 228 44 661
E-post: rek-2@medisin.uio.no
Nettadresse: www.etikkom.no

Dato: 14.03.06
Deres ref.:
Vår ref.: S-05323

S-05323 **Diettbehandling for voksne med sent diagnostisert PKU**

Vi viser til brev datert 28.02.06 med vedlegg: reviderte informasjonsskriv og samtykkeerklæringer.

Komiteen tar svar på merknader til etterretning.

Komiteen har ingen merknader til revidert informasjonsskriv og samtykkeerklæring.

Vi ønsker lykke til med prosjektet.

Med vennlig hilsen

Kristian Hagestad
Fylkeslege cand.med., spes. i samf.med
Fungerende leder

Tone Haug
Rådgiver
Sekretær

Kopi (elektronisk): Masterstudent Ingrid Wiig, Senter for sjeldne sykdommer og syndromer, Rikshospitalet, Rikshospitalet-Radiumhospitalet HF

Appendix 2

Sosial- og helsedirektoratet

Avdelingsleder dr. Bengt Frode Kase
Senter for sjeldne diagnoser
Rikshospitalet
Rikshospitalet-Radiumshospitalet HF
0027 Oslo

Deres ref:
Saksbehandler: ELQ
Vår ref: 06/1146
Arkivkode:
Dato: 03.04.2006

Melding om opprettelse av forskningsbiobank – Diettbehandling for voksne med sent diagnostisert PKU

Det vises til melding av 2. desember 2005 vedrørende ovennevnte, samt til telefonsamtale mellom Ingrid Wiig og Elisabeth Qvigstad den 27. mars 2006.

Sosial- og helsedirektoratet er delegert myndighet til å vurdere meldinger om opprettelse av forskningsbiobanker i henhold til biobankloven § 4.

Beskrivelse av prosjektet
Fenylketonuri, forkortet PKU, er en medfødt stoffskiftesykdom som i dag diettbehandles fra tidlig spedbarnsalder for å sikre normal fysisk og psykisk utvikling. Behandlingen består i å begrense inntaket av aminosyren fenylalanin, og dermed protein, fra vanlig mat.

Hensikten med studien er å se på diettoppfølgningen hos pasienter med sen behandlingsstart og som har hjerneskade fra PKU. Målet for studien er å kartlegge hvordan PKU-dietten gjennomføres og er sammensatt i det daglige. Diettens virkning på fenylalanin i blod er sentralt i studien. For å se om diettanbefalingene følges er det også aktuelt med andre blodprøver for å måle nutrisjonsstatus.

Forskningsbiobanken vil delvis bestå av blod fra prøver tatt som ledd i behandling og delvis fra analyser tatt på overskudd av blod fra denne prøven. Pasientene vil ta rutinemessig blodprøve for fenylalanin i blodet. De andre blodprøvene vil i hovedsak inngå i oppfølgingskontroll ved medisinsk poliklinikk på Rikshospitalet. De prøvene som derimot er mer relatert til diettens sammensetning, vil bli mer spesifikke for denne studien. Disse analysene vil bli gjort på blod som tas venøst samtidig med kontroll ved Rikshospitalet. Blodprøvene merkes med kodenummer, og kodenøkkelen vil bli oppbevart utilgjengelig for uvedkommende.

Alle de om lag 25 studiedeltakerne har hjerneksade fra PKU. Av disse har ca. 10 en lettere utviklingshemning og vil være i stand til å kunne gi et informert samtykke til deltakelse i studien. De resterende 15 er alvorlig skadet med dypere utviklingshemning.

Ansvarlig for forskningsbiobanken er Bengt Frode Kase.

Sosial- og helsedirektoratet
Avdeling for spesialisthelsetjenester

Postadr: Pb 7000 St Olavs plass, 0130 Oslo • Besøksadr: Universitetsgaten 2, Oslo
Tel: 810 200 50 • Faks: 24 16 30 08 • Org.nr.: 983 544 622 • postmottak@shdir.no • www.shdir.no/ts

Vurdering i forhold til biobankloven
Det følger av biobankloven § 12 første ledd at innsamling, oppbevaring og behandling av humant biologisk materiale til forskningsformål krever informert samtykke fra giveren av materialet, med mindre det foreligger særskilt lovhjemmel eller annet gyldig rettsgrunnlag. I og med at opprettelse av forskningsbiobank krever samtykke fra giveren og kun noen av studieteltakerne har samtykkekompetanse, er det naturlig å behandle disse to pasientgruppene hver for seg, jf. nedenfor.

Innsamling av materiale fra pasienter med samtykkekompetanse
Direktoratet har ingen innsigelser mot at forskningsbiobanken for denne pasientgruppen opprettes i henhold til biobankloven. Det forutsettes at de av studiedeltakerne som har samtykkekompetanse avgir et frivillig, uttrykkelig og informert samtykke spesifikt for prosjektet.

Innsamling av materiale fra pasienter uten samtykkekompetanse
Når det gjelder den pasientgruppen med dypere utviklingshemning, er det blitt opplyst pr. telefon at disse pasientene fullstendig mangler samtykkekompetanse. For personer uten samtykkekompetanse etter pasientrettighetsloven § 4-3 gir biobankloven § 12 femte ledd regler om representert samtykke. Det presiseres at stedfortredende samtykke må brukes med varsomhet. Materiale fra personer uten samtykkekompetanse bør kun innhentes til forskningsbiobanker når det kan være til gagn for den gruppen personer forskningen berører og det innebærer liten helserisiko. Hensikten med studie er, som tidligere nevnt, å se på hvordan PKU-dietten gjennomføres og sammensettes, og hvordan den virker på fenylalanin i blodet. Studiedeltakerne må begrense sitt inntak av fenylalanin, og det kan derfor være til gagn for denne gruppen pasienter at diettens sammensetning studeres.

Poenget med prosjektet er å studere dietten i forhold til pasienter som allerede har fått en hjerneskade grunnet sent diagnostisert PKU. Det er derfor ikke aktuelt at personer uten hjerneskade deltar i prosjektet. Kun 10 av studiedeltakerne har imidlertid lettere utviklingshemning, men Shdir ser at dette muligens ikke er et tilstrekkelig antall deltakere for at representativiteten for studiet skal bli tilfredsstillende.

I § 12 femte ledd vises det bl.a til pasientrettighetsloven § 4-7 som omhandler representert samtykke i forbindelse med pasienter som er umyndiggjort. Den umyndiggjorte skal i så stor utstrekning som mulig selv samtykke. Dersom dette ikke er mulig, skal vergen samtykke på vegne av den umyndiggjorte. Innholdet i denne bestemmelsen legges også til grunn selv om studiedeltakerne ikke er umyndiggjorte etter lov av 28. november 1898. Det er de samme hensyn som gjør seg gjeldende når det gjelder samtykke og sterkt utviklingshemmede pasienter, uavhengig av en evt. umyndiggjøring. Det vil derfor være nødvendig med samtykke fra pårørende eller annen hjelpeverge.

Vedtak
Sosial- og helsedirektoratet har ingen innsigelser til at forskningsbiobanken opprettes i henhold til biobanken, forutsatt at det foreligger et gyldig samtykke fra giver eller verge/pårørende.

Adgangen til å tilbakekalle samtykket eller kreve destruksjon, sletting eller utlevering, gjelder ikke dersom materialet eller opplysningene er anonymisert eller dersom opplysningene allerede har inngått i vitenskapelig arbeid, jf. biobankloven § 14. Direktoratet forutsetter at pasientinformasjonen/samtykkeerklæringen endres i tråd med dette, jf. også merknad fra REK i brev av 17. februar 2006.

Direktoratet forutsetter at opprettelsen av den planlagte forskningsbiobanken oppfyller nødvendige krav til godkjenning, konsesjon m.v. i henhold til annet relevant regelverk, herunder bioteknologiloven, helseregisterloven og legemiddelloven.

Meldingen om forskningsbiobanken vil bli sendt til Nasjonalt folkehelseinstitutt som har fått ansvaret for å føre et offentlig tilgjengelig register over landets biobanker, jf. biobankloven § 6.

Med vennlig hilsen

Ragnhild Castberg e.f.
seniorrådgiver

Elisabeth Qvigstad
rådgiver

Kopi: REK Sør
Biobankregisteret

Appendix 3

Rikshospitalet - Radiumhospitalet HF

Notat

Til:	Bengt Frode Kase
Kopi:	
Fra:	Aksel Sogstad
Saksbehandler:	Maria Brask Sanengen
Dato:	08.03.2006
Offentlighet:	Ikke unntatt offentlighet
Sak:	Tilrådning av forskningsstudie unntatt konsesjon

Interne tjenester

Postadresse: 0027 OSLO
Besøksadresse: Sognsvannsvn. 20

Sentralbord: 23 07 00 00
Dir. linje: 23 07 50 34
Telefaks: 23 07 50 30

Rikshospitalet

Tilrådning til innsamling og databehandling av personopplysninger i forskningsstudiet "Diettbehandling for voksne med sent diagnostisert PKU".

Personvernombudet har vurdert det til at den planlagte databehandlingen av personopplysninger tilfredsstiller forutsetningene for melding gitt i personopplysningsforskriften § 7-27 og derfor er unntatt konsesjon. Personvernombudet har myndighet til å foreta denne avgjørelsen på vegne av Datatilsynet.

Det tilrås at prosjektet igangsettes med følgende betingelser:

- Data lagres avidentifisert på RR HFs forskningsserver.
- Alle personopplysninger slettes ved prosjektslutt i desember 2007.
- Informasjonsskriv inneholder en bemerkning om retten til innsyn i egne data.
- Registeret må vurderes og tilrås av Regional etisk komité for medisinsk forskning (REK), eventuelle merknader må følges.

Kontaktperson for prosjektet skal hvert tredje år sende personvernombudet bekreftelse på at behandlingen skjer i overensstemmelse med meldingen og helseregisterlovens regler. Hvis formålet eller databehandlingen endres må personvernombudet informeres om dette.

Vennlig hilsen

Aksel Sogstad
Personvernombud RR HF

Appendix 4

Samtykkeerklæring:

Hvis du vil delta i studien ”Diettbehandling for voksne med sent diagnostisert PKU” skal du skrive under og sende dette arket tilbake til oss i utfylt stand.
Returner denne samtykkeerklæringen innen 20. mars.
Bruk vedlagte frankerte konvolutt.

Les gjennom det vedlagte informasjonsbrevet før du bestemmer deg.
Hvis du har spørsmål om studien, ta kontakt med Ingrid Wiig på telefon 23 07 53 40 eller på e-post ingrid.wiig@rikshospitalet.no

Deltakelse i studien er frivillig og kan når som helst og uten begrunnelse trekkes tilbake.

Dato: _____ Sted: _____

Signatur: _____

Adresse: _____

_____

Telefon: _____

Denne samtykkeerklæringen sendes til:

Ingrid Wiig
Senter for sjeldne diagnoser
Rikshospitalet-Radiumhospitalet HF
0027 Oslo

Den kan også sendes på fax: 22 96 56 59

Appendix 5

Rikshospitalet – Radiumhospitalet HF

Medisinsk Service 1

Senter for sjeldne diagnoser

Postadresse:
0027 OSLO

Besøksadresse:
Forskningsvn. 3b

Sentralbord: 23 07 00 00
Dir. linje: 23 07 53 40
Telefaks: 23 07 53 50

Org.nr. NO 987 399 708 MVA

Rikshospitalet

Deres ref:
Vår ref:
Dato: 10.03.2006

Informasjon om studie vedrørende diettbehandling for voksne med PKU

Vi ønsker å invitere deg til å delta i en studie for å kartlegge diettbehandlingen hos voksne som har PKU og hjerneskade.

Man vet i dag mye om hvordan PKU-dietten bør være, men mindre om hvordan den virkelig gjennomføres. Å få slik kunnskap er viktig blant annet for å kunne gi best mulig råd og oppfølging til hver enkelt.
I studien ønsker vi også å kartlegge hvilken hjelp du og andre med PKU mottar.

Hva vil studien innebære for deg?

- I studien vil du bli spurt om å gjøre en kostregistrering.
  Det betyr at du skal notere alt du spiser og drikker i fire dager. Du vil få nøyaktig beskjed om hvordan kostregistreringen skal utføres før du starter. Du vil få eget hefte å registrere i og du kan låne vekt hvis du ikke har det selv.

- I forbindelse med registreringen vil du bli intervjuet.
  I tillegg ønsker vi å intervjue en av dine pårørende eller en fagperson som jobber for deg. Intervjuet består av spørsmål om hvordan dietten ordnes, når du fikk diagnosen PKU og hva slags støtte du mottar. Informasjon til pårørende og fagfolk er blant papirene du har fått tilsendt.

- Du skal som vanlig ta blodprøver for fenylalanin (i fingeren) hver måned.
  Vi ber om å få kopi av disse blodprøvesvarene.
  I tillegg vil du innkalles til Medisinsk poliklinikk ved Rikshospitalet eller til kontroll hos fastlegen din i løpet av våren 2006. Denne kontrollen er en del av den vanlige PKU-oppfølgingen. Vi ber om kopi av svar fra blodprøvene som tas ved denne kontrollen.

Etter studien vil du få samtale og råd om diettbehandlingen basert på kostregistreringen din.

Hvem kan delta?

- For å delta må du være voksen, ha PKU og leve på PKU-diett.
  Personer som kan delta i studien har større eller mindre hjerneskade, oftest på grunn av sen PKU-diagnose eller utilstrekkelig behandling som barn.
- Pårørende eller fagfolk rundt deg vil bli spurt om å bistå og bidra med nødvendig informasjon så studien kan gjennomføres.

Om studien

Studien er vurdert og tilrådet av Regional komité for medisinsk forskningsetikk.
Blodprøvesvarene samles i en forskningsbiobank som opprettes for denne studien.
Ansvarlig for studien og forskningsbiobanken er dr.med. Bengt Frode Kase, avdelingsleder ved Senter for sjeldne diagnoser.

Studien gjennomføres av mastergradsstudent Ingrid Wiig i samarbeid med Avdeling for ernæringsvitenskap ved Universitetet i Oslo og Senter for sjeldne diagnoser (tidligere Senter for sjeldne sykdommer og syndromer). De som blir spurt om å delta er registrert ved Senter for sjeldne diagnoser.

Personvern

Alle opplysninger vil bli behandlet konfidensielt. Det vil si at kun prosjektansvarlig Bengt Frode Kase og student Ingrid Wiig vet hvem som deltar og hvilke opplysninger som gis. All informasjon oppbevares utilgjengelig for andre.
Alle data vil være fullstendig anonymisert fra utgangen av 2007. Det betyr at når studien er ferdig vil ingen som leser resultatene, kunne knytte informasjonen til bestemte personer.

Deltakelse i studien er frivillig, og du kan trekke tilbake samtykke når som helst og uten begrunnelse. Ved samtykke om deltakelse gis det også tillatelse til gjennomgang av journal ved Rikshospitalet. Du kan be om innsyn i data som angår deg i studien. Hvis du velger å trekke samtykket tilbake før studien er avsluttet, vil opplysninger og blodprøvesvar fra deg ikke inngå i resultatene fra studien. Hvis du trekker deg fra studien, kan du be om at blodprøver ødelegges uten å bli analysert.

Dette brevet inneholder informasjon og er en invitasjon til å delta i studien.
Hvis du ønsker å delta, ber vi om at du skriver under og sender inn den vedlagte samtykkeerklæringen i vedlagte konvolutt, innen 20. mars.

Ved spørsmål, kontakt Ingrid Wiig på telefon 23 07 53 40, på mobiltelefon 976 70 994, eller på e-post: ingrid.wiig@rikshospitalet.no

Vennlig hilsen

Bengt Frode Kase
Avdelingsleder, dr.med.

Vedlagt:
Samtykkeerklæring og informasjon om studien til pårørende og fagfolk.

Appendix 6

Rikshospitalet – Radiumhospitalet HF

Medisinsk Service 1

Senter for sjeldne diagnoser

Postadresse:
0027 OSLO

Besøksadresse:
Forskningsvn. 3b

Sentralbord: 23 07 00 00
Dir. linje: 23 07 53 40
Telefaks: 23 07 53 50

Org.nr. NO 987 399 708 MVA

Rikshospitalet

Deres ref:
Vår ref:
Dato: 10.03.2006

Informasjon til pårørende og fagfolk om studie vedrørende diettbehandling for voksne med PKU

Dette brevet sendes ut sammen med informasjon og forespørsel om deltakelse i studien til personer med PKU. Vi ønsker å gjennomføre en studie for å kartlegge diettbehandlingen hos voksne som har PKU og hjerneskade. Man vet i dag mye om hvordan PKU-dietten bør være, men mindre om hvordan den gjennomføres til daglig. Spesielt lite kunnskap har man om hvordan dietten gjennomføres hos voksne med hjerneskade eller sen behandlingsstart. Å innhente kunnskap om dette er viktig blant annet for å tilpasse råd og oppfølging til hver enkelt.
Studien vil også kartlegge hvilken hjelp som ytes til brukergruppen.
Flere av de forespurte har ikke selv mulighet til å samtykke eller avslå deltakelse i studien.
Gjennomføring av studien er derfor avhengig av velvillighet og støtte hos pårørende og fagfolk.

Hva vil studien innebære?

- Studien omfatter en kostregistrering.
  Alt som spises og drikkes i fire dager skal noteres. Det vil bli gitt nøyaktig beskjed om hvordan kostregistreringen skal utføres før start. Det sendes ut eget hefte å registrere i og vekt kan lånes hvis det ikke er tilgjengelig.
- I forbindelse med registreringen vil en pårørende og/eller fagperson bli intervjuet.
  I intervjuet innhentes informasjon relatert til PKU, behandlingen og eventuelle støttetiltak. Der det er mulig vil også studiedeltakeren/informanten selv bli intervjuet.
- Blodprøver for fenylalanin (i fingeren) skal tas som vanlig hver måned.
  Vi ber om få innhente kopi av disse blodprøvesvarene. I tillegg vil deltakeren bli innkalt til kontroll ved Medisinsk poliklinikk ved Rikshospitalet, eller bli spurt om å foreta tilsvarende kontroll hos fastlege. Denne kontrollen er en del av oppfølgingen ved PKU. Regional komité for medisinsk forskningsetikk har åpnet for at vi kan be om kopi av blodprøvesvar som inngår i oppfølging og legekontroll ved PKU også der personen selv ikke kan gi samtykke om deltakelse. Blodprøvesvarene som samles i studien vil inngå i en såkalt biobank, all informasjon i biobanken vil slettes etter studien.

Utenom rutinemessige fenylalaninprøver og legekontroll, vil studien ikke påvirke hverdagen til de dårligst fungerende i pasientgruppen.
Etter studien vil det bli gitt tilbakemelding og råd basert på kostregistrering og blodprøveresultat.

Hvem kan delta?

- Voksne med PKU som lever på PKU-diett.
  Personer som kan delta i studien har større eller mindre hjerneskade, oftest på grunn av sen diagnose eller utilstrekkelig behandling som barn.
- Pårørende eller fagfolk vil bli spurt om å bistå og bidra med nødvendig informasjon så studien kan gjennomføres.

Ansvarlig for gjennomføring
Studien er vurdert og tilrådet av Regional komité for medisinsk forskningsetikk. Blodprøvesvarene samles i en forskningsbiobank som opprettes for denne studien. Ansvarlig for studien og forskningsbiobanken er dr.med Bengt Frode Kase, avdelingsleder ved Senter for sjeldne diagnoser.
Studien gjennomføres av mastergradsstudent Ingrid Wiig i samarbeid mellom Avdeling for ernæringsvitenskap ved Universitetet i Oslo og Senter for sjeldne diagnoser (tidligere Senter for sjeldne sykdommer og syndromer). Alle som blir spurt om å delta er registrert ved Senter for sjeldne diagnoser.

Personvern
Alle opplysninger vil bli behandlet konfidensielt. Kun prosjektansvarlig Frode Kase og mastergradstudent Ingrid Wiig vet hvem som deltar og hvilke opplysninger som gis. All informasjon oppbevares utilgjengelig for andre og vil være fullstendig anonymisert fra utgangen av 2007.

Deltakelse er frivillig, og studiedeltakerne kan trekke tilbake samtykket sitt når som helst og uten begrunnelse. Hvis samtykket trekkes tilbake før studien er avsluttet, vil opplysninger og blodprøvesvar fra personen ikke brukes i studien. Man kan da også be om at blodprøver ødelegges uten å bli analysert. Ved deltakelse gis det samtidig tillatelse til gjennomgang av journal ved Rikshospitalet. Deltakerne kan be om innsyn i innsamlet data vedrørende egen person.

For personer som ikke selv kan gi informert samtykke til deltakelse, ber vi om at fagfolk og/eller pårørende vurderer deltakelse i studien på vegne av personen med PKU. Fagfolk vil bli involvert i kostregistrering og intervju, mens deltakeren selv følger diettbehandlingen som vanlig.
Ved spørsmål, kontakt Ingrid Wiig på telefon 23 07 53 40, på mobiltelefon 976 70 994,
eller på e-post: ingrid.wiig@rikshospitalet.no

Vi ber om at svarslippen under returneres i utfylt stand i vedlagte konvolutt, innen 20.mars 2006.

Vennlig hilsen

Bengt Frode Kase
Avd.leder, dr.med

Svarslipp: returner innen 20.3.06, til Ingrid Wiig, Senter for sjeldne diagnoser, Rikshospitalet-Radiumhospitalet HF, 0027 Oslo

Vi/jeg kan bidra med informasjon/gjennomføre kostregistrering til studien "Diettbehandling for voksne med sent diagnostisert PKU" på vegne av pasient med PKU.

Navn på pasient: _____

Navn på kontaktperson (-er): _____

Adresse:_____

_____

Telefon: _____

Underskrift: _____

Appendix 7

Intervjuskjema – bruker – pårørende – hjelper

Samme punkter og spørsmål brukt til begge kategorier, bortsett fra siste to sider der spørsmålene var ulike – her er mellomrom og plass til notater fjernet for å redusere sidetallet.

Deltakernummer: Dato:

Innledning, kort

Forklare hensikten med intervjuet:
- Finne ut hvordan dietten gjennomføres i det daglige

Forklare hva jeg ønsker å få informasjon om:
- Hvordan man ordner seg praktisk
- Hvor mye bistand som gis, i form av tiltak fra kommunen/boligen og fra private hjelpere som familie
- Om man mottar trygdeytelser for dietten

Forklare hvordan dataene vil inngå i studien:
- Ingen vil kunne kjennes igjen, andre skal ikke gjenkjenne enkeltpersoner når resultatene leses
- Ingen andre får tilgang til svarene som gis

De fleste spørsmålene vil kun kreve korte svar, men andre kan kreve at du tenker deg mer om og trenger flere ord – ikke vær redd for å bruke tiden du trenger

Bakgrunnsdata

Boforhold i dag:

alene foreldre ektefelle/samboer egne barn andre (relasjoner)
egen bolig tilknyttet pårørendes bolig
kommunal bolig bolig med fagfolk på dagtid døgnbemanning
Hvor lenge hatt nåværende bolig?

Tidligere boforhold eller opphold i institusjon, kort sammendrag:

Faste aktiviteter eller jobb på dagtid:

Arbeid: type antall dager per uke vernet eller veiledet
Annet organisert dagtilbud:
Måltider i løpet av arbeidsdag/dagtilbud: matpakke/kantine/felles matlaging
Fritidsaktiviteter/hobbier:
Organisert/sammen med andre hyppighet
Forekommer det servering eller behov for å spise i løpet av denne tiden:

Lønn/uføretrygd

Trygdeytelser og annen økonomisk bistand utover eventuell uføretrygd

Grunnstønad Hjelpestønad Annet

Hjelp til daglige gjøremål som husarbeide, dietten, annet …

Hjelp fra pårørende, beskriv: Fast organisert eller etter behov
Tilbud fra kommunen, beskriv: timer/uke
- Fast kontaktperson i kommunen/boligen? ja/nei
- Støttekontakt? timer/uke
- Kun til fritidsaktiviteter/hjelper støttekontakten også med diett, andre oppgaver?

Funksjon og behov for hjelp/tiltak ellers (fortrinnsvis til pårørende/fagpersoner):
- Hvem hyppighet
- Årsaken til eller begrunnelsen for disse tiltakene

Ansvarsgruppe? ja/nei
hvem er med møtefrekvens
Individuell plan? ja/nei
Hjelpeverge? ja/nei
Tiltak som er søkt, men avslått: Begrunnelse som ble gitt

Diettbehandlingen

Hvem styrer gjennomføringen av dietten til daglig? Selv/fagfolk/pårørende

Hvordan organiseres menyer/måltider/matlaging, beskriv

Hvor mye PKU-mat lages i stand fra grunnen/etter egne oppskrifter

Baking middagsretter

lite/det meste/alt lite/det meste/alt

Hva mottas av hjelp i forbindelse med den daglige gjennomføringen av dietten, beskriv:

Spiseferdighet: selvstendig verbal/håndledning mating

Behov for tilrettelagt konsistens ja/nei

Dietten i sosiale sammenhenger

Fravikes dietten i noen sammenhenger? ja/nei

I tilfelle hvor ofte:

>1/uke 1/uke 2-3/måned 1/måned sjeldnere

I tilfelle når:

festdager hjemme/borte fritidsaktiviteter kafebesøk ferier/turer

kun på egen hånd sammen med hjelper

Brukes lister og vekt for å måle opp porsjoner/enheter: ja/nei

hva veies

Holdes det nøyaktig regnskap over phe-inntak? ja/nei

Andre ting som er viktige for å mestre dietten, beskriv:

Proteinerstatning

Type(-r) mengde pr dag

Hvordan tas erstatningen? antall ganger for dagen: før/i/etter måltidet

Er den grei å ta (smaksmessig, mengdemessig), beskriv

Hvordan ordnes resept og bestilling, beskriv

Bruk av spesialprodukter

Anskaffelse: butikk/postordre hvem: selv/fagfolk/pårørende

Hvilke proteinreduserte produkter brukes jevnlig:

meltyper ferdige brød annen bakst pasta/ris

PKU-melk fløteerstatning eggerstatning snacks/godter

Annet, beskriv:

Toleranse for fenylalanin

Phe-inntak: Fast mengde hver dag? mg/dag:

Anslåtte mengder?

Behandlingsmål for den enkelte, området for serum-phe du prøver å holde, umol/l:

Hvor enkelt er det å holde disse målene, beskriv:

Merker du om kostendringer påvirker phe-verdi i blodet: ja/nei

Hvor fort merkes ev endring? Samme dag/ved diettavvik over flere dager/merker ikke forskjell

Andre årsaker til endringer i serum-phe enn kosten, beskriv:

Rutinemessige blodprøver

Hvor ofte hvor

Forhold rundt prøvetaking, beskriv kort:

Tas prøven fastende? Ev hvor lenge etter siste måltid?

Medikamenter utenom proteinerstatningen:

PKU - diagnostisering - behandling

Vi har snakket mye om hvordan dietten gjennomføres til daglig og hvilken støtte og hjelp som gis. Jeg ønsker å få noe mer informasjon rundt selve diagnosen, og om behandlingen synes å ha effekt.

Forhold rundt diagnostisering for PKU?

Når ble diagnosen satt

Når ble diettbehandlingen startet:

Behandling fra diagnosetidspunkt? Senere behandlingsstart?

Har det vært opphold i diettbehandlingen:

Hvor lenge har diettbehandlingen vart (i denne omgangen):

Hvor ble den startet oppfølgingsrutiner, beskriv kort

Hvorfor startet ble diettbehandlingen startet på nytt, fortell kort:

Herfra har skjemaet ulike spørsmål til bruker selv og pårørende/hjelper.
1 – til bruker:

Egne erfaringer vedrørende diettens effekt Kun bruker selv

Først perioder uten diett/med dårlig diettoppfølging, så med diett. Jeg nevner områder som ofte påvirkes av dietten, bruk egne ord (regn med å forklare begrepene):

Fysisk/bevegelsesmessig
Oppmerksomhet/konsentrasjon
Kommunikasjon med andre/sosialt samvær
Humørsvingninger
Selvstendighet/initiativ
Ferdigheter/mestringsfølelse
Psykiske vansker
Uro i kroppen
Smerter/kroppslige plager
Søvn
Hud
Kroppslukt
Annet

Egne erfaringer Med diett.

Fysisk/bevegelsesmessig
Oppmerksomhet/konsentrasjon
Kommunikasjon med andre/sosialt samvær
Humørsvingninger
Selvstendighet/initiativ
Ferdigheter/mestringsfølelse
Psykiske vansker
Uro i kroppen
Smerter/kroppslige plager
Søvn
Hud
Kroppslukt
Annet

Avrunding

Bruker: Forklar med egne ord hvordan det er å følge PKU-diett i hverdagen.

Opplever du at behandlingen er nyttig?

Er det andre erfaringer som du gjerne vil trekke fram til slutt?

2 – til pårørende/hjelper:

PKU-symptomer uten og med diett - Besvares av pårørende og/eller fagfolk
(Uvisst hvor mye av dette som kan fås, avhengig av alder/utvikling, nedtegning av erfaringer … be om at man leter frem gamle journaler og nedtegnelser før jeg kommer – hos noen finnes RH-journal)

Jeg ønsker å se på bakgrunnen for at man startet diettbehandlingen.
Før behandlingsstart, hvordan var funksjonen og symptomer, jeg nevner noen områder som ofte påvirkes, gi eksempler:

Fysisk/motorisk
Epilepsi
Adferd
Kognitiv funksjon
Humørsvingninger
Uro
Hud
Fordøyelse
Oppmerksomhet/konsentrasjon
Selvstendighet/initiativ
Annet

Nevrologisk
Medisinske forhold ellers
Kommunikasjon/sosial adferd
Psykiske vansker
Søvn
Aggressivitet/selvskading
Kroppslukt
Tenner og munn
Språk
Evne til å lære nye ferdigheter

Med diett, er noen av symptomene over endret? Jeg bruker de samme punktene som over.

Fysisk/motorisk
Epilepsi
Adferd
Kognitiv funksjon
Humørsvingninger
Uro
Hud
Fordøyelse
Oppmerksomhet/konsentrasjon
Selvstendighet/initiativ
Annet

Nevrologisk
Medisinske forhold ellers
Kommunikasjon/sosial adferd
Psykiske vansker
Søvn
Aggressivitet/selvskading
Kroppslukt
Tenner og munn
Språk
Evne til å lære nye ferdigheter

Hva endret seg raskt, hva tok tid? Pågår det endringer fremdeles?

Til fagfolk som har deltatt i e-læringsprosjektet

Har kurset ført til endringer i brukers diettopplegg? Ja/nei
I matvarevalg/proteinerstatningen/tilberedning/planlegging/organisering
Hvis ja, beskriv
Er det sett forskjell i fenylalaninverdier? Ja/nei
Er det sett forskjell i brukers adferd/velvære/symptomer? Ja/nei
Har kurset medført holdningsendringer overfor dietten blant personalet? Ja/nei

Avrunding

Forklar med egne ord hvordan det er å bistå i gjennomføringen eller være ansvarlig for dietten i hverdagen.
Opplever du at behandlingen er nyttig?
Er det andre erfaringer som du gjerne vil trekke fram til slutt?

Appendix 8

Kostregistrering – PKU-diett

Ved spørsmål kontakt Ingrid Wiig. Telefon: 23 07 53 48 eller 976 70 994.
E-post ingrid.wiig@rikshospitalet.no

Registreringen skal foretas i fire dager etter hverandre.
Registrer alt som spises og drikkes i løpet av disse fire dagene, ikke bare det som er planlagt.

Bruk de grønne heftene til noteringen.
Et hefte per dag: noter dato og ukedag. Det er plass til kommentarer utenpå heftet. Skriv gjerne oppskrifter eller kommentarer vedrørende mat og drikke som er brukt på de blanke sidene.

Det er viktig at registreringen blir så nøyaktig som mulig.
Hver ting som inngår i måltidet skal noteres med type og mengde.
Oppgi nøyaktig navn på matvarene og drikkene. Vei hvor mye som brukes eller oppgi antall desiliter.
For PKU-melk, knekkebrød og annet med fast størrelse, er det nok å skrive opp antall stykker som er brukt.
Send gjerne innpakning med varedeklarasjon på matvarer som er brukt til meg.
Send gjerne med oppskrifter som er brukt til middag, baking osv. For retter der oppskrift er nedskrevet, holder det å gi oppskriften og hvor stor del av retten som ble spist.

Proteinerstatning må beskrives med navn, smaksvariant og mengde.
Noter når den tas og hvor mye som tas til hvert måltid.

Noter også hva som eventuelt brukes av kosttilskudd og medikamenter.
Send de ferdig utfylte heftene til Ingrid Wiig etter registreringen. Bruk vedlagte konvolutt.

Eksempel på registrering:

Måltidstype	Klokkeslett	Spisested	Ikke skriv her
LUNSJ	12.30	HJEMME	
Proteinerstatning – beskriv type	Mengde	Klokkeslett	
XP MAXAMUM, APPELSIN	33 G	12.15	
Annet: f. eks. medisiner eller tilskudd	Mengde		
TRAN	5 ML		

Er dette et vanlig måltid? ja: **X** nei:

Matvare/rett – beskriv type og mengde	Mengde	Vekt	Ikke skriv her
PKU-MELK	1 KARTONG		
PROTEINFRITT BRØD, BAKT AV SEMPER-MEL	2 SKIVER	53 G	
SOFT MARGARIN, VANLIG, til 2 skiver		6 G	
SALAMI	2 ENHETER		
TOMAT	½	57 G	
PKU-VAFFEL, SE VEDLAGT OPPSKRIFT		55 G	
JORDBÆRSYLTETØY, LERØY		20 G	
SETERRØMME		15 G	
BANAN	1 ENHET	83 G	
KAFFE		2 DL	
SOLO	½ FLASKE	2,5 DL	

Appendix 9

Kostregistrering – PKU-diett
Skjemaer for dag xx

Navn: **Dato:** **Dag:**

Deltakernummer:

Spesielle forhold rundt mat, drikke og appetitt for denne dagen, kan noteres her:

Deltakere fikk et hefte i A5-format for hver dag.
Førstesiden var som over – i tillegg var det 8 sider for registrering, utformet som skjemaet under.
Dette ga plass for å skrive opp alle matvarer til måltidene, inklusive mellommål

Registreringsskjema

Måltidstype	Klokkeslett	Spisested	Ikke skriv her
Proteinerstatning – beskriv type	Mengde	Klokkeslett	
Annet: f.eks. medisiner eller tilskudd	Mengde		

Er dette et vanlig måltid? ja: nei:

Matvare/rett – beskriv type og mengde	Mengde	Vekt	Ikke skriv her

Appendix 10

Rikshospitalet – Radiumhospitalet HF

Medisinsk Service 1

Senter for sjeldne diagnoser

Postadresse:
0027 OSLO

Besøksadresse:
Forskningsvn. 3b

Sentralbord: 23 07 00 00
Dir. linje: 23 07 53 40
Telefaks: 23 07 53 50

Org.nr. NO 987 399 708 MVA

Deres ref:
Vår ref:
Dato:

Rikshospitalet

Studie om diettbehandling for voksne med sen behandlingsstart for PKU (fenylketonuri eller Føllings sykdom)

Klinisk ernæringsfysiolog og mastergradsstudent Ingrid Wiig er i gang med en studie om diettbehandlingen hos voksne med PKU og hjerneskade.

Primærkontakt eller andre med daglig oppfølgingsansvar, har vurdert at N.N. kan delta i studien.

Bakgrunn for studien.
Man vet i dag mye om hvordan PKU-dietten bør være, men mindre om hvordan den gjennomføres til daglig. Å innhente kunnskap om hvordan dietten gjennomføres og hvordan behandlingsprinsippene blir fulgt hos voksne med hjerneskade eller sen behandlingsstart er viktig, blant annet for å kunne tilpasse råd og oppfølging til hver enkelt bruker med hjelpere.
I studien vil daglig gjennomføring av diettbehandlingen bli vurdert i forhold til anbefalinger ved PKU og generelle ernæringsmessige behov.
I tillegg vil studien se på hjelp og tiltak som trengs for den enkelte pasient for å gjennomføre dietten.

Det har ikke vært gjort noen tilsvarende studie på denne pasientgruppen i Norge. I utlandet har man sett på den medisinske effekten av behandlingen hos pasientgruppen, men studier om ernæringsmessige konsekvenser og det arbeidet dietten medfører er ikke publisert.

Hva vil studien innebære?

- Rutinemessige blodprøver for fenylalanin skal tas som vanlig, enten dette gjøres hos lege eller av personalet i boligen.
  Kopi av blodprøvesvarene innhentes til studien fra journal og screeninglaboratoriet ved Pediatrisk forskningsinstitutt på Rikshospitalet.

- I tillegg planlegges en større blodprøve for å vurdere diettens effekt på en rekke parametre.

  Fra sommeren 2005 har spesialistoppfølgingen av voksne med PKU vært sentralisert til Rikshospitalet-Radiumhospitalet HF. Blodprøver til studien vil i samarbeid med overlege dr.med. Per Mathisen ved Medisinsk poliklinikk på Rikshospitalet inngå i denne spesialistoppfølgingen. Deltakere med samtykkekompetanse (mindre hjerneskade) vil bli innkalt til poliklinikken. For deltakere med alvorlig utviklingshemning, har vi imidlertid vurdert at reise til Rikshospitalet ikke er tilrådelig, og blodprøvene bes derfor tatt ved lokalsykehus eller hos fastlege. Regional komité for medisinsk forskningsetikk – Sør-Norge har tilrådd studien blant annet på denne bakgrunn.

For deltaker N.N., ønsker vi at blodprøvene tas ved lokalt sykehus eller hos fastlege.

Rekvisisjon og prosedyre for prøvetaking, behandling av prøvene og analysering er vedlagt.

- Studien omfatter også en kostregistrering som gjennomføres av ansatte i deltakers bolig.
- I forbindelse med studien vil en fagperson og/eller pårørende bli intervjuet for å innhente informasjon relatert til PKU og behandlingen. Om mulig vil også deltakeren selv bli intervjuet.

Utenom rutinemessige fenylalaninprøver, og en større blodprøve, vil studien ikke påvirke hverdagen til de dårligst fungerende i pasientgruppen.

Blodprøvesvarene vil bli vurdert i forhold til kostregistreringen for hver enkelt deltaker, og tilbakemelding med eventuelle anbefalinger om endringer i medisinsk eller dietetisk oppfølging vil bli gitt fra overlege Per Mathisen og/eller Ingrid Wiig i samarbeid.

Ansvarlig for gjennomføring
Studien er vurdert og tilrådd av Regional komité for medisinsk forskningsetikk – Sør-Norge, og av personvernombudene ved Norsk samfunnsvitenskapelige datatjeneste og Rikshospitalet-Radiumhospitalet HF. Blodprøvesvarene samles i en forskningsbiobank opprettet for denne studien.

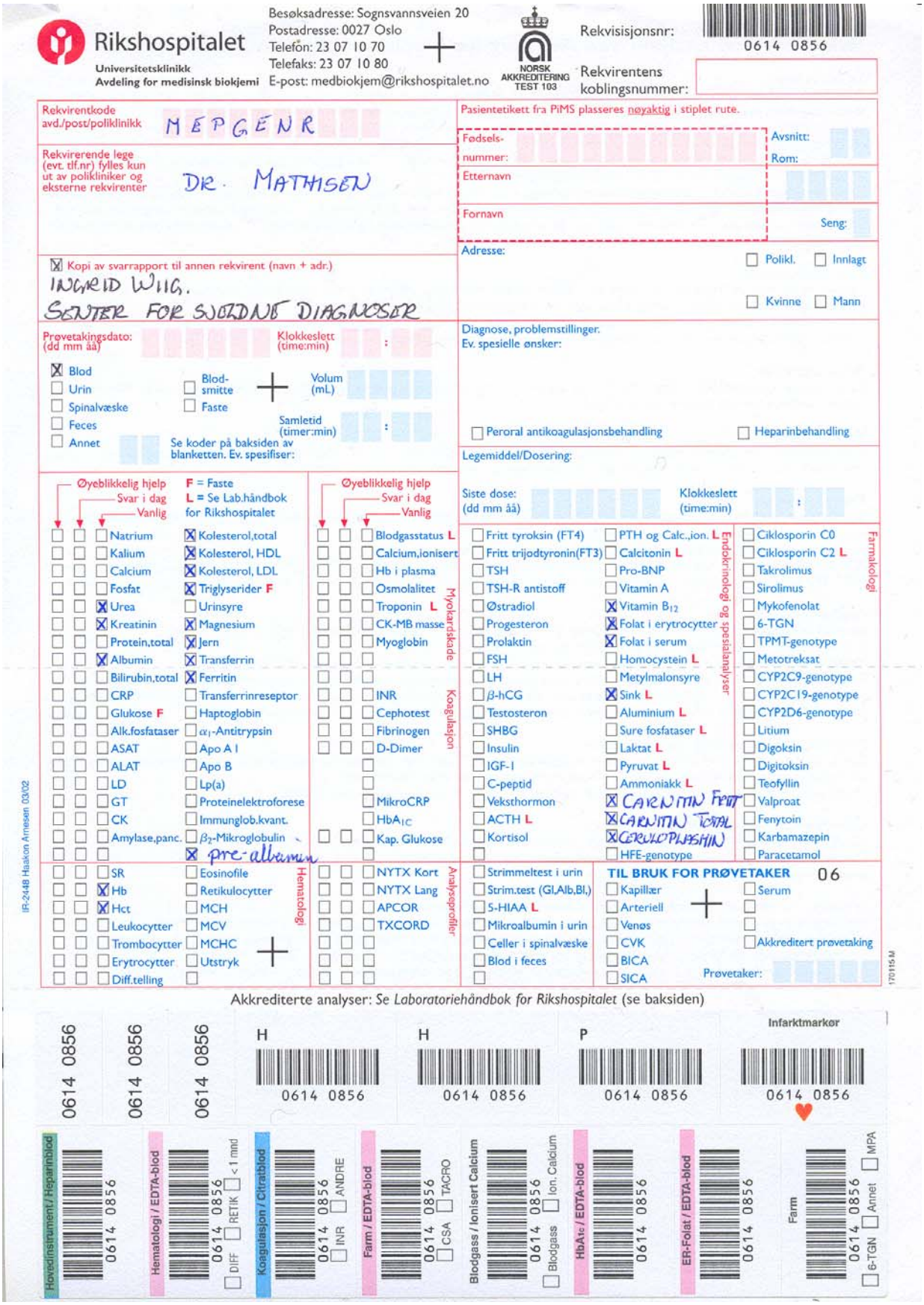
Samtidig vil den enkelte pasients blodprøvesvar inngå i den medisinske oppfølgingen og arkiveres i journal ved Rikshospitalet-Radiumhospitalet HF. Ansvarlig for studien og forskningsbiobanken er dr.med Bengt Frode Kase, avdelingsleder ved Senter for sjeldne diagnoser.

Studien gjennomføres av mastergradsstudent Ingrid Wiig i samarbeid mellom Avdeling for ernæringsvitenskap ved Universitetet i Oslo og Senter for sjeldne diagnoser ved Rikshospitalet-Radiumhospitalet HF.

Vennlig hilsen

Bengt Frode Kase	Per Mathisen	Ingrid Wiig
Avd.leder, dr.med.	Overlege, dr.med.	Student, klinisk ernæringsfysiolog

Appendix 11a



Rikshospitalet
Universitetsklinikk
Avdeling for medisinsk biokjemi

Besøksadresse: Sognsvannsveien 20
Postadresse: 0027 Oslo
Telefon: 23 07 10 70
Telefaks: 23 07 10 80
E-post: medbiokjem@rikshospitalet.no

NORSK AKKREDITERING TEST 103

Rekvisisjonsnr: 0614 0856

Rekvirentens koblingsnummer:

Rekvirentkode avd./post/poliklinikk: MEPGENR

Rekvirerende lege (evt. tlf.nr) fylles kun ut av polikliniker og eksterne rekvirenter: DR. MATHISEN

☒ Kopi av svarrapport til annen rekvirent (navn + adr.)
INGRID WIIG.
SENTER FOR SJELDNE DIAGNOSER

Pasientetikett fra PiMS plasseres nøyaktig i stiplet rute.

Fødsels-nummer: Avsnitt: Rom:
Etternavn
Fornavn Seng:
Adresse: ☐ Polikl. ☐ Innlagt ☐ Kvinne ☐ Mann

Prøvetakingsdato: (dd mm åå) Klokkeslett (time:min)

☒ Blod ☐ Urin ☐ Spinalvæske ☐ Feces ☐ Annet
☐ Blod-smitte ☐ Faste
Volum (mL)
Samletid (timer:min)
Se koder på baksiden av blanketten. Ev. spesifiser:

Diagnose, problemstillinger. Ev. spesielle ønsker:
☐ Peroral antikoagulasjonsbehandling ☐ Heparinbehandling

Legemiddel/Dosering:
Siste dose: (dd mm åå) Klokkeslett (time:min)

Øyeblikkelig hjelp / Svar i dag / Vanlig
F = Faste
L = Se Lab.håndbok for Rikshospitalet

☐ Natrium	☒ Kolesterol,total	☐ Blodgasstatus L	☐ Fritt tyroksin (FT4)	☐ PTH og Calc.,ion. L	☐ Ciklosporin C0	Farmakologi
☐ Kalium	☒ Kolesterol, HDL	☐ Calcium,ionisert	☐ Fritt trijodtyronin(FT3)	☐ Calcitonin L	☐ Ciklosporin C2 L	
☐ Calcium	☒ Kolesterol, LDL	☐ Hb i plasma	☐ TSH	☐ Pro-BNP	☐ Takrolimus	
☐ Fosfat	☒ Triglyserider F	☐ Osmolalitet	☐ TSH-R antistoff	☐ Vitamin A	☐ Sirolimus	
☒ Urea	☐ Urinsyre	☐ Troponin L	☐ Østradiol	☒ Vitamin B_{12}	☐ Mykofenolat	
☒ Kreatinin	☒ Magnesium	☐ CK-MB masse	☐ Progesteron	☒ Folat i erytrocytter	☐ 6-TGN	
☐ Protein,total	☒ Jern	☐ Myoglobin	☐ Prolaktin	☒ Folat i serum	☐ TPMT-genotype	
☒ Albumin	☒ Transferrin		☐ FSH	☐ Homocystein L	☐ Metotreksat	
☐ Bilirubin,total	☒ Ferritin		☐ LH	☐ Metylmalonsyre	☐ CYP2C9-genotype	
☐ CRP	☐ Transferrinreseptor	☐ INR	☐ β-hCG	☒ Sink L	☐ CYP2C19-genotype	
☐ Glukose F	☐ Haptoglobin	☐ Cephotest	☐ Testosteron	☐ Aluminium L	☐ CYP2D6-genotype	
☐ Alk.fosfataser	☐ α_1-Antitrypsin	☐ Fibrinogen	☐ SHBG	☐ Sure fosfataser L	☐ Litium	
☐ ASAT	☐ Apo A I	☐ D-Dimer	☐ Insulin	☐ Laktat L	☐ Digoksin	
☐ ALAT	☐ Apo B		☐ IGF-I	☐ Pyruvat L	☐ Digitoksin	
☐ LD	☐ Lp(a)		☐ C-peptid	☐ Ammoniakk L	☐ Teofyllin	
☐ GT	☐ Proteinelektroforese	☐ MikroCRP	☐ Veksthormon	☒ CARNITIN FRITT	☐ Valproat	
☐ CK	☐ Immunglob.kvant.	☐ HbA_{1c}	☐ ACTH L	☒ CARNITIN TOTAL	☐ Fenytoin	
☐ Amylase,panc.	☐ β_2-Mikroglobulin	☐ Kap. Glukose	☐ Kortisol	☒ CERULOPLASMIN	☐ Karbamazepin	
☐	☒ pre-albamin			☐ HFE-genotype	☐ Paracetamol	

Myokardskade: Blodgasstatus L, Calcium,ionisert, Hb i plasma, Osmolalitet, Troponin L, CK-MB masse, Myoglobin
Koagulasjon: INR, Cephotest, Fibrinogen, D-Dimer, MikroCRP, HbA_{1c}, Kap. Glukose
Endokrinologi og spesialanalyser: Fritt tyroksin (FT4), Fritt trijodtyronin(FT3), TSH, TSH-R antistoff, Østradiol, Progesteron, Prolaktin, FSH, LH, β-hCG, Testosteron, SHBG, Insulin, IGF-I, C-peptid, Veksthormon, ACTH L, Kortisol, PTH og Calc.,ion. L, Calcitonin L, Pro-BNP, Vitamin A, Vitamin B_{12}, Folat i erytrocytter, Folat i serum, Homocystein L, Metylmalonsyre, Sink L, Aluminium L, Sure fosfataser L, Laktat L, Pyruvat L, Ammoniakk L, CARNITIN FRITT, CARNITIN TOTAL, CERULOPLASMIN, HFE-genotype
Farmakologi: Ciklosporin C0, Ciklosporin C2 L, Takrolimus, Sirolimus, Mykofenolat, 6-TGN, TPMT-genotype, Metotreksat, CYP2C9-genotype, CYP2C19-genotype, CYP2D6-genotype, Litium, Digoksin, Digitoksin, Teofyllin, Valproat, Fenytoin, Karbamazepin, Paracetamol

☐ SR	☐ Eosinofile	☐ NYTX Kort	☐ Strimmeltest i urin	TIL BRUK FOR PRØVETAKER 06	
☒ Hb	☐ Retikulocytter	☐ NYTX Lang	☐ Strim.test (Gl,Alb,Bl,)	☐ Kapillær	☐ Serum
☒ Hct	☐ MCH	☐ APCOR	☐ 5-HIAA L	☐ Arteriell	☐
☐ Leukocytter	☐ MCV	☐ TXCORD	☐ Mikroalbumin i urin	☐ Venøs	☐
☐ Trombocytter	☐ MCHC		☐ Celler i spinalvæske	☐ CVK	☐ Akkreditert prøvetaking
☐ Erytrocytter	☐ Utstryk		☐ Blod i feces	☐ BICA	
☐ Diff.telling	☐		☐	☐ SICA	Prøvetaker:

Hematologi: SR, Hb, Hct, Leukocytter, Trombocytter, Erytrocytter, Diff.telling, Eosinofile, Retikulocytter, MCH, MCV, MCHC, Utstryk
Analyseprofiler: NYTX Kort, NYTX Lang, APCOR, TXCORD

Akkrediterte analyser: *Se Laboratoriehåndbok for Rikshospitalet* (se baksiden)

IR-244B Haakon Arnesen 03/02

170115M

0614 0856 (×3)
H 0614 0856
H 0614 0856
P 0614 0856
Infarktmarkør 0614 0856

Hovedinstrument / Heparinblod 0614 0856
Hematologi / EDTA-blod 0614 0856 ☐ DIFF ☐ RETIK ☐ < 1 mnd
Koagulasjon / Citratblod 0614 0856 ☐ INR ☐ ANDRE
Farm / EDTA-blod 0614 0856 ☐ CSA ☐ TACRO
Blodgass / Ionisert Calcium 0614 0856 ☐ Blodgass ☐ Ion. Calcium
HbA1c / EDTA-blod 0614 0856
ER-Folat / EDTA-blod 0614 0856
Farm 0614 0856 ☐ 6-TGN ☐ Annet ☐ MPA

Appendix 11b

[redacted]
Avdeling for medisinsk biokjemi
Seksjon for biokjemisk genetikk, 0027 Oslo
Tlf. 2307 1048 Faks. 2307 1080

Vennligst skriv ut skjemaet og send sammen med prøven

Dato mottatt ved RH: Sign.:

REKVISISJON FOR ANALYSER VED MISTANKE OM MEDFØDT STOFFSKIFTESYKDOM

Rekvirent:	**Pasient:**
Rekvirentnavn: DR. PER MATHISEN	Fødselsnr.(11 siffer):
Rekvirentkode/ID: MED POL	Etternavn:
Avd./sykehus:	Fornavn:
Adresse:	Adresse:
Postnr./-sted:	Postnr./-sted:
Telefon/calling:	

Kopi til: INGRID WIIG, SENTER FOR SJELDNE DIAGNOSER

Innlagt ☐ Poliklinisk ☐ Kvinne ☐ Mann ☐

Prøvemateriale:
Urin ☐ Heparinplasma ☒ Serum ☐
EDTA-plasma ☐ EDTA-blod ☐ Spinalvæske ☐ Annet ☐

Prøvetaking: Fastende ☐
Dato:
Klokkeslett:

Kliniske opplysninger/sammenfatning av sykehistorie/spesielle ønsker:

PKU - Kontroll aminosyre

Medikamenter/spesiell ernæring:

Kliniske data/laboratoriefunn:

Generelle funn:
☐ Vekstretardasjon
☐ Mikrocephali
☐ Macrocephali
☐ Dysmorfe trekk
☐ Leversykdom
☐ Splenomegali
☐ Hudanomalier
☐ Øyeanomalier
☐ Påfallende lukt
☐ Døvhet
☐ Gjentatte infeksj.
☐ Hyperventilasjon
☐ Skjelettanomalier
☐ Rakitt

Nevrologiske funn:
☐ Mental retardasjon
☐ Motorisk retardasjon
☐ Hypertoni
☐ Hypotoni
☐ Muskelsvakhet/pareser
☐ Nystagmus
☐ Ufrivillige bevegelser
☐ Epileptogene anfall
☐ Letargi/koma
☐ Avvikende oppførsel

Gastrointestinale funn:
☐ Brekninger
☐ Diaré
☐ Spisevegring

Nefrologiske funn:
☐ Nyrestein

Ernæring:
☐ Oral
☐ Parenteral

Genetikk:
☐ Foreldre beslektet
☐ Metabolsk sykd. i familien
Etnisitet.....

Laboratoriefunn:
☐ Acidose pH.....
☐ Ketose Laktatverdi...
☐ Hyperglykemi Glukose...
☐ Hypoglykemi Glukose...
☐ Hyperammonemi NH_3...
☐ Anemi Hb.....
☐ Neutropeni
☐ Trombocytopeni
☐ Koagulasjonsforstyrrelse
☐ Vakuoliserte lymfocytter

Prøvetaking:
Urin*: Minimum 10 mL urin, helst morgenurin. Ingen tilsetninger.
Plasma fra heparinblod og spinalvæske til aminosyreundersøkelse*: 0,5 - 1 mL prøvemateriale. Heparinblod og spinalvæske sentrifugeres og avpipetteres innen 30 min. Pasienten bør være fastende når blodprøve tas. Når det tas spinalvæske, må det samtidig tas heparinplasma.
Plasma fra EDTA-blod til acylcarnitinundersøkelse*: 0,5 mL prøvemateriale. Plasma avpipetteres innen 30 min.

***Må fryses umiddelbart, og sendes på tørris til laboratoriet.**

Serum til ultralange fettsyrer/fytansyre og CDT: 1 mL prøvemateriale. Kan sendes ufrosset.
DNA-analyse: 0,5-1 mL EDTA-blod. Kan sendes ufrosset. Etter avtale med laboratoriet.
Enzymanalyser: Kun etter avtale med laboratoriet.
Dersom rask analyse ønskes, må behandlende lege kontakte en av avdelingens leger.
Analyserepertoar se Laboratoriehåndboken på:
Riksnett http://10.11.10.77/klkinfo/labboka/KLK_labbok.htm#sbgtekst eller
internett http://avd.rikshospitalet.no/klkinfo/labboka/KLK_labbok.htm#sbgtekst

Appendix 12

Veiledning for blodprøvetaking i forbindelse med
"Studie om diettbehandling hos voksne med sen behandlingsstart for PKU"

Prøvene tas i samarbeid med overlege Per Mathisen ved Medisinsk poliklinikk på Rikshospitalet og inngår i den polikliniske oppfølgingen for voksne med PKU. Se vedlagte informasjonsskiv til deltakers fastlege.

Rekvisisjoner er vedlagt og ferdig utfylt, bortsett fra pasientens navn.
Blodprøvene bes tatt ved lokalt sykehus eller laboratorium som kan behandle prøvene i henhold til veiledningen nedenfor.
Alle blodprøvene sendes og analyseres ved Rikshospitalet.
(Hct og Hb kan analyseres lokalt siden de må analyseres inne 24 timer, ved lokal analyse er det viktig å føre opp svarene på rekvisisjonen for senere beregning av folat i erytrocytter).

Svar går til dr. Mathisen, Medisinsk poliklinikk ved Rikshospitalet, og Ingrid Wiig, Senter for sjeldne diagnoser, Rikshospitalet. Hvis fastlegen ønsker kopi tilsendt direkte, må det skrives inn på skjemaet.

Vi ønsker at blodprøvene tas fastende. Dersom det er umulig, ber vi om at det har gått minst 4 timer siden siste måltid.

Aminosyrer:

Heparinblod, 0,5 -1 ml prøvemateriale. Prøven sentrifugeres og avpipetteres innen 30 minutter.
Må fryses umiddelbart og sendes på tørris til Rikshospitalet.

Hct, Hb og folat i erytrocytter:

EDTA-blod – Hct og Hb må analyseres innen 24 timer – rør til folat i erytrocytter må lysbeskyttes, pakkes inn i folie.
Hvis Hct analyseres lokalt, skal svaret føres på rekvisisjonen til Rikshospitalet for beregning av folat i erytrocytter.

Sink:

Serum – glass til spormetaller er nødvendig

Serum brukes til alle analysene utenom aminosyrer og Hct, Hb og folat i erytrocytter.

Dersom transporten til Rikshospitalet drøyer, og det lokale laboratoriet selv måler hb/hct, bør serum/plasma til alle de øvrige analysene fryses og sendes frosset på tørris.
EDTA-blod til folsyre i erytrocytter kan også fryses og sendes frosset,
Det eneste som ikke tåler frysing er glasset til Hb/Hct.

Se også veiledning på laboratoriehåndboken fra Avdeling for medisinsk biokjemi på Rikshospitalet: http://avd.rikshospitalet.no/klkinfo/labboka/KLK_labbok.htm

Eventuelt kan Ingrid Wiig kontaktes på 23 07 53 48/23 07 53 40 eller på e-post ingrid.wiig@rikshospitalet.no

Ingrid Wiig, mai 2006

Appendix 13

The following phenylalanine free protein substitute products were used in the study, producers are listed alphabetically:

Prekulab Ltd, Korsør, Denmark:	Avonil and PreKUnil
SHS International Ltd, Liverpool, UK:	Lophlex and XPMaxamum
Vitaflo International Ltd, Liverpool, UK:	PKUexpress

PreKULab
we conduct research for a better life...

Avonil®

AA TABLETS

For the treatment of PKU

One Avonil tablet gives 0,5 g Amino Acids (AA), vitamins and minerals.
Avonil tablets are for the dietary management of the proven PKU. The product does not contain the amino acid phenylalanine, and is well qualified to meet the daily need of amino acids, vitamins and minerals for persons with phenylketonuria from 4 years of age, including maternal PKU patients.

Avonil tablets are not intended for use as a sole source of nutrition. Avonil must be supplemented with a low protein diet and taken under strict medical supervision.

Avonil tablets are without any smell or taste.

The recommended amount of tablets is individual, depending on lean body mass, physical activity and the ability to metabolise natural protein.

Avonil tablets daily dosage should be calculated by a metabolic doctor or clinical dietician. Avonil tablets should be divided into three or more dosages, distributed over the day and taken along with a meal. The optimal effect of Avonil, preventing phenylalanine from remaining in the blood stream and thus entering the brain, does only work if food and Avonil are eaten simultaneously.

Avonil tablets are swallowed along with water like any other tablets.

900 TABLETS.
Amino Acids: Glutamine, Tyrosine, Leucine, Aspartic acid, Proline, Lysine, Valine, Isoleucine, Serine, Threonine, Alanine, Arginine, Methionine, Histidine, Glycine, Cystine, Tryptophane;
Vitamins and Minerals.
Tablets accessory agents: Microcrystalline cellulose, Colloid hydrated silica, Magnesium salts of fatty acids, rice starch.
Coating: HPMC/hypromellose, olive oil.

Store in a cool, dry place.
Keep away from children.

Nutritional Information

	Contents Pr. 100 g	% of RDA pr. 100 g	Contents per 120 tablets	% of RDA pr 120 tablets
Vitamins:				
Vitamin A	903 RE	113 %	800 RE	100 %
Thiamin B1	1,6 mg	113 %	1,4 mg	100 %
Riboflavin B2	1,8 mg	113 %	1,6 mg	100 %
Vitamin B6	2,3 mg	113 %	2,0 mg	100 %
Vitamin B12	1,1 µg	113 %	1,0 µg	100 %
Folic Acid	226 µg	113 %	200 µg	100 %
Niacin	20 NE	113 %	18 NE	100 %
Pantothenic Acid	6,8 mg	113 %	6,0 mg	100 %
Biotin	169 µg	113 %	150 µg	100 %
Vitamin C	68 mg	113 %	60 mg	100 %
Vitamin D	5,6 µg	113 %	5,0 µg	100 %
Vitamin E	11 α-TE	113 %	10 α-TE	100 %
Vitamin K	79 µg	113 %	70 µg	100 %

	Contents Pr 100 g	% of RDA pr 100 g	Contents per 120 tablets	% of RDA pr. 120 tablets
Minerals:				
Calcium	903 mg	113 %	800 mg	100 %
Phosphoros	903 mg	113 %	800 mg	100 %
Magnesium	339 mg	113 %	300 mg	100 %
Iron	16 mg	113 %	14 mg	100 %
Zinc	17 mg	113 %	15 mg	100 %
Copper	2,3 mg	113 %	2,0 mg	100 %
Iodine	169 µg	113 %	150 µg	100 %
Manganese	2,8 mg	113 %	2,5 mg	100 %
Chromium	56 µg	113 %	50 µg	100 %
Selenium	56 µg	113 %	50 µg	100 %
Molybdenum	169 µg	113 %	150 µg	100 %
Sodium	133 µg	-	118 µg	-
Potassium	1148 mg	-	1017 mg	-
Chloride	734 µg	-	630 µg	-

	Per 100 g
Energy	974 kJ/ 232 kcal
Amino Acids	68 g
Protein equivalent	55,8 g
Carbohydrate	1 g
Fat	0-1 g

PreKULab

Marketed by:
PreKUlab Ltd.
Rewej 41
DK-4220 Korsør
Phone: (+45) 58 37 31 00
Fax.: (+45) 58 37 31 01
www.prekulab.com
info@prekulab.com

PreKULab
we conduct research for a better life...

PreKUnil®

LNAA TABLETS

For the treatment of PKU

1 tablet = (750 mg) includes 500 mg amino acids.

PreKUnil tablets are for dietary management of phenylketonuria (PKU) in patients, from teenage.
PreKUnil tablets are an amino acid (AA) supplement, including all essential AAs with a large dosage of two selected amino acids:
Tyrosine and Tryptophane are precursors to serotonin, dopamine and noradrenaline and also inhibit the uptake of phenylalanine across the blood-brain barrier. In addition, PreKUnil tablets contain the large neutral amino acids (LNAAs): arginine, leucine, histidine, methionine, isoleucine, valine and threonine, which lower the influx of phenylalanine to the brain and thereby increase the possibility of normal neuropsychological performance.

PreKUnil tablets are not suitable as a sole source of nutrition.
PreKUnil tablets are swallowed with water.
PreKUnil tablets are without any smell or taste.

PreKUnil tablets must be supplemented with Lysine and a moderate restricted PKU diet consisting of normal bread, rice, pasta, vegetables, fruits, fatty fish and meat. Fish, lean meat and dairy products such as cottage cheese, milk, and yoghurt should be discussed or avoided. Always consult a metabolic doctor or clinical dietician.

PreKUnil tablets must be used under strict medical supervision.
PreKUnil tablets must not be used by maternal PKU patients

Dosage and administration
The recommended amount of tablets depends on lean body mass.
Body weight x 0.4 = number of tablets.
It is important to take the tablets in three or more dosages distributed over the day along with a meal. The blocking effect of tyrosine and tryptophan, preventing phenylalanine from entering the brain, does only work if food and PreKUnil are eaten at the same time.

The phenylalanine plasma concentration should be monitored regularly and kept below 1500 µ/l.

Store in a cool, dry place.
Keep away from children.

Nutritional information — 550 TABLETS

Ingredients:
256 mg L-Tyrosine, L-Tryptophane
244 mg L-Methionine, L-Isoleucine, L-Treonine, L-Valine, L-Leucine, L-Histidine, L-Arginine

Constituents:
Dicalcium phosphate, corn- & potato starch, Talcum, Polyvinylpyrrolidon, Silicon dioxide, Magnesium salts of fatty acids. Hypromellose, Glycerol.

100g tablets	
Energy:	1146 kJ/273 Kcal
Amino acids:	67 g
Protein equivalent:	55 g
Carbohydrate:	12,8 g
Fat:	0-1 g

No vitamins or minerals.
Nutritionally incomplete.

PreKULab

Marketed by:
PreKUlab Ltd.
Rewej 41
DK-4220 Korsør
Phone: (+45) 58 37 31 00
Fax.: (+45) 58 37 31 01
www.prekulab.com
info@prekulab.com

• Phenylalanine free

Lophlex Powder

DESCRIPTION
Lophlex is a phenylalanine free drink mix containing a balanced mixture of essential and non-essential amino acids, vitamins, trace elements and minerals. Available in Unflavoured, Berry and Orange flavours. A food for special medical purposes.

INDICATIONS
Lophlex is for use in the dietary management of proven Phenylketonuria (PKU) in children aged 8+ years and adults including pregnant women.

SUGGESTED INTAKE
The recommended dosage of Lophlex is dependent on the age, bodyweight and medical condition of the patient and should be determined by a clinician or dietitian only. The daily intake of Lophlex should be divided into equal portions and distributed throughout the day.

This product must be supplemented with natural protein, fluid and other nutrients in medically prescribed quantities to meet the phenylalanine and general nutritional requirements of the patient. Lophlex contains only trace amounts of sodium, potassium and chloride.

PREPARATION & ADMINISTRATION
Water or diluted drinks should be offered / taken at the same time as Lophlex. To ensure tolerance, Lophlex may initially need to be introduced at a lower concentration.

Lophlex can be prepared by pasting or shaking:
1. To make a paste, mix the contents of one sachet with a small amount of water. Continue stirring while adding water to make a final volume of approximately 80mls.
2. Alternatively, to prepare Lophlex by shaking, pour 65mls cold water into a container with a screw top lid. Empty the contents of the sachet into the container. Seal and shake well until the powder is dissolved.

Lophlex is best prepared with chilled water and consumed immediately after preparation.

PRECAUTIONS
Must only be used under strict medical supervision.
Not intended for use as the sole source of nutrition.
Not for parenteral use.
Not suitable for metabolic disorders other than PKU or as a supplement for individuals who do not have PKU.

STORAGE
Store in a cool, dry place.

PACK SIZE
30 x 27.8g sachets.

NUTRITION INFORMATION	per 100g	per Sachet*
Energy kJ	1384 (1316)	385 (366)
kcal	326 (310)	91 (88)
Protein Equivalent g	72	20
Amino Acids g	86.5	24
Carbohydrate g	9 (5)	2.5 (1.4)
as sugars g	0.82 (0.7)	0.23 (0.19)
	(0.42)	(0.11)
Fat g	0.2	0.06
as saturates g	0.05	0.01
monounsaturates g	0.01	<0.01
polyunsaturates g	0.13	0.04
Fibre g	0.8	0.22
Vitamins	**per 100g Powder**	**per Sachet***
Vitamin A µg RE	1024	285
IU	3410	948
Vitamin D µg	12.8	3.6
IU	512	142
Vitamin E mg α T.E.	11.5	3.2
IU	17.1	4.8
Vitamin C mg	64	17.8
Vitamin K µg	89.6	24.9
Thiamin mg	1.5	0.42
Riboflavin mg	1.8	0.5
Niacin mg	25.6	7.1
mg NE	53.9	15
Vitamin B6 mg	2.1	0.58
Folacin Acid µg	896	249
Vitamin B12 µg	6.4	1.8
Biotin µg	192	53.4
Pantothenic Acid mg	6.4	1.8
Choline mg	546	152
Inositol mg	146	40.6
Minerals	**per 100g Powder**	**per Sachet***
Sodium mg	<20	<5.6
mmol	<0.87	<0.24
Potassium mg	<10 (<25)	<2.8 (<7)
mmol	<0.25 (<0.64)	<0.07 (<0.18)
Chloride mg	<5	<1.4
mmol	<0.14	<0.04
Calcium mg	1280	356
Phosphorus mg	992	276
Magnesium mg	384	107
Calcium : Phosphorus	1.3:1	
Trace Elements	**per 100g Powder**	**per Sachet***
Iron mg	19.2	5.3
Copper µg	1900	528
Zinc mg	14.1	3.9
Manganese mg	1.9	0.53
Iodine µg	210	58.4
Molybdenum µg	90	25
Selenium µg	96	26.7
Chromium µg	38	10.6

Amino Acid Profile	per 100ml
L-Alanine	3.3
L-Arginine	5.8
L-Aspartic Acid	5.4
L-Cystine	2.2
Glycine	5.1
L-Histidine	3.3
L-Isoleucine	5.1
L-Leucine	8.7
L-Lysine	5.9
L-Methionine	1.4
L-Phenylalanine	nil added
L-Proline	6.2
L-Serine	3.8
L-Threonine	4.3
L-Tryptophan	1.7
L-Tyrosine	7.8
L-Valine	5.6
L-Carnitine mg	57
Taurine mg	113
L-Glutamine mg	3950

* Each sachet contains 27.8g powder

Information is for unflavoured Lophlex Powder unless noted in brackets
( ) *Orange & Berry* flavours
( ) *Berry* flavour

• Phenylalanine free

XP Maxamum

DESCRIPTION
XP Maxamum is a phenylalanine free drink mix containing essential and non-essential amino acids, carbohydrate, vitamins, minerals and trace elements. Available in Orange flavour (contains colours, sugar and sweeteners), Strawberry flavour (contains colours, sugar and sweeteners) or Unflavoured. A food for special medical purposes.

INDICATIONS
XP Maxamum is for use in the dietary management of children over 8 years of age, and adults, including pregnant women, with proven phenylketonuria.

SUGGESTED INTAKE
The quantity of XP Maxamum should be determined by a clinician or a dietitian only and is dependent on the age, bodyweight and medical condition of the patient.

The diet must be supplemented with natural protein and other nutrients in medically prescribed quantities to meet the phenylalanine and general nutrient requirements of the patient.

PREPARATION & ADMINISTRATION
The recommended dilution is 1 to 5 (i.e. 20g XP Maxamum plus 100mls water). It is advised for osmotically sensitive patients to start with a 1 to 7 dilution.

1. Add a small amount of water to the prescribed amount of XP Maxamum. Stir with a fork until a smooth paste is obtained.
2. Continue stirring whilst adding the remaining volume of water.

XP Maxamum is now ready for use.

XP Maxamum can be taken as a chilled drink or it can be taken as a paste. If taken as a paste additional water or diluted drinks must be consumed at the same time.

OSMOLALITY
The osmolality of XP Maxamum (unflavoured)
1 to 5 dilution = 1000 mosm/kg.
1 to 7 dilution = 690 mosm/kg.

The osmolality of XP Maxamum (orange flavour)
1 to 5 dilution = 1150 mosm/kg.
1 to 7 dilution = 800 mosm/kg.

PRECAUTIONS
Use under medical supervision.
Not suitable for use as a sole source of nutrition.
Not suitable for infants.
Not for parenteral use.

STORAGE
Store in a cool, dry place.
Always replace container lid after use.
Once opened, use within one month.

PACK SIZE
500g cans.
30 x 50g sachets

SHELF LIFE
3 years.

NUTRITION INFORMATION	per 100g powder
Energy kJ	1260
kcal	297
Protein Equivalent g	30
Total Amino Acids g	47
Carbohydrate g	34
of which sugars g	3.1(31.7)
of which lactose g	nil added
Fat g	<0.5
of which saturates g	Trace
monounsaturates g	-
polyunsaturates g	-
% LCT	-
% MCT	-
Ratio n6 : n3 fatty acids	-
% energy from linoleic acid	-
% energy from α linolenic acid	-
Fibre g	nil added

Amino Acid Profile	g per 100g powder
L-Alanine	1.7
L-Arginine	3.2
L-Aspartic Acid	3
L-Cystine	1.2
L-Glutamic Acid	nil added
Glycine	3
L-Histidine	1.8
L-Isoleucine	2.8
L-Leucine	4.8
L-Lysine	3.7
L-Methionine	0.8
L-Phenylalanine	nil added
L-Proline	3.4
L-Serine	2.1
L-Threonine	2.4
L-Tryptophan	0.9
L-Tyrosine	4.2
L-Valine	3.1
L-Carnitine	0.02
Taurine	0.15
L-Glutamine	5.2

Vitamins	per 100g powder
Vitamin A µg RE	710
IU	2364
Vitamin D µg	7.8
IU	312
Vitamin E mg α TE	5.2
IU	7.7
Vitamin C mg	90
Vitamin K µg	70
Thiamin mg	1.4
Riboflavin mg	1.4
Niacin mg	13.6
mg NE	20.3
Vitamin B_6 mg	2.1
Folic Acid µg	500
Vitamin B_{12} µg	3.6
Biotin µg	140
Pantothenic Acid mg	5.0
Choline mg	321
Inositol mg	85.7

Minerals	per 100 g powder
Sodium mg	560
mmol	24.3
Potassium mg	700
mmol	17.9
Chloride mg	560
mmol	15.8
Calcium mg	670
Phosphorus mg	670
Magnesium mg	286

Trace Elements	per 100g powder
Iron mg	23.5
Copper mg	1.4
Zinc mg	13.6
Manganese mg	2.1
Iodine µg	107
Molybdenum µg	107
Selenium µg	50
Chromium µg	50

Note: Figures in brackets represent flavoured XP Maxamum.

Nutritional Information for PKU express powder

Typical composition of dry powder		per 100g	per 25g sachet
Energy	kJ	1260	315
	kcal	302	76
Protein equivalent	g	60	15
Total amino acids	g	72	18.2
Carbohydrate	g	15	3.8
of which sugars	g*	0.0	0.0
Total fat	g	<0.5	<0.1
of which saturates	g	Trace	Trace
Vitamins			
Vitamin A	µg	1008	252
Vitamin D	µg	13	3.3
Vitamin E	mg	11.5	2.9
Vitamin C	mg	108	27
Vitamin K	µg	101	25.3
Thiamin	mg	2	0.5
Riboflavin	mg	2.3	0.6
Niacin	mg	25.2	6.3
Vitamin B_6	mg	2.9	0.7
Folic acid	µg	400	100
Vitamin B_{12}	µg	9.4	2.4
Biotin	µg	187	46.8
Pantothenic acid	mg	7.9	2
Minerals			
Sodium	mg	568	142
	mmol	24.4	6.1
Potassium	mg	1045	261
	mmol	27.2	6.8
Chloride	mg	874	219
	mmol	24.5	6.1
Calcium	mg	1116	279
Phosphorus	mg	1105	276
Magnesium	mg	415	104

Typical composition of dry powder		per 100g	per 25g sachet
Trace Elements			
Iron	mg	21.6	5.4
Copper	mg	2.2	0.6
Zinc	mg	21.6	5.4
Manganese	mg	3.2	0.8
Iodine	µg	166	41.5
Molybdenum	µg	144	36
Selenium	µg	86	21.5
Chromium	µg	86	21.5
Amino acids			
L-Alanine	g	2.56	0.64
L-Arginine	g	4.14	1.04
L-Aspartic acid	g	6.56	1.64
L-Cystine	g	1.67	0.42
L-Glutamine	g	5.10	1.28
Glycine	g	6.53	1.63
L-Histidine	g	2.55	0.64
L-Isoleucine	g	4.47	1.12
L-Leucine	g	7.02	1.76
L-Lysine	g	4.64	1.16
L-Methionine	g	1.24	0.31
L-Phenylalanine	g	0.00	0.00
L-Proline	g	4.67	1.17
L-Serine	g	2.91	0.73
L-Threonine	g	4.54	1.14
L-Tryptophan	g	1.40	0.35
L-Tyrosine	g	6.59	1.65
L-Valine	g	5.17	1.29
L-Carnitine	mg	65.10	16.28
Taurine	mg	129.60	32.40

* With sugar and sweetener in flavoured version.
Average sugar content of flavoured versions is 4g per 100g of dry powder.