Diet, bone- and body composition in pediatric patients with home parenteral nutrition and a group of healthy children

Christina Nicolaisen Kjeserud

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Christina Nicolaisen Kjeserud

Supervisors:
Janne Anita Kvammen

Christine Henriksen

Department of Nutrition

Faculty of Medicine

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Oslo, March 2018, Christina Nicolaisen Kjeserud.

Abstract

Background and aims: Pediatric patients with intestinal failure receiving home parenteral nutrition (HPN) has been found to be at risk for growth retardation, metabolic bone disease and nutritional deficiencies. The primary aim of this thesis was to describe diet, bone- and body composition in Norwegian pediatric HPN patients and a group of healthy children and adolescents. Secondary, vitamin D-status and physical activity were described, as these factors might affect bone health.

Subjects and methods: This cross-sectional study was conducted at the Oslo University Hospital and the University of Oslo. Nineteen HPN-patients and a reference group of 50 healthy children and adolescents aged 2 – 18 years, were included from February to September 2017. Dietary intake were assessed by a 4 days record. Measurements of bone and body composition were done by dual energy x-ray absorptiometry (DXA). Blood samples were analyzed for 25(OH) vitamin D. Physical activity was objectively registered by an accelerometer (GENEActiv) and a self-reported questionnaire.

Results: Compared to the reference group**,** the HPN-patients had lower dietary intake of fat (27 vs 33 E %) and protein (13 vs 16 E %), and higher intake of carbohydrate (56 vs 48 E %). They also had a higher intake of vitamin D (149 vs 44 % of RDI) and a lower intake of calcium (45 vs 114 % of RDI) and phosphorous (100 vs 248 % of RDI). The HPN-patients had significantly lower height-for-age z-score (-1.8) and weight-for-age Z-score (-0.5) than the reference-group. They also had a significantly lower bone mineral density (BMD) Z-score for total body (-0.70) and spine (-1.1), a higher body fat mass (34 vs 25 %) and a lower body lean mass (63 vs 71 %). A third of the HPN patients had low spine BMD. No differences were found in either 25(OH)D or moderate-to-vigorous physical activity measured by the accelerometer between the two groups. However, the frequency and intensity measured by the questionnaire were significantly lower in the HPN-group than in the reference-group.

Conclusion: The low dietary intake of calcium in the HPN-group are worrisome and needs further attention. The lower height-for-age, BMD Z-score and the higher fat mass in the HPN-group compared to the reference-group illustrates the importance of follow-up of these patients. Further research is however needed to investigate the longitudinal impact of nutritional status and physical activity on HPN children's growth and bone health.

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Abbreviations

1.25(OH)2D	=	1.25-dihydroxy-vitamin D
25(OH)D	=	25-hydroxy-vitamin D
BMC	=	Bone Mineral Content
BMD	=	Bone Mineral Density
CIPO	=	Chronic Intestinal Pseudo Obstruction
CRF	=	Case Report Form
DBP	=	Vitamin D Binding Protein
DXA	=	Dual Energy X-ray Absorptiometry
EN	=	Enteral Nutrition
ENS	=	Enteral Nutrition Support
ESPGHAN 2005	=	European Society for Paediatric Gastroenterology, Hepatology and Nutrition 2005
FM	=	Total Body Fat Mass
HPN	=	Home Parenteral Nutrition
IF	=	Intestinal Failure
Spine	=	Anterior-posterior lumbar spine vertebral body 2-4
LM	=	Total Body Lean Mass
MBD	=	Metabolic Bone Disease
MVPA	=	Moderate-to-vigorous Physical Activity
NNR 2012	=	Nordic Nutrition Recommendations 2012
OUH	=	Oslo University Hospital
PA	=	Physical Activity
PBM	=	Peak Bone Mass
PTH	=	Parathyroid Hormone
RDI	=	Recommended Daily Intake
RH	=	Rikshospitalet
RXR	=	Retinoic acid X Receptor
SBS	=	Short Bowel Syndrome
SLPA	=	Sedentary-to-Light Physical Activity
SVM	=	Sum Vector Magnitude
UH	=	Ullevål Hospital
UiO	=	University of Oslo
VDR	=	Vitamin D Receptor
VDRE	=	Vitamin D Response Element
WHO	=	World Health Organization

1. Introduction

1.1 Intestinal failure (IF)

Pediatric intestinal failure (IF) is a collective name for a heterogenic group of medical conditions in the gastrointestinal tract that results in inadequate absorption of necessary nutrients for proper development and growth. The causes of IF can include short bowel syndrome (SBS), different types of dysmotility disorders (including chronic intestinal pseudo obstruction (CIPO)) and congenital disorders with absorptive defects (including enteropathies and inflammatory bowel disease) (1, 2). To secure the nutritional needs in children and adolescents with IF, parenteral nutrition (PN) support is necessary (2, 3).

As IF is a rare condition with atypical etiology and varied definitions, the overall treatment guidelines and potential outcomes are not fully established (3). Despite the atypical etiology of IF, there are some common long-term outcomes like growth retardation, metabolic bone disease (MBD) and nutritional deficiencies, which are observed in various degrees in most of the IF-patients (2, 4).

At Oslo University Hospital (OUH) there was by May 2017 registered 19 pediatric patients with IF, age 2 – 18 years, being treated with long-term PN at home.

1.2 Nutritional management of IF

The nutritional management of IF involves both parenteral nutrition (PN) and enteral nutrition (EN) (5). Percentage distribution of PN and EN given to maintain the nutritional needs in a growing child depends on how severe the compromise of the gastrointestinal tract is and the capacity of absorption (3). In managing IF, the main goal is to secure optimal nutritional status, especially in children and adolescents who has enhanced needs due to growth and development (6).

Enteral nutrition (EN)

If the patient has at least a partially functioning gastrointestinal tract, the use of EN is emphasized to avoid atrophy of the intestinal mucosa (7). Enteral nutrition (EN) includes the intake of a normal diet and enteral nutrition support (ENS). ENS includes supplemental

nutritional drinks and tube feeding to the stomach or postpylorically. There are several products suitable for ENS-use, among them are polymeric feeds based on cow's milk protein or low-molecular formulas which are based on hydrolysates of protein or elemental feeds based on free amino acids (5).

Fully nutritional support is mixtures containing all the essential nutrients and can cover 100 % of recommended daily intake (RDI) if adequate volume is used. These products are used when intake of normal food items are not achievable. Supplemental nutritional support is mixtures with different amounts of energy and a different selection of nutrients. These products are meant as an addition to normal diet and often used to increase a patient's energy intake (kcal/kg) or to make sure the nutrient requirements are fully covered (4, 5).

The choice of product and its volume is prescribed in accordance with the patient's age and function and tolerance of the gastrointestinal tract (3-5).

Parenteral nutrition (PN)

Parenteral nutrition (PN) is an intravenous nutritional treatment, given to patients who cannot meet their nutritional needs orally or by tube feeding. PN is provided through a central or peripheral vein and given either as a cyclic or a continuous infusion (8). Composition of PN is individually adapted according to the patient's nutritional status, medical condition and age (9). PN is a mix of the required carbohydrates, amino acids, fatty acids, electrolytes, vitamins, trace elements and fluid (9, 10).

1.2.1 Home parenteral nutrition (HPN)

The length and severity of an IF-diagnosis is varied and when PN is expected to be long-term (>3-6 months) the use of home parenteral nutrition (HPN) is considered (9). HPN is possible for those patients with a stabilized condition in regards to their disease and which could safely receive treatment outside the hospital. The parents are carefully trained in the procedure and many patients might obtain this nutritional regime for many years (2, 6, 9, 11).

1.3 Bone composition

1.3.1 Bone development

The skeleton develops rapidly during childhood and adolescence. The bone provides mechanical support, protection of the soft tissue and is a storage place for the minerals phosphorus (80 – 85 %) and calcium (85 – 90 %) (12). The bones will in childhood and adolescence both expand and lengthen (13). The structure and composition of the bones is affected by puberty, gender, the amount and type of physical activity, nutritional factors, genetics and sickness, among other factors (13-15).

The composition of bones involves modeling, growth and development of the skeleton and is a tightly regulated process (13). It involves the 4 cell types; osteoclasts, osteoblasts, bone lining cells and osteocytes (16, 17). The bones are continuously in a remodeling process where old bones are replaced by new bones. Modeling happens during childhood and puberty when the bones are on continuous growth (18). Remodeling includes reabsorption by the osteoclasts and rebuilding by osteoblasts, with both lining bone cells and osteocytes being a part of this (Figure 1). Normal homeostasis of calcium and phosphorous is dependent upon the bones being normally remodeled. The accumulation of bone mass is due to mineralization of the bones (13). This process involves deposition of organic matrix into the bones and calcium and phosphorous being formed into hydroxyapatite-crystals ($Ca_{10}(PO_4)_6(OH)_2$. The strength of the bones, is due to the combination of collagen and hydroxyapatite-crystals among other inorganic and organic molecules (17, 19).

The size and shape of the bones is decided by the cortical bone and trabecular bone (Figure 1). The cortical bone is the outer layer of the bones, which is compact and serves as a protector of the bone marrow and the trabecular bone. The trabecular bone defines the structural strength of the bone, with its sponge-like structure and is most abundant in the vertebra area. The amount of both cortical bone and trabecular bone is involved in the strength and integrity of the bones (16, 20). The cortical bone is affected in size all the way in to the third decade of life, and by the reach of adulthood the skeleton consists of 80 % cortical bone. The increasing thickness and separation of the trabecular bone early in life results in a consistent bone volume. The trabecular bone is the most metabolically active during childhood and adolescence compared to the cortical bones (16, 19).

The longitudinal growth of the bones occurs at the epiphyseal plate, also called the growth plate and decides the height of an individual (19). In the early and mid-pubertal years, the growth in height (modeling process) exceeds the rate of the mineralization (remodeling) and the accrual of bone mass. This causes the skeleton to be fragile and sensitive to pressure during this transcending period in life (16, 20). The bone mineral content (BMC) reflects the amount of minerals the bone tissue consists of in grams (g). The bone mineral density (BMD) reflects the density of the minerals in a region-specific site (area) in the skeleton as g/cm^2 (13, 21). Under constant BMC (g), the larger the size of the bone is the lower the BMD (g/cm^2) (22).

There are gender- differences in both trabecular and cortical bones, where boys have been shown to have bones that are thicker and larger, with a stronger micro-architectural framework in the trabecular bone compared to girls. Girls' cortical bones are shown to be denser and not equally porous as the boys' cortical bones (20, 23).

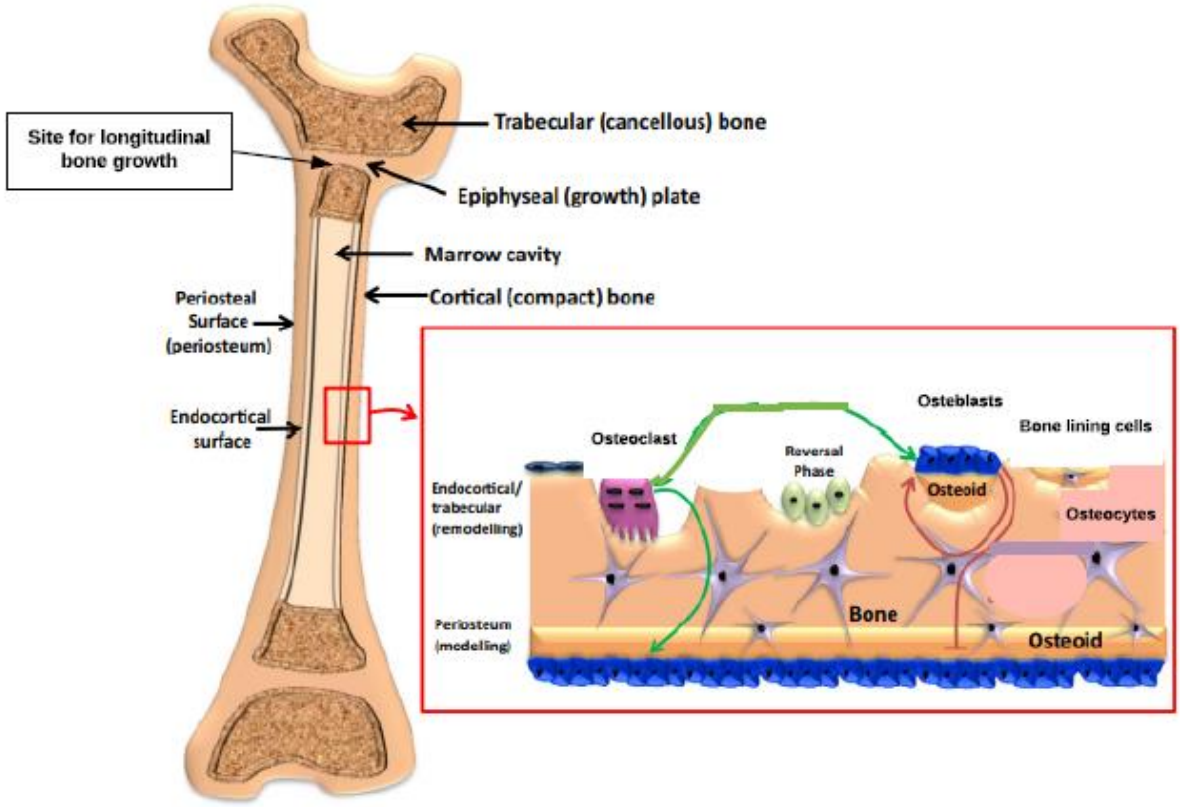

Figure 1: Formation of cortical and trabecular bone. ***Adapted from Sims et al. (19).***

1.3.2 Bone composition in childhood and adolescence

During childhood the amount of bone mass acquired is relatively low, but when the onset of puberty occurs the bone accretion shows a spurt in regards to height and density (24). The onset of puberty for girls is at average around 11 years and at around 13 years for boys. The spurt in growth might be an indicator of the onset of puberty, but not a valid parameter alone. To recognize puberty it's important to evaluate a combination of factors such as chronological age, bone age and sexual development. During the high increase of growth in the pubertal years of girls (11-15 years) and boys (13-17 years), the upper body grows more substantially than the lower limbs (23).

Before the establishment of peak bone mass (PBM) during the second decade of life, there is a peak velocity in both height and BMC, where the peak velocity in height occurs several months before the peak bone mineral content velocity. The peak height velocity happens when girls have a bone age between 11- 13 years and boys have a bone age between 13 – 15 years. After this period the height gain has a considerably decrease in its velocity (20, 23). During late puberty the growth rate slows down, but the accrual of bone mass continuous up until around the age of 30, where PBM is achieved (16).

1.3.3 Development of peak bone mass (PBM)

One definition of PBM is "*Peak bone mass is attained when age-related changes in a bone outcome are no longer positive and have attained a plateau or maximum value"* (13). PBM is attained during young adulthood and is crucial for bone composition later in life (16). PBM is found to be an important factor to increased risk of development of osteoporosis and increased fracture risk in adulthood (13). When comparing boys to girls in early adulthood, the boys have a tendency to have a higher PBM than the girls. The amount of bone mass one individual can obtain during young adulthood is influenced by genetics, ethnicity, amount and type of physical activity (13, 16, 24). When seen at population-level, the bone mass reaches its peak when it hits a plateau and the modeling and growth process of the bones stops (13, 18).

The PBM is shown to vary across different regions of the skeleton. As the lumbar spine being one of the region-specific sites for having a distinct increase of both BMC and BMD during pubertal years it's important to evaluate this during bone composition assessments in the

pediatric population (18). The lumbar spine consists of five segments named L1 – L5, where the BMC (g) is shown to be increasing from L1 to L5. The lumbar spine is approximately 16 cm in men and 15.5 cm in women.. In regard to the sitting height, the lumbar spine contributes with 18 % of this height. The lumbar spine has a rapid growth from the age of 0 to the age of 5 years, and then it slows down the growth between the age of 5 years and the age of 10 years, before it has a spurt in growth between 10 – 18 years of age (23).

1.3.4 Bone composition – pediatric patients with HPN

Studies from other countries have shown that pediatric patients on HPN, with and without neurological disabilities, had a lower BMD Z-score compared to the healthy population (14, 15, 25-31). In Norway there are no studies on bone composition in pediatric patients using HPN.

1.3.5 Bone composition – healthy children and adolescents

Studies have suggested that the bone composition in childhood and adolescent years can affect the fracture-risk later in life (13). As Norway being one of the top countries in regards to fractures in adults and elderly (32), the importance of evaluating the bone composition early in life should be emphasized. Although there has not been conducted many studies in the young Norwegian population in regards to bone composition, the Tromsø study, which is a population-based study, has investigated several factors related to bone composition (33-35). Their findings suggest that BMD (g/cm^2) is positively correlated to the amount of physical activity (34). That both lean mass (LM) and fat mass (FM) is strong predictors of BMD (g/cm^2) in the hip-area (35) and that the fracture risk in the young Norwegian population (33) is similar to what is found in earlier epidemiological studies conducted in both Norway and Sweden (36, 37).

1.4 Body composition

Body composition describes the distribution of total bone mass, total body lean mass (LM) and total body fat mass (FM). The total body weight differs through childhood and adolescence. Up until 5 years of age, the child would normally have an increase in weight at about 32 % of what the future adult weight would be. At the age of 10 years, about 48 % of

the individual's future adult weight would be attained. The weight of a child normally doubles between the age of 10 and 17 years because of different stages of puberty among other factors. A low weight is unfavorable in regards to skeleton-strength (16, 23).

During the child's growth both LM and FM increases. The site of where the weight-accumulation of both LM and FM is important when observing the potentially positive and negative effects of fat mass on both bone and body composition. Fat accumulation in skeletal muscle has an adverse effect because it can decrease the sensitivity of several factors related to muscle growth. This can then decrease the amount of muscles and thereby body and bone strength. During the last phase of adolescent growth spurt and around the timing of PBM, the more gains in LM, the stronger the correlation is to the increased BMC (13, 20). High amount of FM is associated with increased risk of development of coronary heart disease and metabolic syndrome later in life (38).

1.4.1 Body composition – pediatric patients with HPN

A study conducted in England (38) investigating the body composition by DXA, found that children with HPN had higher FM and lower LM compared to the healthy children. LM has been shown to be positively correlated to bone mineralization and BMD (g/cm^2) (13). It's also shown that a low LM could have a negative impact on the bone composition in the pubertal years (39).

1.4.2 Body composition – healthy children and adolescents

There are few studies on body composition in healthy Norwegian children. A prospective study by Steinsbekk et al. (40) investigated the impact of FM and LM on appetite regulation in a group of 6 year olds and found both FM and LM were predictors of certain appetite traits over time.

One study by Park et al. (41) showed that when comparing the amount of FM and LM in healthy Korean boys and girls, the boys had a higher amount of LM compared to the girls in all age-groups. Another study by Taylor et al. (42), found that when categorizing the children according to their pubertal stage, the girls had an overall higher amount of FM compared to the boys.

One study by Wilkinson et al. (43) showed that for highly physical active boys around the age of 13 years, the amount of LM was a stronger predictor of BMD (g/cm^2) than what was shown for FM. Another study, by Guo et al. (44), analyzed the relationship between bone and body composition in a group of Chinese children and adolescents and found that BMC was highly correlated with the amount of LM.

1.5 Vitamin D

1.5.1 Definition and function of vitamin D

Vitamin D is a fat-soluble vitamin, with an endocrine function (45). It consists of two sub-groups, vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol), where vitamin D2 comes mainly from plants and fungus and vitamin D3 from animals (46).

The main function of vitamin D is to regulate calcium – and parathyroid hormone (PTH) metabolism and maintain adequate serum-levels of calcium and phosphorous in the bloodstream which affects bone composition (47, 48). Vitamin D has also been shown to have an effect on several other mechanisms in the body and therefore having a deficiency could result in increase of infectious diseases, cardiovascular disease, deadly cancers, type 2 diabetes, autoimmune disorders, dental problems, skeletal weakness and neurological disorders (45, 46, 49, 50).

1.5.2 Physiology of vitamin D

The main source of vitamin D is sunlight, diet and supplements. When exposed to sunlight vitamin D3 is produced by UVB-light at a wavelength of 280 – 315 nm from the sterol 7-dehydrocholesterol and becomes previtamin D3 (Figure 2). Vitamin D3 starts of as a previtamin before UV-irradiation converts the previtamin to a stable vitamin D3 in the skin, because of its thermodynamically properties. The first sequence takes place in the top layer of the skin (epidermis). This last sequence takes place in the lower layer of the skin (subcutis) (45, 51, 52).

Vitamin D from sunlight (vitamin D3) and diet (vitamin D2 and D3) goes through a transportation process when synthesized cutaneous or absorbed through the gastro intestinal tract and entering the circulation. The chylomicrons incorporate vitamin D2 and D3 from the

diet, and transport the vitamin via the lymphatic system and into the venous circulation. The circulatory transport of vitamin D to the liver for metabolism requires a special transport-protein called the vitamin D-binding protein (DBP) (45, 46, 49).

Vitamin D is inactive until it's transported to the liver for activation by DBP. In the liver there is a 25-hydroxylation of vitamin D, by the enzyme 25-hydroxylase (25-OHase) and the product is 25-hydroksyvitamin D (25(OH)D), which is the major circulating form (Figure 2) (53).

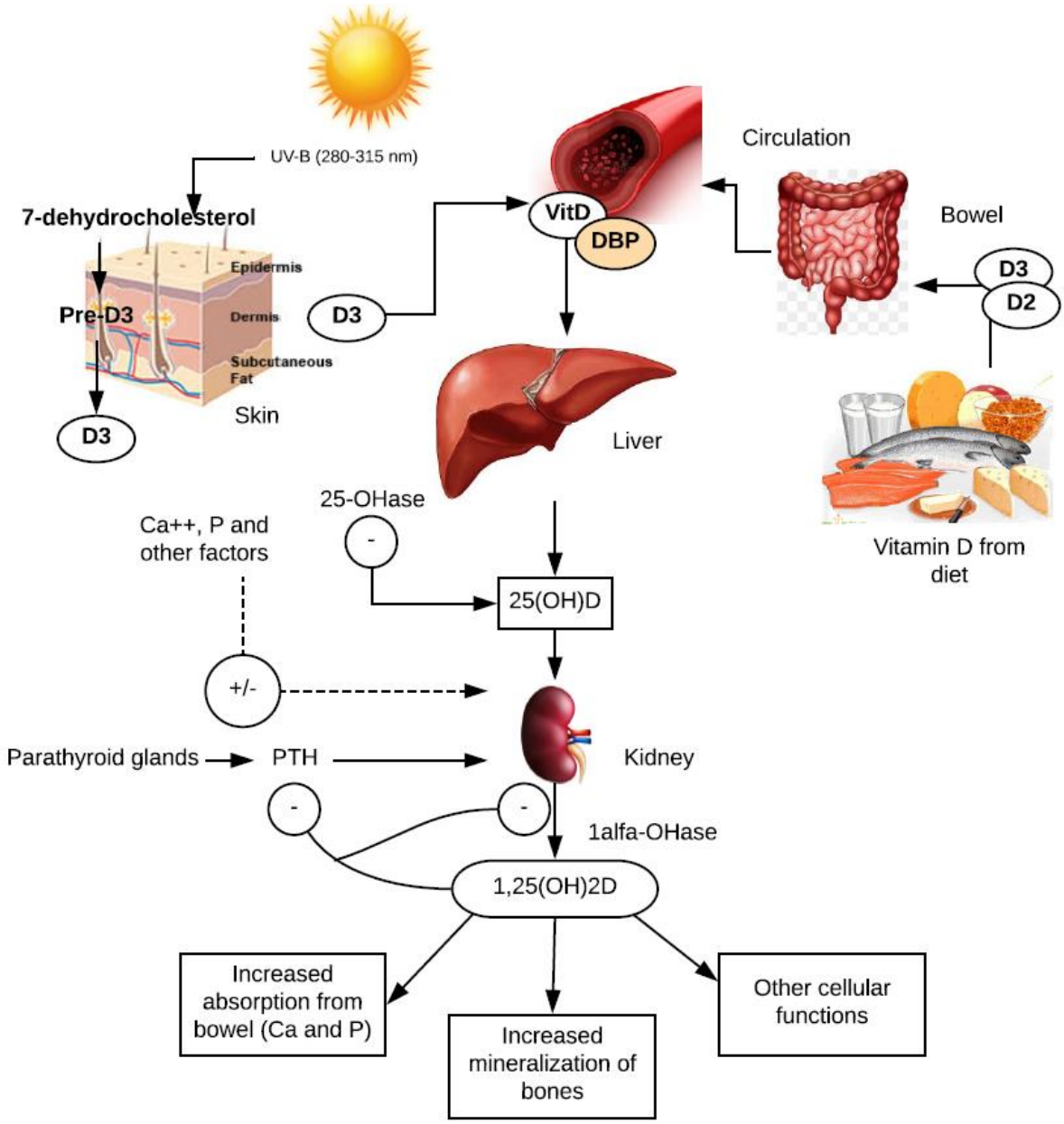

Figure 2: The synthesis and metabolism of vitamin D. ***Adapted from Rosas-Peralta et al. (54).***

The vitamin 25(OH)D leaves the liver and reenters the circulation to be converted in the kidneys and other tissues by its active form, 1,25-dihydroksyvitamin D ($1,25(OH)_2D$). The 25(OH)D function as a prohormone to $1,25(OH)_2D$ (51). The active form of vitamin D in the body is $1,25(OH)_2D$. The major function of the active $1,25(OH)_2D$ is to maintain calcium and phosphorous within physiological range. Absorption of calcium and mobilization of calcium and phosphorous from the skeleton is due to the enhancement of $1,25(OH)_2D$-actvity (52, 55).

The kidneys are the main site for activation of vitamin D. The activation of $1,25(OH)_2D$ is regulated by serum-level of PTH, calcium and phosphorous and dietary intake of calcium (46). The serum level of calcium decreases when the amount of dietary calcium intake and absorption is low. This is detected by calcium-sensing cells on the parathyroid cells, which regulates the production and release of PTH into the circulation. These sensory cells detects the decreased serum level of calcium and sends a signal for increased PTH gene expression and production to the parathyroid glands which increases PTH release into the circulation (48).

The activation of 25(OH)D to $1,25(OH)_2D$ in the kidneys is performed by a mitochondrial P-450 enzyme (CYP27B1) called 1-alpha-hydroxylase (1α-OHase). The 1α-OHase enzyme is produced due to an increased gene expression of CYP27B1 when the receptor on the proximal tubular cells in the kidneys interacts with the increased serum level of PTH (51).

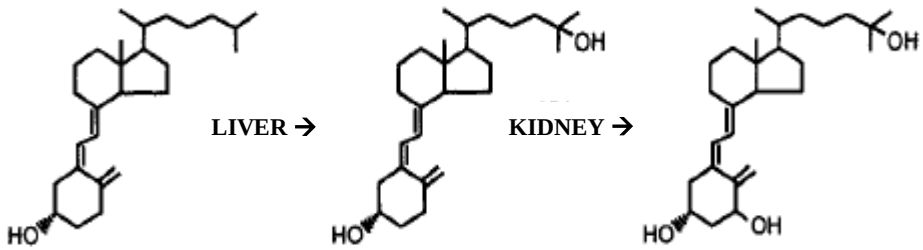

Figure 3: Activation of vitamin D in liver (25(OH)D) and in kidneys ($1,25(OH)_2D$). ***Adapted from DeLuca et al. (55).***

In the target cells $25(OH)_2D$ interacts with the vitamin D receptor (VDR), which is a specific nuclear receptor. The VDRs recognize specific DNA sequences called Vitamin D Response Elements (VDREs) because of their properties as ligand-dependent transcription factors (55). The VDRs are found in almost every cell and organ in the body (56). The interaction between

the activated 1, 25$(OH)_2$D and the VDR causes the formation of a heterodimeric complex with another receptor called the retinoic acid X receptor (RXR). When this complex (VDR/RXR) is formed it can alter transcriptional activity of the vitamin D genes throughout the body. The increase of 1,25$(OH)_2$D in the circulation will in interaction with the VDREs control the VDR-regulated genes related to the gastrointestinal tract and the skeleton and thereby affect these (48). By controlling the VDR-regulated genes in the gastrointestinal tract and skeleton, the intestinal absorption of calcium and phosphorus will increase and the bone mineral phase will release more calcium and phosphorous (46, 51).

1.5.3 Vitamin D, Ca and phosphorous in food

In Norway there are few food items that has been fortified with vitamin D. Food items containing the most of dietary vitamin D, calcium and phosphorous are presented in table 1.

Table 1: Main dietary sources of the micronutrients.

Dietary sources of nutrients[1,2]	Content per 100 gram edible product[1]
Vitamin D, µg:	
- *Cod liver oil*	217.0
- *Roe*	13.4
- *Margarine (fortified)*	10.0
- *Salmon*	10.0
- *Egg yolk*	8.0
- *Trout*	6.9
- *Mackerel*	5.4
- *Milk (fortified)*	0.4
Calcium, mg:	
- *Dairy products*	120.0 - 820.0
- *Milk*	100.0 - 120.0
- *Legumes*	50.0 - 100.0
- *Nuts*	30.0 - 270.0
- *Vegetables*	20.0 - 60.0
Phosphorous, mg:	
- *Oatmeal*	450.0 - 550.0
- *Meat (red and white)*	100.0 - 300.0
- *Milk*	90.0 - 100.0
- *Rice*	90.0 - 100.0
- *Legumes*	50.0 - 450.0
- *Dairy products*	50.0 - 650.0

[1]The Norwegian Food Composition Database 2016, (57)

[2]Nordic Nutrition Recommendations 2012 (NNR 2012), (58)

Nutrients sources from PN are provided by additives. The sources of vitamin D in PN are "Vitalipid Infant" (1.0 µg/ml), of calcium are "CaCl" (1 mmol Ca/ml) and of phosphorous are "Monokaliumphosphate" (1 mmol P/ml) and "Glycophosphate" (1 mmol P/ml). Some of the pediatric patients with HPN also receives ENS to secure adequate nutritional intake. The ENS contain different amounts of vitamin D, calcium and phosphorous, but most of them provide about 1.0 µg vitamin D/100 ml, 100 mg calcium/100 ml and 100 mg phosphorous/ml.

1.5.4 Recommended daily intake of vitamin D, calcium and phosphorous

Recommendations from Nordic Nutrition Recommendations 2012 (NNR 2012) (58) on daily dietary intake (RDI) of vitamin D, calcium and phosphorous for the healthy Norwegian population are presented in table 2.

Table 2: Recommended daily dietary intake of the micronutrients in enteral nutrition.

Dietary nutrients:	**Recommended daily intake[1]**
Vitamin D (µg)	
- 1 - 18 years	10
Calcium (mg/day)	
- 2 - 5 years	600
- 6 - 9 years	700
- 10 -13 years	900
- > 13 years	800
Phosphorous (mg/day)	
- 2 - 5 years	470
- 6 - 9 years	540
- 10 -13 years	700
- > 13 years	600

[1]Recommendations from Nordic Nutrition Recommendations 2012 (NNR 2012). (58)

Recommendations on daily intake of vitamin D, calcium and phosphorous for PN are presented in table 3.

Table 3: Recommended daily dietary intake of micronutrients in parenteral nutrition.

Nutrients from PN[1]:	Recommended daily intake[2]
Vitamin D, µg/day:	
- 1 - 18 years	10
Calcium, mg(mmol)/kg/day:	
- 1 - 13 years	11 (0.2)
- 14 - 18 years	7 (0.2)
Phosphorous, mg(mmol)/kg/day:	
- 1 - 18 years	6 (0.2)

[1]PN: parenteral nutrition

[2]Recommendations for PN from European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN 2005). (6)

Recommended supplement-intake in the pediatric population at risk for vitamin D deficiency has been suggested to be 25 - 125 µg/day for 2-3 months to establish sufficient 25(OH)D. The dose is however dependent upon baseline 25(OH)D (59, 60).

1.5.5 Vitamin D and bone composition

Several studies (61-65) has been conducted in both the pediatric patient population and the healthy pediatric population in regards to finding the link between vitamin D deficiency and the effect it might have on bone composition.

Vitamin D, calcium and phosphorous has been shown to be important for long term bone composition (13). When the serum level of 25(OH)D is low, production of PTH increases and the conversion of 25(OH)D to $1,25(OH)_2D$ increases. This increases the calcium and phosphorous absorption from the bowels and reduces renal losses. An elevated level of PTH will also affect the increased production of osteoclasts to further increase the release of calcium from the skeleton. The evaluation of bone composition should include analysis of 25(OH)D, calcium, PTH and phosphorous (66-68).

Several studies have investigated the connection of 25(OH)D and its effects on bone composition. Some studies (67-69) has investigated the threshold of 25(OH)D for avoiding elevated PTH levels and thereby a negative effect on bone composition. Their findings suggest a cut-off by 34 – 50 nmol/l 25(OH)D to establish vitamin D deficiency and avoid elevated levels of PTH. Other studies (62, 70) has found that low 25(OH)D was associated with low BMD Z-score in both total body and lumbar spine.

1.5.6 Vitamin D deficiency

There are several definitions and no international consensus to what the appropriate serum level of 25(OH)D should be to establish a vitamin D deficiency. Deficiency generally occurs when 25(OH)D is inadequate to maintain normal bone composition and other bodily functions (71).

It occurs that most of the pediatrics societies has set a deficiency cut-off for 25(OH)D at below 50 nmol/l in the population of pediatric populations (Table 4). Vitamin D deficiency affect absorption of both calcium and phosphorous in a negative manner, where absorption of calcium and phosphorous is decreased to 10-15 % and 60 %, respectively (46).

The 25(OH)D has a strong affinity to DBP and a half-life of two – three weeks. It's therefore an optimal representation of an individual's serum level of vitamin D. In humans, the serum level of 25(OH)D is normally between 25 – 200 nmol/l (45, 46, 52).

When a vitamin D deficiency occurs, the serum-level of $1,25(OH)_2D$ can both be normal or elevated. The elevation is caused by secondary hyperparathyroidism and the increase in renal-production of $1,25(OH)_2D$. Because of this, the most reliable method to measure vitamin D-status is by measuring 25(OH)D in serum (45, 46).

Vitamin D deficiency can cause a spectrum of diseases, seen all the way from childhood throughout the adult part of life. Rickets is one of the adverse outcomes of vitamin D deficiency. The characterization of rickets is insufficiently mineralized or calcified bone matrix, which affects the growth plate in the long bones. There are several signs of potential established rickets, which can portray itself as failure to thrive, irritability, both wrists and ankles could be widened and observation of the legs bowing (24, 52). Symptoms of vitamin D deficiency can also be non-specific, such as frequent infections especially in the respiratory tract or pain in the skeleton-muscles. Radiologic images of children with a vitamin D deficiency often have signs of osteomalacia, widening of the epiphyseal area and the link between the bones is looser. For older children it might lead to short stature and potential anorexia. When the deficiency becomes severe, this results in hypocalcemia and might cause both seizures and tetany (46, 72).

Table 4: Definition of 25(OH)D-deficiency.

	Serum level of 25(OH)D (nmol/l)		
	Sufficient	**Insufficiency**	**Deficiency**
The Endocrine Society - Global Consensus Recommendations (2016)[1]	>75	50 - 30	<30
Nordic Nutrition Recommendations (NNR, 2012)[2]	>50	50 - 30	<30
British Pediatrics And Adolescent Bone Group (2012)[3]	>75	50 - 25	<25
The Institute of Medicine (IOM, 2011)[4]	>75	-	-
American Academy of pediatrics (2008)[5]	>75	-	<50
The ESPGHAN Committee on Nutrition (2005)[6]	>50	-	<25

[1]Munns et al. (72), [2]NNR 2012 (58), [3]Arundel et al. (73), [4]Ross et al. (74), [5]Wagner et al. (75), [6]Braegger et al. (45).

Vitamin D-deficiency in pediatric patients

Pediatric patients with medical conditions resulting in malabsorption, inadequate diet, IF, HPN, neurological disabilities or hospitalized for a long time has been shown to have vitamin D-deficiency (46, 61, 63, 64, 76-79). There are no studies on the effect of vitamin D deficiencies on bone composition in Norwegian pediatric patients receiving HPN.

Vitamin D-deficiency in healthy children and adolescents

Several studies has shown low 25(OH)D in healthy children and adolescents, with insufficiency and deficiency of varying degree (80-83). Individuals living in the northern part of the world (55ºN – 72ºN) are especially exposed to vitamin D deficiency because less sunlight, colder weather and thereby more clothes (45, 51, 58, 84). There are no established guidelines for routine screening for vitamin D deficiency for healthy children and adolescents, but individuals at risk could benefit from screening guidelines (56, 84).

1.6 Physical activity

An activity is categorized as physical activity (PA) if the body-movements results in a muscle contraction that again results in an increase of energy expenditure above resting level. PA is important to maintain muscle function and a healthy skeleton (13). The World Health

Organization (WHO) recommend children and adolescents to have at least 60 minutes a day of moderate-to-vigorous intensity of physical activity (MVPA) (85). Studies in the healthy young population have shown that exercise, and especially weight-bearing PA is important in regards to the osteogenic effects on the bones. And that increased amounts of sedentary-to-light physical activity (SLPA) could have a negative impact on bone and body composition (86).

1.6.1 Physical activity – pediatric patients with HPN

There are few studies (87) on PA in the Norwegian population of pediatric patients with disabilities and no studies on pediatric patients receiving HPN. Studies (88-93) on PA in children with disabilities have been conducted internationally. Their findings suggest that increased PA could have a positive effect on bone composition, but there are no consistent findings in regards to the amount necessary to maintain bone composition in pediatric patients. The studies conducted concluded that the findings were weak and even though PA might be beneficial to the pediatric patients, the results are not consistent enough to make any suitable recommendations.

1.6.2 Physical activity – healthy children and adolescents

Several studies on PA and its relation to bone composition have been conducted in healthy children and adolescents (86, 94-97). These findings suggest that PA, especially weight-bearing PA, could have a positive effect on bone and body composition.

2. Aim of this thesis

The overall aim of this thesis was to describe diet, bone- and body composition in the Norwegian pediatric patients, compared to a group of healthy children and adolescents. Secondary, vitamin D-status and physical activity were also described, as these factors might affect bone health.

Specific aims:

- Describe diet (using diet records) and nutritent intake (vitamin D, calcium and phosphorous) in HPN patients and healthy children.
- Describe BMD Z-score in total body and spine (L2-L4) by DXA-measurements in HPN patients and healthy children.
- Describe body composition in HPN patients and healthy children.
- Describe vitamin D status, using 25(OH)D) in HPN patients and healthy children.
- Describe physical activity levels (using a questionnaire and a wrist-worn accelerometer) in HPN patients and healthy children.

3. Methods

3.1 Study design

This was done as part of a larger study called NUTRIENT-study (Nutritional status in children treated with advanced nutrition therapy), where the aim was to investigate diet, nutritional status, physical activity and bone health among children treated with stem cell transplantation, HPN-patients and healthy children. This sub-study was a cross-sectional study of HPN-patients and healthy children aged 2-18 years.

3.2 Recruitment of subjects

HPN-group

Inclusion of HPN-patients started 8th of February and ended 18th of May 2017 and took place at the hospital in conjunction with their quarterly check-up. Co-workers in the study participated in recruitment.

Reference-group

The reference-group was included between 15th of March and 24th of September 2017 by a costume made web form (Appendix 1) published in social media and with the help from co-workers in the study. Consultations were done at the Nutrition outpatient clinic at the University of Oslo (UiO) by two master students. The recruitment consisted of two periods, first period was from 15th of March to 30th of June 2017 and second period was from 1th of August and until 24th of September 2017.

For the main part of the Nutrient-study, 50 healthy subjects were needed to assess iodine status in healthy children. This was considered to be appropriate according to the time limit for the master thesis work and economics of the study.

3.2.1 Data-inclusion

The inclusion of data is presented in figure 4. Each participant received the necessary information (Appendix 2) and equipment included information of use (Appendix 3) in

advance of their appointments at either the hospital (HPN-group) or at UiO (reference-group). The purpose was to register both diet and physical activity for 4 days in advance.

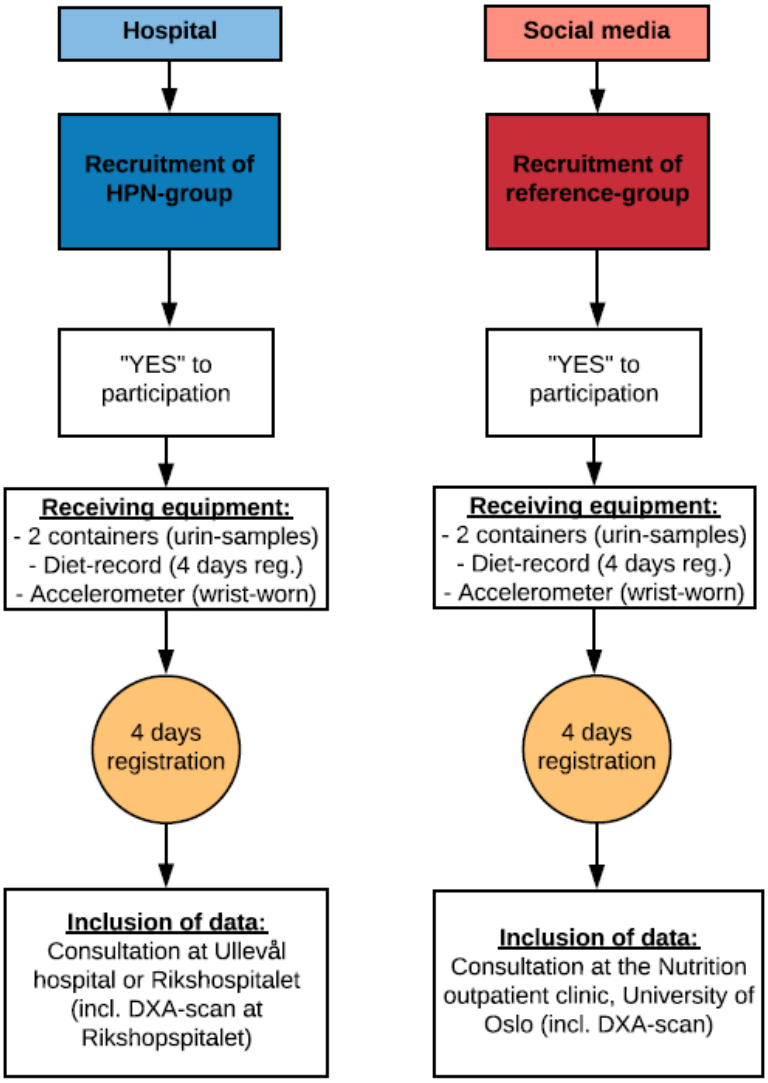

Figure 4: Flow-chart of data-inclusion in the study population.

3.2.2 Inclusion and exclusion-criteria

In table 5, the inclusion and exclusion-criteria for the HPN-group and the reference-group are presented.

Table 5: Inclusion – and exclusion criteria in the study population.

Inclusion-criteria	Exclusion-criteria
HPN-group:	**HPN-group:**
- Receiving HPN	*- Pacemakers or other implants (DXA-scan)*[1]
- Treatment and follow-up at Oslo University Hospital (OUH)	
- Age 2 - 18 years	
Reference-group:	**Reference-group:**
- Age 2 - 18 years	*- Congential syndromes*
- Healthy	*- Gastrintestinale diseases*
- Living in the Oslo-area	

[1]DXA-scan=Dual energy x-ray absorptiometry scan.

3.1 Dietary data

3.1.1 Registration of total daily dietary intake

To obtain information about the subject's diet, a 4 days dietary registration was used to register daily dietary intake of three weekdays and one weekend-day. Dietary registration was conducted with a costume made registration-booklet (Appendix 4) and a picture-booklet from Norkost 3 (98), which has been validated in the adult population (99).

The Norkost 3 picture-booklet (98) had a total of 34 different food items shown as images. Each food was displayed in four different images based on portion size where (A) was a small portion and (D) was a large portion. Beverages were displayed according to size of cup or glass. Pictures of bread-type included size, shape and thickness of the bread.

The costume made registration-booklet was personalized for each subject with an ID-number. The first page in the registration-booklet gave information on how to register food items. Each page thereafter had four columns, "Time of day", "Amount", "Type of food and drink" and "Description, preparation and name of product". The registration of total daily dietary intake included supplements taken orally, like cod fish oil, vitamin bears and Nycoplus vitamin – supplements.

3.1.2 Registration of parenteral nutrition

The parents of the HPN-patients were asked about the PN regime at the hospital; number of days per week and received volume (ml) per day (Appendix 6). The declaration of the PN solutions, including additives of each patients PN was retrieved from the hospital pharmacy. Information was also obtained from the medical journal and from the dietitians treating the patients.

3.1.3 Dietary analysis

Two master students (Camilla Sæland and Christina N. Kjeserud) did the dietary analysis. The dietary registration was analyzed by the software Dietist Net Pro (100). This was a diet- and nutrition software developed by "Kost och næringsdata" in Sweden. The Norwegian Food Composition Database 2016 (57) was used as reference. The database consisted of 1600 food items and had values from 38 nutrients. The food items in the database are presented as energy and nutrient –content per 100 grams of eatable food (without bone, shell, skin and other parts of the food items that are normally not eaten).

For each subject, each food item was plotted into the Dietist Net Pro- software. If suitable, the meals were divided into breakfast, lunch, dinner and snack for each of the 4 registration days. The Norkost 3 – picture booklet had an associated sheet which described each of the food items in the booklet with weight in grams at different portion-size.

Each participant was asked to register every homemade meal as accurate as possible with a detailed recipe. The subjects own recipes were registered in Dietist Net Pro as costume made foods. When the weight (g) of the food items included in the recipes were missing, a similar recipe was found online and used as reference.

When single food items were missing the amount in either grams or portion-size, the mean value in grams from the Norkost 3 – associated sheet were used as estimated amount.

Two categories were established when diet of each subject were registered, "Enteral with supplements" and "Enteral without supplements". Each subject were registered into both categories for the purpose of investigating potential differences in regards to the use of supplements or not.

Within the HPN-group, ENS and food items ingested per os or by tube feeding were combined and assessed as their total daily EN. These were combined due to a generally poor orally nutritional intake within the HPN-group. The nutritional information of the ENS-products were found in the database of Dietist Net Pro.

The HPN-patients PN-composition were plotted into Dietist Net Pro as a costume made nutrient. Before plotting, calculations of the average intake per day were made. Average intake were based on volume (ml) received per day of PN and the number of days per week using PN. If for example one patient received PN for 4 out of 7 days a week, the volume (ml) given each of those 4 days were multiplied by 4 and then divided by 7 to get the average volume (ml) received per day in a week. The calculated volume was then plotted as a meal in each of the 4 registration days.

Evaluation of total dietary intake within the HPN-group and the reference-group in this master thesis was based on recommended daily intake (RDI) from NNR 2012 (58). The evaluation of PN was based on ESPGHAN 2005 – guidelines (6). Micronutrients selected for presentation in this thesis was vitamin D, calcium and phosphorous.

3.1 Anthropometric measurements

3.1.1 Anthropometry - HPN-group

For HPN-patients, weight (kg) and height (cm) were measured at the hospital by a trained nurse. The same Seca-weight (model 770 1321004) was used for all the patients. Their height (cm) was obtained by a stadiometer (Holtain.Limited, Britain) mounted on the wall. The children stood up against the wall, without shoes, facing straight ahead.

3.1.2 Anthropometry - reference-group

Within the reference-group both weight (kg) and height (cm) were measured at UiO by a combined digital measuring station for weight and height (Seca 284). The subjects stood up against the heel positioner in the back, facing straight ahead. The headpiece was dragged downwards to the top of the head.

3.2 Dual energy x-ray absorptiometry (DXA)

DXA – instrument and software

The DXA-scan of the HPN-patients were done by using the DXA densitometer Lunar Prodigy with software enCORE 2015, version 16 (GE Healthcare Lunar Corporation, Madison, Wisconsin, USA). The DXA-scan in the reference-group was done using the DXA densitometer Lunar iDXA and analyzed using the same software, enCORE 2015 version 16. Interpretation of the scan-results was conducted in cooperation with a certified technician at the department of Endocrinology, RH (Kristin Godang).

DXA – measurement technique

The enCORE-software required registration of ethnicity, gender, birthdate, weight (kg) and height (cm) before the DXA-scan began. The individual lay with arms and legs within marked lines (Figure 5). The total body scan took about 10 minutes and the spine-scan scan took about 5 minutes.

Figure 5: Dual energy x-ray absorptiometry (DXA) – instrument at UiO. Private picture.

DXA measured three components in the body; FM, LM and BMC. The Lunar Prodigy and the Lunar iDXA was based on the same principle of using a narrow fan beam with low-dose x-ray two-dimensional technology for differentiating between soft tissue and bone. The x-ray dose ranged from 0.03 to 15.2 micro-Sievert (µSV) (13). Bone attenuate the x-ray beams to a greater extent than FM and LM, this is due to the minerals in the bone. The x-ray source was placed under the bench and the detector above the bench where the subject laid. The measurements started from the top of the head and moved downwards across the total body of the subject. The low-dose x-ray beam passed through the subject's body, centimeter by centimeter. After finishing the total body scan, a scan of the spine was conducted. The individual lay still with arms and legs within the marked lines, while the machine scanned from 5 centimeters below their belly button and across their hips.

The coefficient of variation (CV) for both Lunar Prodigy and Lunar iDXA is 1.1 % CV for BMC 2.0 % CV for FM and 1.1 % CV for LM (22). Calibration of the instruments were done each day before scanning the first subject, by using a spine phantom. Validation of the calibration-method of the DXA densitometer has been conducted several times (101, 102).

Measurements from the Lunar Prodigy and Lunar iDXA have been shown in a cross-calibration study (103) to be comparable with each other. The reference database provided by the manufacturer (Lunar Corporation) was the same in both of the DXA densitometers. The reference group consists of 8056 pediatric patients <20 years of age from the National Health and Nutrition Examination survey (NHANES) from the United States (104).

DXA-variables used in the study

This study included scan of total body (TB) and anterior-posterior lumbar vertebral body 2-4 (spine). Variables used were BMD (g/cm^2), BMC (g), BMD Z-score, FM (%) and LM (%). Measurement of the spine was included due to the rapid growth in the lumbar spine region between the age of 10 and 18 years and was therefore a good estimate of the relationship between BMD and BMC (23).

Calculation of the Z-score for BMD was done by comparing the individual's BMD against age, gender and race matched mean (22, 105). According to "The International Society for Clinical Densitometry (ISCD 2013)", a Z-score equal to or below – 2.0 is categorized as "low

bone mass or bone density" (106). In present study, the subjects were categorized as having "decreased BMD" with a Z-score of -1.0 to -2.0 and "low BMD" with a Z-score of < -2.0.

The DXA-scan in the HPN-group was conducted at the department for Endocrinology at Rikshospitalet (RH), by certified personnel. DXA-scan of the subjects in the reference-group was conducted at UiO by two master students.

3.3 Blood samples

Blood-samples used in the study was 25(OH)D (nmol/L), calcium (mmol/l), ionized calcium (mmol/l) and PTH (pmol/l). These blood-samples were chosen because of their physiological impact on bone composition and due to their potential correlation with each other (13, 62, 67, 68, 72).

Blood samples in the HPN-group were taken by trained personnel in conjunction with their quarterly check-up at the hospital and analyzed at the laboratory for medical biochemistry at UH. Blood samples in the reference-group were taken at UiO and analyzed at the laboratory for medical biochemistry at RH.

The methods of analysis were based on the same measurement-principle across the two laboratories. To ensure high precision and quality of the results, the laboratories within the OUH has a system for reporting the variation coefficient across the different laboratories (107). The variation coefficient describes the analytical variation, where 1 SD is the percentage (%) of the average value of each measurement. This is part of the laboratories quality control and ensures that the results obtained from each laboratory within OUH are comparable.

Determination of s-25(OH)D

All the blood samples for vitamin D-detection in serum was analyzed at Aker Hormone laboratory, OUH. The principle of the method was based on liquid chromatography mass-spectrometry where 25-OH-vitamin D2 and 25-OH-vitamin D3 was separated from any interference by reverse-phase liquid chromatography. Total 25(OH)D includes both 25-OH-vitamin D2 and 25-OH-vitamin D3. Detection was done with electrospray-mass-spectrometry (107).

Determination of vitamin D-deficiency in the study

In this study, the cut-off for 25(OH)D-deficiency were set to <30 nmol/l and insufficiency were set to <50 nmol/l. This was in accordance to NNR 2012 (58).

3.1 Questionnaires

The questionnaires were costume made for the main study (Nutrient-study) and developed by clinicians working in the study. All questionnaires were filled out and collected at scheduled appointments.

Background-information

Each participant was given a costume made self-reporting questionnaire for collection of background-information (Appendix 5). The questionnaire registered information about the child's age, gender, educational-level, living situation, indigestion-related questions, detection of smoking and snuff-habits, PA and the educational-level for both parents. The questions on PA included type, frequency and intensity. For further description of the self-reported questions on PA, see section under "Physical activity" (3.2.2).

Case report form (CRF)

One CRF was assigned each participant to keep track of completed tasks related to each subject in the study (Appendix 6). This included information about time of dispatch of equipment, date for DXA-scan, if consent was obtained, information about completed blood samples, urine samples, use of supplements, their body weight (kg) and height (cm)

For the HPN-group, an extra page in the form was established to collect information about their parenteral nutrition (PN) - regime in regards to hours per day, number of days per week, volume per day and nutrient composition. Information of tube feeding was also collected as to what product, regime and amount received. Losses of fluid related to diarrhea, stoma-output or vomit were also registered.

3.2 Physical activity measurements

3.2.1 GENEActiv wrist – worn accelerometer

Accelerometers have been used in large epidemiological studies (108, 109) to objectively measure the amount of PA within all age groups. This includes studies in groups of children with disabilities (110). To measure physical activity for 4 consecutive days within the HPN-group and the reference-group, the wrist-worn GENEActive Accelerometer was used. The accelerometer was developed by Activinsights Limited, Unit 11, Harvard Industrial Estate, Kimbolton, Cambs, in England and Wales.

Validation of the GENEActiv accelerometer has been conducted for both children and adults (111-114), presenting the accuracy of detection of both SLPA and MVPA.

Figure 6: GENEActiv wrist-worn accelerometer. ***Published with permission from Activinsights Limited, copyright 2017.***

Each subject received one accelerometer with instructions (Appendix 3) by post in advance of their scheduled appointments. Before this, the accelerometers were configured using the GENEActive Software, version 2.1. This consisted of applying the right setting in the accelerometer which was registration based on a frequency of 100 Hz for 7 days, an "On-button-press" to start the accelerometer and registration of ID-number of current subject who was supposed to wear it. The participants were asked to collect their amount of physical activity in the same week as the 4 days of diet registration was completed.

Principle of measurement

The GENEActive is a triaxle accelerometer which measures the acceleration in three axes (X, Y and Z). It's waterproof and can store up to 0.5 GB raw acceleration data (+/- 8g) at a frequency of 100 Hz for 7 days (115). The data extraction was done by using the GENEActive Software, version 2.1. The extraction of raw data first consisted of storing the default data format as a .bin file, which then was converted to a .csv format file, readable in Excel.

Because of the amount of raw accelerometer data, the .csv format file was converted to a compressed file, a 60sec .csv epoch file due to difficulties in exploring the data material in Excel as raw and uncompressed data. By converting the raw accelerometer data into 60 seconds .csv epoch files, all the measurements are minimized to readings of PA per 60 second as opposed to the unconverted .csv format file which has readings per second.

When the raw data is converted into 60 seconds .csv epoch files, the GENEActive Software calculates the means for each measurement and the Sum Vector Magnitude (SVM) for each epoch. Calculation of SVM for each .csv epoch file is shown in figure 7 and consists of subtracting the effect of the Earth's gravity from the sum of vectors. This means that the vector magnitude was created for each measurement in the epoch and 1g was subtracted.

The recording frequency (100 Hz) multiplied by the epoch length (60 seconds) gave the total number of measurements in the sum. The SVM-values were then associated with a metabolic equivalent (MET) used for establishing if the activity were categorized as sedentary, light, moderate or vigorous. One MET is either equal to an energy expenditure of 1 kcal/kg body weight/hour or an oxygen uptake of 3.5 ml of VO2/kg/hour. The MET is normally calculated by dividing the metabolic rate during exercise on the metabolic rate during rest (112, 116). Calculations of MET's were not done in our study, therefore MET's and associated cut-points established from other studies has been used in present study. The cut-points established by Shaefer et.al (116) and van Loo et al. (117) were used in present study (*sedentary (≤1.5 MET), light (>1.5 – 2.99 MET), moderate (3-5.99 MET) and vigorous (≥ 6 MET)*).

$$SVM^{g}s = \sum [(x^2 + y^2 + z^2)^{½} - 1g]$$

Figure 7: Formula for calculation of Sum Vector Magnitude ($SVM^{g}s$). *By the GENEActive Software, version 2.1. (112).*

The .csv epoch files were imported into a costume made macro-program produced by Activinsights Limited, GENEActive's homepage, "Open platform - Macro"(118). By importing the files into the macro-program, the 60sec .csv epoch files were converted into average minutes per day of either SLPA or MVPA. Average minutes of PA per day were then converted into average minutes per 4 days and the software IBM SPSS statistics were used for further analysis.

The choice of selecting 2 categories of intensity of PA was based on studies (112, 116, 119) done on the accuracy of classification of either 4 categories (sedentary, light, moderate or vigorous) or 2 categories (sedentary/light and moderate/vigorous). These studies showed that the accuracy of measuring PA based on only 2 groups instead of 4 was improved.

3.2.2 Physical activity – questionnaire

Self-reporting questionnaires and self-administered diaries are the most common type of questionnaire used in assessing PA (120-122). The self-reporting questions on PA in present study were retrieved as part of the questionnaire about background (Appendix 5). The purpose of using the self-reported questionnaire alongside the accelerometer was to get an assessment of PA over a longer time-period. Details of type, frequency and intensity were registered. Although the questionnaire were costume made for the main study, Nutrient-study, the use of questions about type, frequency and intensity of PA has been validated in previous studies (123).

The paragraph in the background-questionnaire regarding PA was divided into three sections. First section was a question about how often the child participated in any PA (frequency per week); *"Never or less than once a week", "1-3 sessions per week" or "4 sessions a week or more".* The child was also asked to state if they did not participate in any physical activity at all. The second section was a question about the intensity of each session; *"Takes it easy without getting short of breath or sweaty"* or *"I get short of breath and sweaty".* The third section was an open question, where the children could write what type of PA they participated in.

The second section on intensity was redesigned when processing the data, divided into three levels of intensity instead; *"Low intensity", "Medium intensity" or "High intensity".* The

level of *"Low intensity"* represented the once who did not participate in any specific PA. The level of *"Medium intensity"* was the once who had answered with *"Takes it easy without getting short of breath or sweaty".* The level of *"High intensity"* was the once who had answered with *"I get short of breath and sweaty".*

The third section on type of PA the children participated in, was categorized when processing the data. The data was divided into five categories. Category one called *"Ball sports",* which included all types of sports involving a ball. Category two called *"Athletics",* which included sports like sprint, relay race, track – and field running, swimming and high jump. Category three called *"Martial arts"* included boxing, kickboxing, and wrestling. Category four called *"Sports in general"* included all types of sports not mentioned above, like ballet, tap-dance, gymnastics, hip hop- dancing and theatre. And the last and fifth category, *"No sports"* included those who did not participate in any PA at all.

3.3 Feedback – reference-group

In September 2017, all subjects in the reference-group received a written feedback on their diet registered for 4 days, the results from their blood samples and the DXA-scan. An example of a written feedback is presented in appendix 7. The feedback on diet consisted of an overview of average macro – and micronutrient intake in the 4 days of diet registration.

Nordic Nutrition recommendations 2012 (NNR 2012) (58) were used as reference when evaluating the total daily nutritional intake. Nutritional advice was given according to each subject's dietary registration. Feedback on blood samples were given based on deviance from the reference-area of each blood-analysis. Feedback on DXA-scan was given in accordance with BMD Z-score.

3.4 Documentation in database

For registration and data documentation of all the information collected in the study the software Epidata Entry was used. Epidata Entry Software was based on the Epidata Entry version 2.0, which was developed by "The Epidata Association, 2000-2017" in Odense, Denmark.

One database were encoded for the results from the blood samples, one for the background-questionnaire, one for anthropometric measurements, one for EN, one for PN. Each of these databases was merged into the statistical software IBM Statistical Packages for Social Sciences (SPSS).

3.5 Statistical Methods

The statistical analytical software used in this study was IBM SPSS Statistics version 24 for Windows 10. All results from the statistical tests were considered significant at $p < 0.05$ and all were analyzed as two-sided.

Normality of the continuous variables was checked by Kolmogorov – Smirnov and Shapiro Wilks tests. All the descriptive variables are shown as median and range.

Mann Whitney U-tests for non-parametric data were used to investigate potential differences between the HPN-group and the reference-group. For description of frequency and proportion of the categorical variables either Chi Square tests or Fischer Exact tests were used, based on what was applicable for the actual proportions.

Separations into gender or age-groups were not conducted due to the small sample sizes.

For description of possible correlations, a correlation bivariate analysis was performed using the Spearman correlation coefficient due to non-normally distributed data. The level of statistical significance were set to $p<0.05$.

Calculations of standard deviations (SD) for height, weight and BMI within the reference-group was conducted by Pétur B. Júlíusson, MD, PhD, Professor, Department of Clinical Science, University of Bergen and the Morbid Obesity Centre, Vestfold Hospital Trust, Norway. Calculations of SD for height, weight and BMI within the HPN-group was collected from the patient's electronic patient journal in DIPS (supplier of electronic health systems to Norwegian hospitals).

Missing subjects was excluded in the statistical analysis by using "Exclude cases pairwise" in SPSS. The subjects were therefore only excluded if he or she did not have the actual variable in that specific analysis. Every subject was included in the analysis if they had the necessary information.

3.6 Ethical approval

This study was conducted according to the guidelines established in the Declaration of Helsinki and approved by the Regional Committee for Research Ethics (REK – 2016/391) in all procedures involving human subjects (Appendix 8). The head of the children's clinic and the data protection officer at OUH approved the study.

All subjects and parents received written information about the study. Written consent was obtained from both parents. If the subjects were above 16 years, the subjects co-signed the consent-form before inclusion.

3.7 My contribution

I contributed to this study by managing the data-inclusion of both the HPN-group (n=19) and part of the reference-group (n= 35) during the spring of 2017, together with my fellow student, Camilla Sæland. This included dietary analysis, anthropometric measurements and DXA-scan. The data-inclusion of the remaining part of the reference-group (n=15) I managed myself during the autumn of 2017. This included dietary analysis, anthropometric measurements, DXA-scan, analysis of physical activity obtained by both the accelerometers and from the questionnaires.

4. Results

4.1 Study population - characteristics

Overview of the recruitment of subjects is presented in figure 8. All 19 eligible HPN patients (100 %) were included in the study, but only 12 patients completed the DXA-scan and the registration of PA with the accelerometer. Of the 58 healthy children and adolescents invited to the study, 86 % participated.

The 7 missing patients in the DXA-scan analysis was due to low age for 5 patients which were below the lower pediatric reference-area of DXA (< 5 years of age). Two patients had a physical handicap which prevented them from participation in the scanning-procedure.

The 4 missing subjects in the reference-group in the total body DXA-scan was due to being under the age of 5 years (n=3) or unwillingness (n= 1). The 8 missing subjects in the spine-scan was due to unwillingness (n=2) or the technicians incompletion of the scanning-procedure. The incompletion of the scanning procedure involved two of the children not being able to cooperate before the scanning of the spine, which took place right after the total body scan. The remaining six whom did not get their spine scanned was due to stress and then forgetting this last part of the scanning procedure.

Blood-sampling had 3 missing subjects in the reference-group, due to unwillingness (n=1) or to little sample-material (n=2).

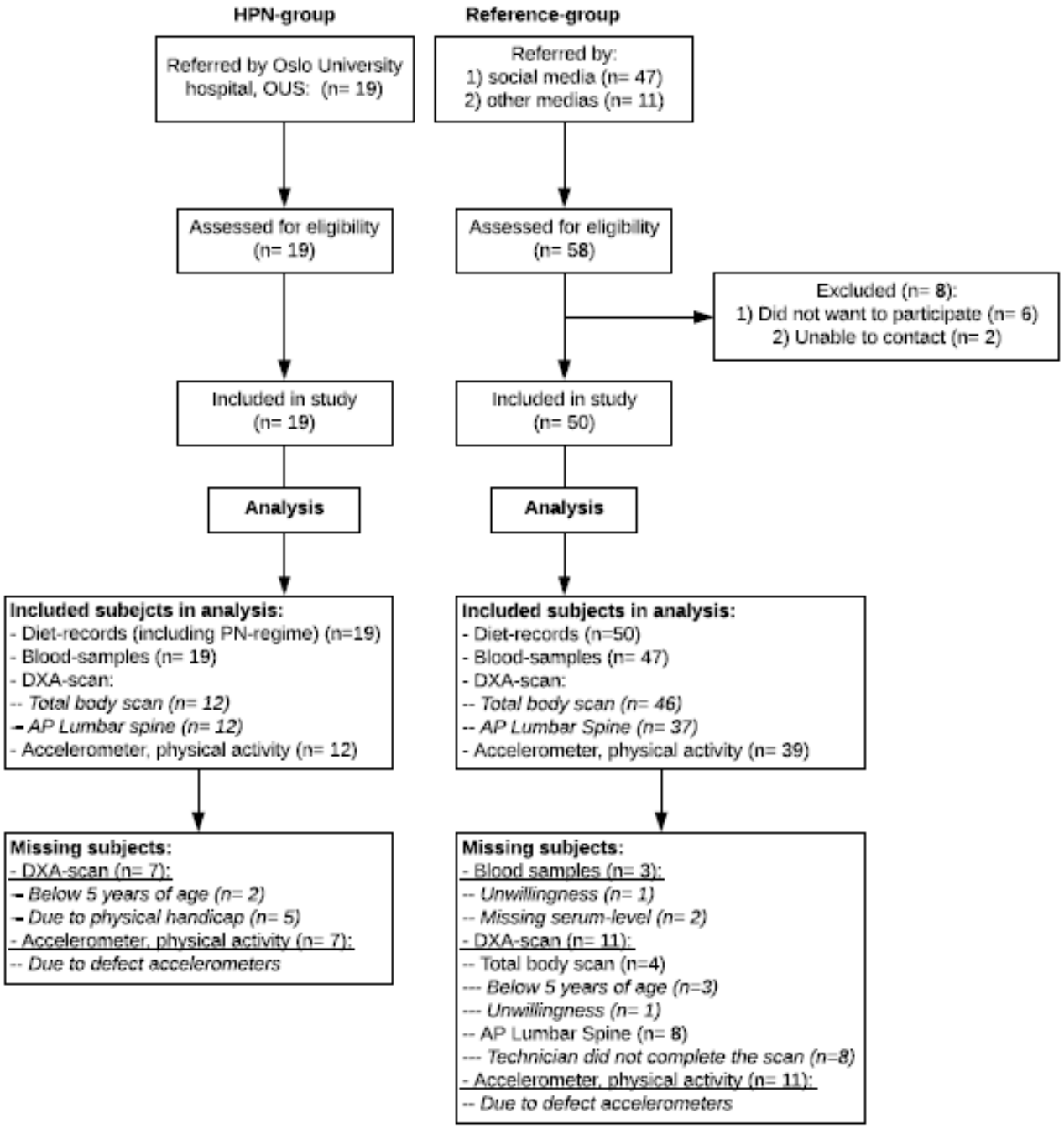

Figure 8: Flow-chart of eligibility assessment in the study population.

Table 6 shows the characteristics for anthropometry, distribution of gender, distribution of age-groups, the mother's educational level within the HPN-group and reference-group and the main diagnosis and medical conditions within the HPN-group, respectively. There were one subject in the HPN-group and one subject in the reference-group who were non-Caucasian, but no ethnical differences were found between the two groups (data not shown). There was no significant difference between the HPN-group and the reference-group in either age or the

anthropometric measurements. The HPN-patients were lower and weighed less compared to the reference-group.

There were a significant difference (p=0.03) in the distribution of gender within the HPN-group and the reference-group, with a higher percentage of boys in the HPN-group (68.0 %) compared to the reference-group (36.0 %) and a higher percentage of girls in the reference-group (64.0 %) compared to the HPN-group (32.0 %).

No significant differences were shown between the two groups in the distribution into age-groups or in regards to the mother's educational level.

Also shown in table 6 is the main diagnosis and medical conditions within the HPN-group. Most of the patients had severe dysmotility, including chronic intestinal pseudo-obstruction (CIPO) (n= 11) as their main diagnosis. Second was the diagnosis of short bowel disease (n=5) and third was the diagnosis of severe malabsorption/enteropathies/inflammatory disease (n=3). Fifteen of the patients in the HPN-group also had a medical condition combined with their main diagnosis, where there was 9 patients who had a syndrome which includes being either or both physical and mentally disabled. Two patients had autism spectrum disease and 2 patients had gone through kidney transplantation. One patient had an immune disease and 1 patient had gone through acute lymphocytic leukemia (ALL) – treatment.

The span of counties from whom the HPN-patients came from was Vest-Agder, Aust-Agder, Rogaland, Telemark, Vestfold, Østfold, Akershus, Oslo, Oppland and Hedmark, where Akershus contributed with the majority of patients. The reference-group came from the counties Buskerud, Akershus and Oslo, where the majority came from Oslo.

Table 6: Characteristics of the study population.

	HPN-group (n=19)	Reference-group (n=50)	p – value[1]
Age (years):			
- Median	10.1	9.9	0.80[2]
- Range	(4.1 - 16.4)	(3.7 - 16.8)	
Height (cm):			
- Median	133.8	138.3	0.08[2]
- Range	(101.5 - 162.4)	(99.8 - 173.9)	
Weight (kg):			
- Median	31.4	34.1	0.17[2]
- Range	(15.9 - 55.0)	(14.3 - 71.3)	
BMI (kg/m2):			
- Median	17.5	17.5	0.71[2]
- Range	(14.1 - 22.6)	(13.4 - 27.2)	
Distribution of gender (%):			
- Girls	6 (32.0)	32 (64.0)	**0.03[3]**
- Boys	13 (68.0)	18 (36.0)	
Distribution of age (%):			
- 2 - 5 years	6 (32.0)	18 (36.0)	
- 6 - 9 years	3 (16.0)	8 (16.0)	0.96[4]
- 10 - 13 years	6 (32.0)	12 (24.0)	
- 14 - 18 years	4 (20.0)	12 (24.0)	
Mothers eduactional level (%):			
- Primary school	1 (5.0)	1 (2.0)	
- Secondary school	1 (5.0)	0 (0.0)	0.41[4]
- High school	2 (10.0)	5 (10.0)	
- College/University	15 (80.0)	44 (88.0)	
Main diagnosis (%):			
- Severe dysmotility, including chronic intestinal pesudo-obstruction (CIPO)	11 (58.0)		
- Severe malabsorption/enteropathies/inflammatory disease	3 (16.0)		
- Short bowel disease	5 (26.0)		
Medical conditions (%):			
- Syndromes	9 (60.0)		
- Autism spectrum disease	2 (13.0)		
- Kidney transplantation	2 (13.0)		
- Immune disease	1 (7.0)		
- Previous ALL treatment	1 (7.0)		

[1]Difference between the HPN-group and the reference-group, significant, p<0.05 (bold writing).
[2]Mann Whitney U-tests
[3]Chi-square test for independence – continuity correction.
[4]Fischer Exact test.

4.2 HPN-group - characteristics

Description of the PN-regime in the HPN-group are presented in table 7. Duration of using PN had a median of 4.5 years (0.8 – 16.4 years). The patient's age for initiation of PN had a median of 3 years (0 - 10 years). Days of PN per week had a median of 7 days (4-7 days). Number of hours connected to PN per day had a median of 12 hours (9 – 15 hours). Volume (ml) of PN received per day had a median of 1268 ml (297 – 2030 ml).

Table 7: Description of parenteral nutrition (PN)-regime.

	HPN-group (n= 19)	
	Median	**Range**
Duration of PN, years	4.5	(0.8 - 16.4)
Age at beginning of PN, years	3.0	(0.0 - 10.0)
Days of PN per week	7	(4 - 7)
Hours of PN per day	12.0	(9.0 - 15.0)
Volume of PN per day, ml	1268.0	(297.0 - 2030.0)

Different types of PN were used (Table 8). Most HPN-patients (79 %) received an individualized custom made PN, produced at the hospital pharmacy. PN composition was based on different carbohydrate-, protein-, and fat sources (glucose 20 – 50 %, Vamin 18, Vamin 14, Vaminolac, Smoflipid and Omegaven). Smoflipid was used by all, but one had a combination with Omegaven. Fat-free PN was used by one patient.

Additives of trace-elements and vitamins used in the PN are also presented in table 8. Products used for trace-elements were Addaven (79 %) and Peditrace (20 %). Product used to secure the fat-soluble vitamins was Vitalipid Infant (95 %) and for the water-soluble vitamins Soluvit (100 %) was used. Vitalipid was used by all except one who had fat-free PN. Calcium chloride ($CaCl_2$) was an ingredient in everyone's PN. Only one received Monokaliumphosphate, all the others received Glycophos. Carnitene was used by 63 % (n= 12).

Table 8: Description of type-, composition- and additives in parenteral nutrition (PN).

	HPN-group (n=19)
	Number (%)
Type of PN[1]:	
- Standard 10 - 15 kg	1 (5.0)
- Standard 15 - 40 kg	3 (16.0)
- Custome made	15 (79.0)
Composition within type of PN:	
Standard 10-15 kg:	
- Vaminolac	1 (5.0)
- Glucose	1 (5.0)
- Smoflipid	1 (5.0)
Standard 15-40 kg:	
- Vamin 18	3 (16.0)
- Glucose	3 (16.0)
- Smoflipid	3 (16.0)
Costume made:	
- Vamin 18	12 (63.0)
- Vamin 14	2 (10.0)
- Vaminolac	1 (5.0)
- Glucose	15 (79.0)
- Smoflipid	14 (74.0)
- Omegaven/Smoflipid	1 (5.0)
- Fat-free composition	1 (5.0)
Additives in PN:	
Trace-elements:	
- Addaven	15 (79.0)
- Peditrace	4 (21.0)
Fat-soluble vitamins:	
- Vitalipid infant	18 (95.0)
Water-soluble vitamins:	
- Soluvit	19 (100.0)

[1]PN = Parenteral nutrition

Enteral nutrition support (ENS) was used by 5 HPN-patients (Table 9). Products used was Isosource Mix (6x150 ml/day), Neocate Advance (700 ml/day), Pregestimil (8x30 ml/day), Peptamen (5x100 ml/day) and Fortini Creamy Fruit (30 g/day).

Table 9: Description of the enteral nutrition support (ENS) in the HPN-group.

	HPN-group (n=5)
	Number (%)
Enteral nutrition support (ENS)[1]:	
- Isosource Mix (Nestle Health Science)	1 (5.0)
- Neocate Advance (Nutricia)	1 (5.0)
- Pregestimil (Mead Johnson Nutrition)	1 (5.0)
- Peptamen Jr. Adcance (Nestle Health Science)	1 (5.0)
- Fortini Creamy Fruit (Nutricia)	1 (5.0)

[1]ENS – Tube feeding and specialized oral nutritional supplement (5)

Enteral nutrition (EN) intake of macro- and micronutrients within the HPN-group are presented in table 10. With a median of 24 kcal/kg/day the whole group received in average 36 % of RDI from EN. Daily EN of protein, with a median of 1.0 g/kg/day was in average 106 % of RDI.

EN of vitamin D (μg/day), both with and without supplement, showed a median of 2 μg/day and 3 μg/day, respectively (Table 10). In average, the HPN-group received 37 % without supplements and 77 % with supplements of vitamin D – RDI. The median EN of both calcium (187 mg/day) and phosphorous (368 mg/day) showed that the HPN-group received 41 % and 69 % of RDI, respectively. One HPN-patient received calcium Sandoz (500 mg/day) as supplement (data not shown).

Table 10: Daily intake of enteral nutrition (EN) in the HPN-group.

ENTERAL NUTRITION	HPN-group (n= 19)	RDI (NNR2012)[1]
Energy (kcal/kg/day):		**Energy (kcal/kg/day):**
- *Median*	24	**45 - 85 kcal/kg/day**
- *Range*	(0 - 72)	
- *% daily intake of RDI (mean ± SD)*	36.0 ± 32.0	
Protein (g/kg/day):		**Protein (g/kg/day):**
- *Median*	1.0	**0.9 g/kg/day**
- *Range*	(0.0 - 2.5)	
- *% daily intake of RDI (mean ± SD)*	106.0 ± 88.0	
Vitamin D (µg/day), excl.suppl:		**Vitamin D (µg/day):**
- *Median*	2	**10 µg/day**
- *Range*	(0 - 10)	
- *% daily intake of RDI (mean ± SD)*	37.0 ± 38.0	
Vitamin D (µg/day), incl.suppl:		
- *Median*	3	
- *Range*	(0 - 37)	
- *% daily intake of RDI (mean ± SD)*	77.0 ± 99.0	
Calcium (mg/day):		**Calcium (mg/day):**
- *Median*	187	**2-5 years: 600 mg/day**
- *Range*	(0 - 927)	**6-9 years: 700mg/day**
- *% daily intake of RDI (mean ± SD)*	41.0 ± 41.0	**10-13 years: 900mg/day**
		>13 years: 800 mg/day
Phosphorous (mg/day):		**Phosphorous (mg/day):**
- *Median*	368	**2-5 years: 470 mg/day**
- *Range*	(0 - 1112)	**6-9 years: 540 mg/day**
- *% daily intake of RDI (mean ± SD)*	69.0 ± 61.0	**10-13 years: 700 mg/day**
		>13 years: 600 mg/day

[1]Recommendations from Nordic Nutritional Recommendations 2012 (NNR2012). Presented as REExmedianPAL from NNR2012, for girls and boys at age 2 to 17 years. REE = Resting Energy Expenditure (Henry 2005). PAL= Physical Activity Level (SACN 2011). (58)

Parenteral nutritional (PN) intake in the HPN-group are presented in table 11. The median for energy (37 kcal/kg/day) in the HPN-group were in average 69 % of RDI. PN intake of protein, with a median of 1.3, was in average 146 % of ESPGHAN 2005-guidelines. The median PN intake for both fat (1.1 g/kg/day) and carbohydrate (5.5 g/kg/day) in the HPN-group were in average 56 % and 59 % of ESPGHAN 2005-guidelines, respectively.

Also presented in table 11, is the intake of micronutrients from PN. In average for vitamin D, with a median of 10 µg/day, the whole HPN-group received 112 % of ESPGHAN 2005-guidelines. The PN intake of calcium, with a median of 0.1 mmol/kg/day, were in average 75 % of ESPGHAN 2005-guidelines. Phosphorous received from PN, with a median of 0.2 mmol/kg/day, were in average 101 % of ESPGHAN 2005-guidelines.

Table 11: Daily intake of parenteral nutrition (PN) in the HPN-group.

PARENTERAL NUTRITION	HPN-group (n= 19)	RDI (ESPGHAN 2005)[1]
Energy (kcal/kg/day):		**Energy (kcal/kg/day)[2]:**
- Median	37	**41 - 83 kcal/kg/day**
- Range	(16 - 69)	
- % daily intake of RDI, NNR 2012 (mean ± SD)	69.0 ± 27.0	
Amino acids (g/kg/day):		**Amino acids (g/kg/day):**
- Median	1.3	**1.0 - 2.0 g/kg/day**
- Range	(0.5 - 2.0)	
- % daily intake of ESPGHAN 2005 guidelines (mean ± SD)	146.0 ± 49.0	
Fat (g/kg/day):		**Fat (g/kg/day):**
- Median	1.1	**1-3 g/kg/day**
- Range	(0.0 - 1.9)	
- % daily intake of ESPGHAN 2005 guidelines (mean ± SD)	56.0 ± 25.0	
Carbohydrate (g/kg/day):		**Carbohydrate (g/kg/day):**
- Median	5.5	**3-10 kg: 16-18 g/kg/day**
- Range	(2.6 - 11.5)	**10-15 kg: 12-14 g/kg/day**
- % daily intake of ESPGHAN 2005 guidelines (mean ± SD)	59.0 ± 24.0	**15-20 kg: 10-12 g/kg/day**
		20-30 kg: <12g/kg/day
		>30 kg: <10 g/kg/day
Vitamin D (µg/day):		**Vitamin D (µg/day):**
- Median	10	**10 µg/day**
- Range	(0 - 25)	
- % daily intake of ESPGHAN 2005 guidelines (mean ± SD)	112.0 ± 60.0	
Calcium (mmol/kg/day):		**Calcium (mmol/kg/day):**
- Median	0.1	**1- 18 years: 0.2 mmol/kg/day**
- Range	(0.1 - 0.2)	
- % daily intake of ESPGHAN 2005 guidelines (mean ± SD)	75.0 ± 17.0	
Phosphorous (mmol/kg/day):		**Phosphorous (mmol/kg/day):**
- Median	0.2	**1- 18 years: 0.2 mmol/kg/day**
- Range	(0.1 - 0.3)	
- % daily intake of EPSGHAN 2005 guidelines (mean ± SD)	101.0 ± 29.0	

[1]Recommendations for PN from European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN 2005). RDI = Recommended daily intake.

[2]Recommendations from Nordic Nutritional Recommendations 2012 (NNR2012). Presented as REExmedianPAL from NNR2012, for girls and boys at age 2 to 17 years. REE = Resting Energy Expenditure (Henry 2005). PAL= Physical Activity Level (SACN 2011).

4.3 Total daily nutrient intake - study population

The total daily nutrient intake within the HPN-group and the reference-group are presented in table 12. No significant difference was found in daily intake of energy (kcal/kg) between the HPN-group (67 kcal/kg/day) and reference-group (52 kcal/kg/day). However, the energy intake in the HPN-group was in average 105 % of RDI, while 93 % of RDI in the reference-group.

No significant difference was found between the two groups in protein (g/kg/day) and both groups were within the RDI (Table 12). The HPN-group and the reference-group was within the RDI for both protein (E %) and fat (E %), but both protein and fat was significantly lower ($p<0.001$) in the HPN-group (13 E % and 27 E %) compared to the reference-group (16 E % and 33 E %), respectively. Carbohydrate was significantly higher ($p<0.001$) in the HPN-group (56 E %) than in the reference-group (48 E %).

Also presented in table 12, are the daily intake of micronutrients. Both with and without supplement, the HPN-group had a significantly higher ($p<0.001$) daily intake of vitamin D (14 µg/day excl.suppl. and 17 µg/day incl.suppl.), compared to the reference-group (4 µg/day excl.suppl and 5 µg/day incl.suppl), respectively.

In the HPN-group, 5 of 19 subjects registered taking vitamin D-supplements. In the reference-group, 14 of 50 registered taking vitamin D-supplements. The HPN-group had an average intake of vitamin D without and with supplement of 149 % and 189 % of RDI, while the reference-group had in average 44 % and 75 % of RDI, respectively (Table 12). The nutritional intake of calcium and phosphorous was significantly lower ($p<0.001$) within the HPN-group than the reference-group. While the HPN-group had a calcium intake of 45 % of RDI, the reference-group had an average intake of 114 % of RDI. The average intake of phosphorous within the HPN-group was 100 % of RDI, while the average intake within the reference-group was 248 % of RDI.

Table 12: Total daily nutrient intake in the study population.

	HPN-group (n= 19)	Reference-group (n= 50)	p-value[1]	RDI (NNR2012)[2]
Energy (kcal/kg/day):				**Energy (kcal/kg/day)[3]:**
- Median	67.0	52.0	0.21	**45 - 85 kcal/kg/day****
- Range	(33.0 - 140.0)	(28.0 - 112.0)		
- % daily intake of RDI (mean ± SD)	105.0 ± 39.0	93.0 ± 25.0		
Protein (g/kg/day):				**Protein (g/kg/day):**
- Median	2.1	2.4	0.32	**0.9 g/kg/day**
- Range	(1.0 - 4.3)	(1.0 - 4.1)		
Protein (E%):				**Protein (E %):**
- Median	13	16	**<0.001**	**10 - 20 E%**
- Range	(9 - 19)	(11 - 25)		
Carbohydrate (E%):				**Carbohydrate (E %):**
- Median	56	48	**<0.001**	**45 - 60 E%**
- Range	(50 - 64)	(35 - 59)		
Fat (E%):				**Fat (E %):**
- Median	27	33	**<0.001**	**25 - 40 E%**
- Range	(23 - 36)	(24 - 44)		
Vitamin D (µg/day), excl.suppl:				**Vitamin D (µg/day):**
- Median	14	4	**<0.001**	**10 µg/day**
- Range	(7 - 27)	(0 - 17)		
- % daily intake of RDI (mean ± SD)	149.0 ± 62.0	44.0 ± 32.0		
Vitamin D (µg/day), incl.suppl:				
- Median	17	5	**<0.001**	
- Range	(7 - 57)	(0 - 25)		
- % daily intake of RDI (mean ± SD)	189.0 ± 112.0	75.0 ± 68.0		
Calcium (mg/day), Total:				**Calcium (mg/day):**
- Median	193	830	**<0.001**	**2-5 years: 600 mg/day**
- Range	(5 - 931)	(299 - 1550)		**6-9 years: 700mg/day**
- % daily intake of RDI (mean ± SD)	45.0 ± 46.0	114.0 ± 39.0		**10-13 years: 900mg/day**
				>13 years: 800 mg/day
Phosphorous (mg/day), Total:				**Phosphorous (mg/day):**
- Median	492	1369	**<0.001**	**2-5 years: 470 mg/day**
- Range	(123 - 1267)	(605 - 2577)		**6-9 years: 540 mg/day**
- % daily intake of RDI (mean ± SD)	100.0 ± 58.0	248.0 ± 62.0		**10-13 years: 700 mg/day**
				>13 years: 600 mg/day

[1]Difference between the HPN-group and the reference-group, Mann Whitney U-test. Significant, p<0.05 (bold writing)
[2]Recommendations from Nordic Nutritional Recommendations 2012 (NNR2012)
[3]Energy (kcal/kg/day) presented as REExmedianPAL from NNR2012, for girls and boys at age 2 to 17 years.
REE = Resting Energy Expenditure (Henry 2005). PAL= Physical Activity Level (SACN 2011).

4.3.1 Nutritional sources - vitamin D and calcium

The main dietary sources of vitamin D within the HPN-group are presented in figure 9. Vitamin D from PN contributed with 55 %. Contribution from ENS was 25 %, while dietary supplements (9 %), milk (7 %), fish (3 %) and yoghurt (1 %) contributed to a lesser extent.

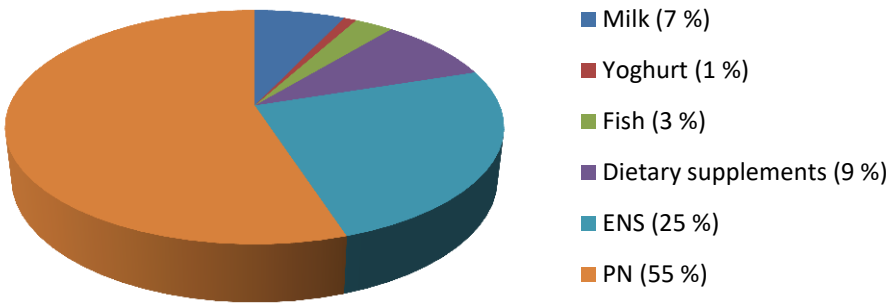

Figure 9: Main dietary sources of vitamin D in the HPN-group. ***ENS: enteral nutrition support, PN: parenteral nutrition.***

The main dietary sources of calcium within the HPN-group are presented in figure 10. The greatest contribution of nutritional calcium came from milk (35 %). Calcium intake from both ENS (24 %) and PN (21 %) contributed almost equally. The dairy-products cheese (13 %) and yoghurt (4 %) only contributes with a small amount of nutritional calcium.

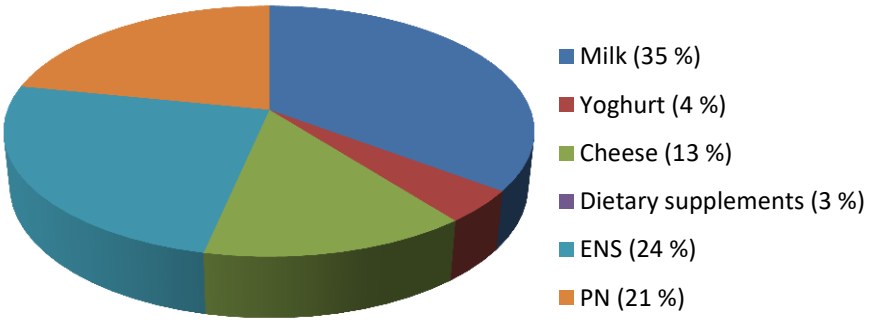

Figure 10: Main dietary sources of calcium in the HPN-group. ***ENS: enteral nutrition support, PN: parenteral nutrition.***

The main dietary sources of vitamin D within the reference-group are presented in figure 11. Dietary supplements contributed with 37 %, fish with 26 % and the dairy-products milk and yoghurt contributed almost equally with 19 % and 18 %, respectively.

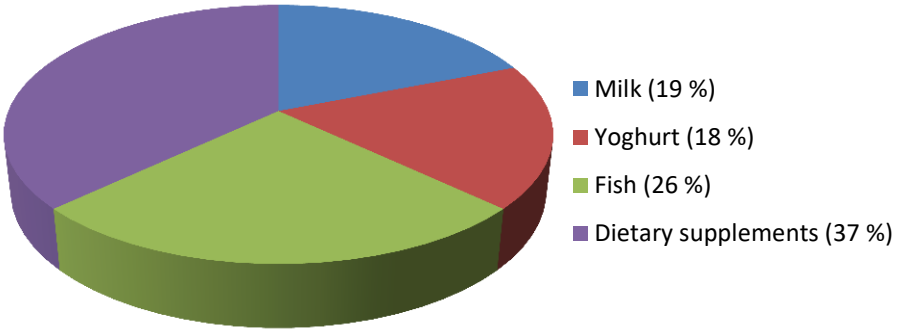

Figure 11: Main dietary sources of vitamin D in the reference-group.

The main dietary sources of calcium within the reference-group are presented in figure 12. Milk (45 %) was the greatest contributor of dietary calcium, second came calcium derived from cheese (33 %), yoghurt (12 %) and other sources (10 %) which included vegetables, legumes and nuts.

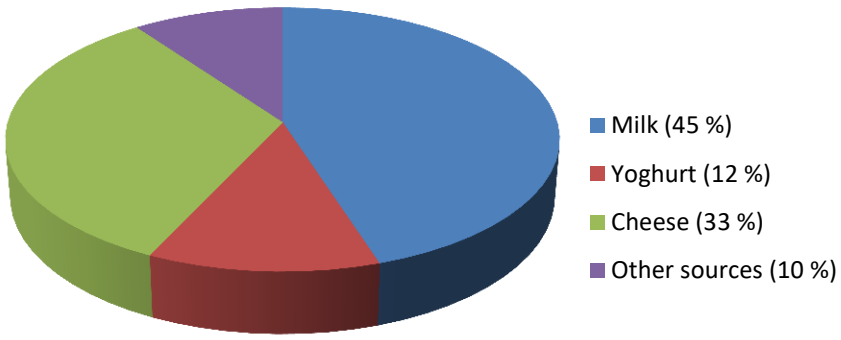

Figure 12: Main dietary sources of calcium in the reference-group.

4.4 Bone and body composition in the study population

The anthropometric Z-scores in the HPN-group and reference-group are presented in table 13. The HPN-group had a significantly lower median Z-score for height (-1.8) and weight (-0.5) compared to the median height (-0.1) and weight (0.0) within the reference-group. No significant difference was found between the two groups in BMI Z-score.

The body composition within the HPN-group and the reference-group is also presented in table 13. The median percentage of LM were significantly lower (p=0.02) in the HPN-group (62.7 %) compared to the reference-group (70.9 %). While the median percentage of FM was significantly higher (p=0.02) in the HPN-group (33.6 %) than in the reference-group (24.9 %).

Table 13: Anthropometric Z-scores and body composition in the study population.

	HPN-group (n=19)**		**Reference-group (n=50**)**		
	Median	**Range**	**Median**	**Range**	**p – value[1]**
Height Z-score (SD):	-1.8	(-4.2 - 1.4)	-0.1	(-2.7 - 2.9)	**<0.001**
Weight Z-score (SD):	-0.5	(-5.5 - 1.7)	0.0	(-1.6 - 1.8)	**<0.01**
BMI Z-score (SD):	0.0	(-4.0 - 2.1)	0.2	(-2.5 - 2.0)	0.97
Total lean body mass (%):	62.7	(55.4 - 76.8)	70.9	(54.0 - 81.6)	**0.02**
Total fat mass (%):	33.6	(19.9 - 42.5)	24.9	(15.5 - 42.2)	**0.02**

[1]Differences between the HPN-group and reference-group, a Mann Whitney U-test was used. Significant, p<0.05 (bold writing).

Total body BMD (g/cm^2) and BMC (g) in the HPN-group and the reference-group are presented in table 14. There was a significant difference (p=0.01) between the two groups in BMD (g/cm^2), where BMD in the HPN-group (0.742 g/cm^2) was lower compared to the reference-group (0.861 g/cm^2). No significant differences between the HPN-group and the reference-group were found total body BMC (g).

Table 14: Total body BMD (g/cm^2) and BMC (g) in the study population.

TOTAL BODY	HPN-group (n= 12)	Reference-group (n= 46)	p-value[1]
BMD (g/cm^2)			
- *Median*	0.742	0.861	**0.01**
- *Range*	(0.610 - 0.973)	(0.643 - 1.323)	
BMC (g)			
- *Median*	1134.0	1326.0	0.07
- *Range*	(509.0 - 1767.0)	(671.0 - 2691.0)	

[1] Mann Whitney U-test was used. Significant, p<0.05 (bold writing).

A significant difference (p<0.001) was found in total body BMD Z-score between the two groups (Figure 13), where the HPN-group had a significantly lower BMD Z-score, -0.70 SD, (range -2.4 – 2.2 SD) compared to the reference-group, 1.05 SD, (range -0.7 – 2.9 SD).

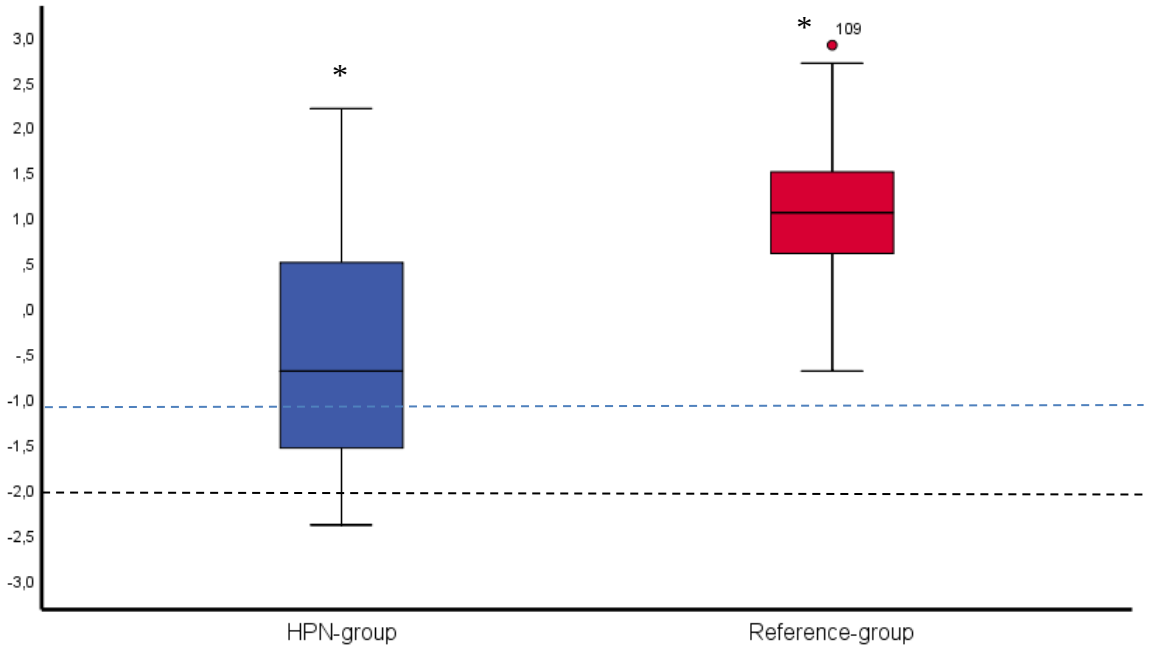

Figure 13: Total body BMD Z-score in the study population. ***Significant difference between the HPN-group and reference-group, p<0.05. The blue stapled line indicates the cut-off for decreased BMD Z-score (- 1.0 to -2.0) and the black stapled line indicates the cut-off for low BMD Z-score (<-2.0).***

In table 15, the spine BMD (g/cm^2) and BMC (g) in the HPN-group and reference-group are presented. Both the BMD (g/cm^2) and the BMC (g) was significantly lower (p=0.02, p=0.01) in the HPN-group (0.698 g/cm^2, 16.7 g) compared to the reference-group (0.824 g/cm^2, 21.7 g), respectively.

Table 15: Spine BMD (g/cm^2) and BMC (g) within the HPN-group and reference-group.

Spine [1]	HPN-group (n= 12)	Reference-group (n= 46)	p-value[2]
BMD (g/cm^2)			
- *Median*	0.698	0.824	**0.02**
- *Range*	(0.305 - 0.979)	(0.567 - 1.285)	
BMC (g)			
- *Median*	16.7	21.7	**0.01**
- *Range*	(5.5 - 35.2)	(10.6 - 51.8)	

[1]Spine: Anterior-posterior lumbar vertebral body 2-4.
[2]Mann Whitney U-test was used. Significant, p<0.05 (bold writing).

A significant difference (p<0.01) between the HPN-group and the reference-group was found spine BMD Z-score (Figure 14). The HPN-group had a significantly lower Z-score, -1.1 SD (range -4.1 – 2.3 SD), compared to the reference-group, 0.1 SD (range-1.4 – 2.5).

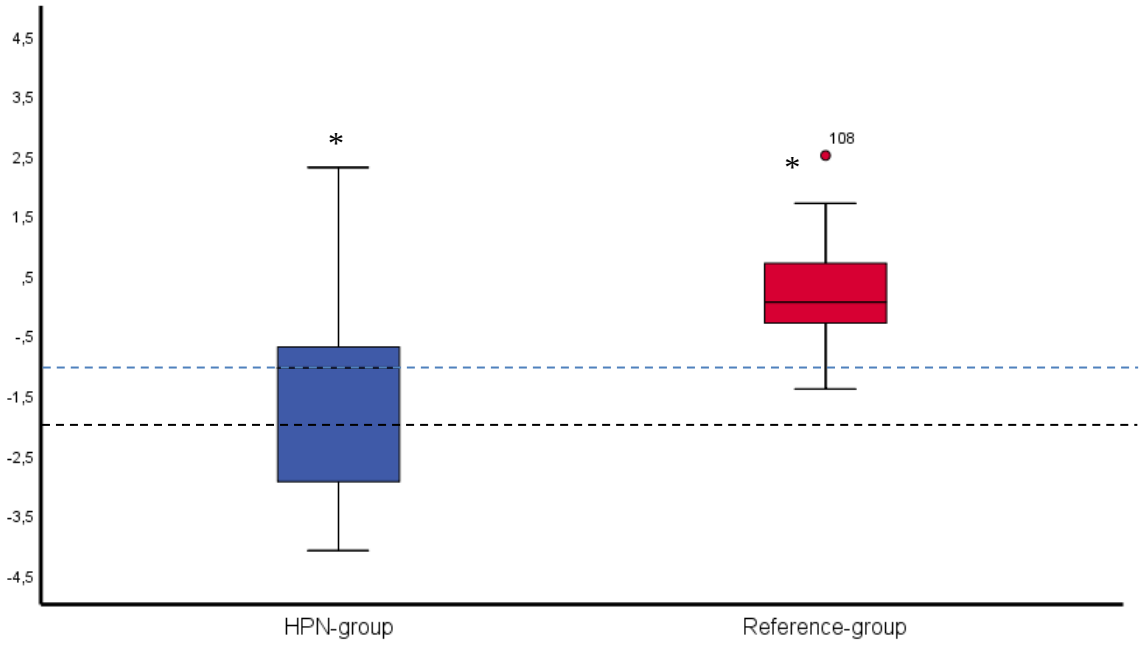

Figure 14: Spine BMD Z-score in the study population. ***Significant difference between the HPN-group and reference-group, p<0.05. The blue stapled line indicates the cut-off for decreased BMD Z-score (- 1.0 to -2.0) and the black stapled line indicates the cut-off for low BMD Z-score (<-2.0).***

Presented in table 16 are the number of subjects (%) categorized as having either "decreased BMD" or "low BMD" based on BMD Z-score. In the HPN-group, 33 % had decreased total body BMD Z-score and 8 % had low TB BMD Z-score. None were found to have decreased or low total body BMD Z-score in the reference-group. In the HPN-group, 17 % had a

decreased spine BMD Z-score and 33 % had a low spine BMD Z-score. In the reference-group, 25 % were found to have a decreased spine BMD Z-score.

Table 16: Number (%) of subjects with decreased and low BMD Z-score.

	HPN-group (n=12)	Reference-group (n=46)
Total body BMD Z-score:		
"Decreased BMD" *-1.0 to -2.0 SD*	4 (33 %)	0
«Low BMD» *< - 2.0 SD*	1 (8 %)	0
Spine BMD Z-score[1]:		
"Decreased BMD" *-1.0 to -2.0 SD*	2 (17 %)	3 (25 %)
«Low BMD» *< - 2.0 SD*	4 (33 %)	0

[1]Spine: Anterior-posterior lumbar vertebral body 2-4.

4.5 Vitamin D-status in the study population

The vitamin D-status (25(OH)D), included other relevant blood-markers for bone composition are presented in table 17. No significant differences were found between the HPN-group and reference-group for either of the blood-markers.

Out of the 47 subjects in the reference-group who gave blood, 34 of them gave blood in the first period of collecting data, between March and June. The remaining 13 gave blood in the second period, during August and September. The potential seasonal differences in the references-group, depending upon if blood samples were taken before or after the summer, was taken into account when statistical analysis were performed. No significant differences was found in 25(OH)D of children who gave blood before summer compared to those giving blood after summer (data not shown).

Table 17: Serum-level of the blood variables.

	HPN-group (n=19*)		Reference-group (n=47*)		
	Median	**Range**	**Median**	**Range**	**p-value[1]**
25(OH)D-serum level *(37 - 131 nmol/l**)*	71.0	(14.0 - 153.0)	81.0	(43.0 - 135.0)	0.29
Calcium (mmol/l) *(2.15 - 2.65 mmol/l**)*	2.35	(2.09 - 2.45)	2.36	(2.16 - 4.00)	0.28
Ionized calcium (mmol/l) *(1.15 - 1.33 mmol/l**)*	1.27	(1.16 - 1.32)	1.26	(1.15 - 1.34)	0.68
PTH (pmol/l) *(1.5 - 7.0 pmol/l**)*	4.6	(1.5 - 8.5)	4.1	(1.6 - 8.4)	0.97
Phosphate (mmol/l) *(0.9 - 1.9 mmol/l**)*	1.58	(0.96 - 1.71)	1.50	(0.94 – 1.81)	0.10

[1] Mann Whitney U-test (2 independent samples). Significant p<0.05.
*Missing subjects, Reference-group: 25(OH)D (n=3).
**Reference-values, from Aker Hormone Laboratory and Medical biochemistry laboratory e-handbook (RH and UH (OUH)) (107).

Percentage of subjects categorized as either sufficient (>50 nmol/l), insufficient (30-50 nmol/l), or deficient (<30 nmol/l) of 25(OH)D are presented in figure 15. In the HPN-group, 84 % had an sufficient serum level of 25(OH)D, 11 % had an insufficient serum level and 5 % had a serum level of 25(OH)D that indicated a deficiency. In the reference-group, 92 % had sufficient 25(OH)D, 4 % had insufficient 25(OH)D and none was deficient. No significant differences (p=0.20) were found between the HPN-group and the reference-group in distribution of subjects in each category.

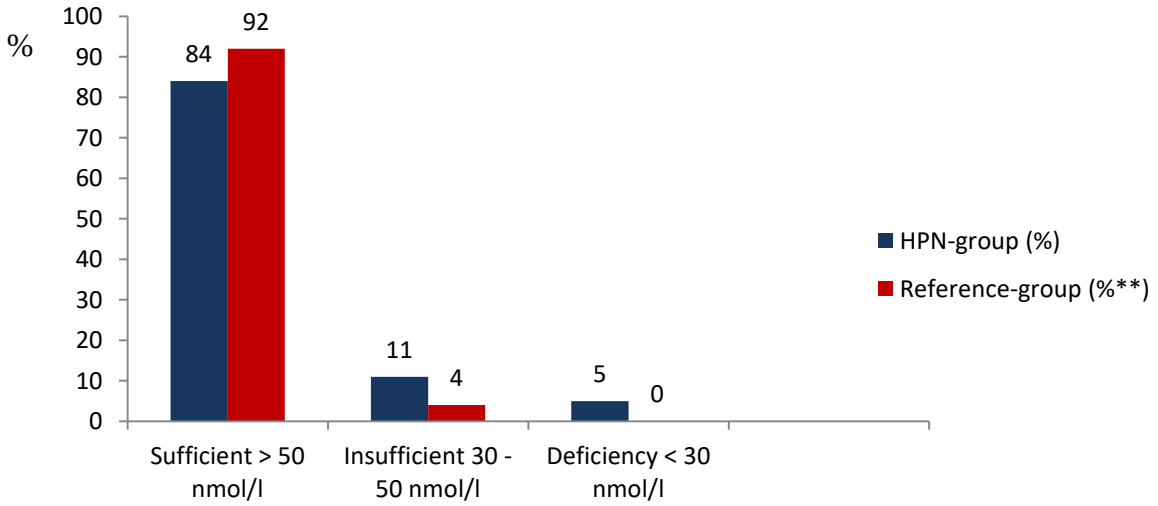

Figure 15: Percentage (%) of subjects with sufficient-, insufficient-, or deficient 25(OH)D. *Reference-values from NNR 2012 (56).*

4.6 Physical activity in the study population

The results from the wrist-accelerometers are shown as SLPA in minutes and MVPA in minutes (Table 18). No significant difference was found between the HPN-group and reference-group in either SLPA or MVPA.

Table 18: Physical activity measured with a wrist-worn accelerometer.

	HPN-group (n=12**)		Reference-group (n=39**)		
	Median	**Range**	**Median**	**Range**	**p-value[1]**
Physical activity – Sedentary-to-light (minutes):	570	(409 - 859)	574	(179 - 728)	0.63
Physical activity – Moderate-to-vigorous (minutes):	210	(64 - 326)	282	(110 - 373)	0.08

[1]Mann Whitney U-test. Significant, $p<0.05$.
**Missing subjects, HPN-group (n=7) and reference-group (n=11).

The results from type, frequency and intensity of PA measured by the questionnaire are presented in table 19. There was a significant difference ($p=0.01$) in type of PA between the HPN-group and the reference-group. The HPN-group had a higher percentage (26 %) of subjects who did not participate in any sports. The reference-group had a higher percentage (48 %) which participated in sports in general. The frequency of physical activity per week (Table 19) showed a significant difference ($p<0.001$) between the two groups. The majority of the HPN-group (63.0 %) had a frequency of 1-3 sessions per week and the majority of the reference-group (42 %) had a frequency of 4 sessions or more per week.
A significant difference ($p<0.001$) was found between the HPN-group and the reference-group in the intensity of each session per week (Table 19). The HPN-group (53 %) had a lower percentage of individuals within the high intensity-category compared to the reference-group (90 %).

Table 19: Physical activity measured by a questionnaire.

	HPN-group (n=19)	Reference-group (n=50)	
	Number of subjects (%)	**Number of subjects (%)**	**p-value[1]**
Type of physical activity:			
- *Ball sports*	7 (37.0)	19 (38.0)	
- *Athletics*	2 (11.0)	4 (8.0)	
- *Martial Arts*	1 (5.0)	2 (4.0)	**0.01**
- *Sports in general*	4 (21.0)	24 (48.0)	
- *No sports*	5 (26.0)	1 (2.0)	
Frequency per week:			
- *Never or less than once a week*	5 (26.0)	1 (2.0)	
- *1 -3 sessions a week*	12 (63.0)	28 (56.0)	**<0.001**
- *4 or more sessions a week*	2 (11.0)	21 (42.0)	
Intensity of the physical activity:			
- *Low intensity*	5 (26.0)	1 (2.0)	
- *Medium intensity*	4 (21.0)	4 (8.0)	**<0.001**
- *High intensity*	10 (53.0)	45 (90.0)	

[1] Crosstabulation - Fischer Exact test was used. Significant, p<0.05 (bold writing).

5. Discussion

In this cross-sectional study the nutritional intake from parenteral nutrition was in accordance with the ESPGHAN 2005 – guidelines. The HPN-group had a higher intake of carbohydrate and a lower intake of fat and protein compared to the reference-group. The HPN-group had a higher dietary intake of vitamin D and a lower dietary intake of calcium and phosphorous than the reference-group. The HPN-group had a lower Z-score for height, weight and BMD and a higher body fat mass compared to the reference-group. As much as 1/3 of the HPN patients had low spine BMD. No differences were found in 25(OH)D between the two groups. According to the questionnaire, the frequency and intensity of physical activity was lower in the HPN-group compared to the reference-group.

5.1 Methods

5.1.1 Study design

The cross-sectional design of this study made it possible to investigate, at a single point in time, a selection of dietary and environmental factors that could possibly affect the bone composition. The strengths of using a cross-sectional design was that it was easy to conduct and achievable within the timeframe of a master thesis. And it relied on the subject's participation only once and it was possible to investigate several variables associated to exposure and outcome at the same time. The weakness of using a cross-sectional study design was that it was only possible to make associations and not causations in interpretation of the results (124).

5.1.2 Study population

As OUH is the largest center in Norway for follow-up and treatment of pediatric patients with HPN, the recruitment of the HPN-patients was coordinated with their follow-up at the hospital. This made the recruitment-process easier and less stressful for the patients. The inclusion of data was conducted as part of the routine check-up, except the DXA-scan. As there were only 19 pediatric patients with HPN available per May 2017, the recruitment of them all was a strength in this study. The impression was that they all wanted to participate

due to the importance of further research on pediatric patients with HPN, as all were included (100 % participation).

The recruitment of the reference-group was at first initiated by the costume made web form which was shared only on the social media of Facebook. The hope was that this approach could secure the number of 50 participants. As the participation-rate in epidemiological studies has decreased the last years (125), it became important to use a recruitment-method that was easily accessible for the parents and children in the target age. This approach enrolled 42 eligible participants in the study between March and June 2017, but 7 of these were excluded due to unwillingness (n=6) and not being able to contact (n=1). This gave 35 included subjects before summer. Between August and September 2017, alongside the already established use of web form, the use of co-workers to spread the word was tried as an additional approach. This secured 16 new eligible subjects, but one subject was excluded due to not being able to contact. By the end of summer, representing the reference-group, the study had 50 healthy children and adolescence included in the study.

Bias in the study population

Bias of in epidemiological studies is almost unavoidable (125, 126) and the representability of the reference-group in this study might have been affected by it.

Selection-bias (127) might have occurred as the entire reference-group was located in the eastern part of Norway (Oslo, Akershus and Buskerud) and the HPN-group represented counties across south-east and western parts of Norway. The reason for selecting healthy participants from only this part of Norway was for practical reasons. No traveling expenses were covered, only the parking fee when participating at their scheduled appointments at either the hospital or at UiO. This could have made the reference-group less generalizable.

The non-responsive bias could have affected the generalization of the findings due to those who chose to participate might have represented a group of people especially interested in nutrition and PA. Higher education has been proven to be one of the factors contributing to an increased willingness to participate in epidemiological studies (125, 128). The mother's educational level was found to be high within both the HPN-group and the reference-group.

Although as the mothers in both groups had similar higher education, and most of them having a health care profession, this could be a strength of the study, but non-generalizable to

the rest of the population. Individuals whom have a health care background might have a special interest in both their own and their children's health, thereby also the nutritional aspects of it. One might think this could have affected the outcome in regards to both their daily composition of food items, the use of supplements and the level of PA. Those who did not participate in the study might have had a nutritional intake or a PA level which differed from those who did participate.

Information bias might have occurred during the inclusion of data (126). As both the dietary registration and the questionnaires on PA were self-reported it might have occurred a self-reporting bias, included a social desirability bias. The self-reporting bias could be due to misunderstanding the procedure of dietary registration, under-and overestimation of PA. The social desirability bias might be a factor affecting the self-reporting procedure as one might avoid registration of socially undesirable food items or registration of a higher frequency and intensity of PA to project as a more active human being than what is true.

The advantage with the reference-group was that they were highly motivated and presumably having high compliance with the different procedures. When interpreting the results, the reference-group must be regarded as an "ideal group" and not representative for the whole country.

5.1.3 DXA

DXA is considered to be the "gold standard" in measuring bone and body composition (13) and was therefore the preferred choice in this study. The procedure was quick, easy, safe due to low radiation dose, non-invasive, precise and gave information about total body – and spine BMD (g/cm2), BMC (g), BMD Z-score, FM (%, g) and LM (g).

Although the measurements within the HPN-group and the reference-group were conducted by different individuals, the results from both instruments were interpreted by the same technician, (Kristin Godang), to ensure quality of the results. As the two DXA-instruments have been proven to be comparable (103), the results obtained from the measurements of the HPN-patients could be compared to the measurements within the reference-group.

The weakness of using DXA to measure bone composition was that the instrument used a two-dimensional technic rather than a three-dimensional technic on an object that was

originally three-dimensional. The result was therefore expressed in areal of BMD (g/cm^2) and not volumetric BMD (g/cm^3). This could have resulted in an underestimation of the bone composition in children with small bones or lower density due to growth or disease (129). If a child was short for his/her age, and thereby had smaller bones, the DXA-scan would underestimate the density of the child's bones. Likewise in the other direction, if a child was tall for his/her age, and possibly then had bigger bones, the DXA-scan would overestimate the density (130).

In this study, due to the heterogeneity of the HPN-group, some of the children might have had a growth-retardation related to their chronic disease. This gave rise to a potential underestimated BMD Z-score in the group of HPN-patients. Several technics have been suggested for correction of this possible misinterpretation (130), including the use of bone age (131). Due to practical reasons the determination of bone age was not possible in the present study. This might have interfered with the interpretation of the BMD Z-scores in the HPN-group and is important to have in mind when assessing the BMD Z-score within the HPN-group.

5.1.4 Blood-samples

Seasonal variation has been found to affect 25(OH)D in children and adults, (132-134), where the peak in 25(OH)D most often occurs between April and August. As all of the HPN-patients gave blood in the same period before summer, this was not considered an issue in that group. There were possibilities of seasonal differences in the reference-group, due to one group (n=34) gave blood before summer and the other group (n=13) gave blood after the summer. However, no significant differences were found. One reason for not finding a difference might be that the part of the reference-group who gave blood after summer (n=13) were a lot smaller in size compared to those before summer (n=34), resulting in a type II error due to the lack of power. Based on these results, there was no need to differentiate the reference-group according to having taken blood before or after summer in any of the statistical analysis conducted in this study.

Type II error might have occurred in the 25(OH)D analyses between the HPN-group and the reference-group. The sample size in each group were small (19 vs. 47), and the range of values were wide in the HPN-group (14 – 153 nmol/l) and the reference-group (43 – 153 nmol/l).

5.1.5 Dietary registration

The use of 4 days of dietary registration in present study were considered to be an appropriate amount of days due to less burden and keeping as much quality in the registration as possible. Studies have found that the use of self-reported dietary registration, included non-consecutive days, gave a good estimate of a subjects habitual dietary intake (135-138). The number of included registration days varied among studies (139, 140), but recent findings suggested that the more registrations days included, the worse the quality of the dietary registration was (137).

The instructions of diet registration in present study were to include three weekdays and one day of the weekend. The use of both weekdays and weekend days has been found to increase the probability of detecting the day-to-day variation among free living individuals (140, 141).

It was a challenge that the present study included subjects with a vast range in age, as the method of dietary registration also involved the parents in some cases. This was especially the case for those being disabled in the HPN-group and those being below the age of 12 in the reference-group. Although as children gets older, the ability to self-report dietary intake of food and beverages increases (136). The literature suggests that the age of 12 years or older is when the child is most capable to manage a dietary registration on their own. This also depends upon the cognitive abilities of the child (135).

Burrows et.al (142) compared the registration accuracy among children, mean age 9.8 years, and their parents in regards to the children's dietary intake. The results showed that the children had a higher accuracy in registration of their own diet than both of the parents, with the mother's having the lowest accuracy. This could reflect that the parents might not always register the diet of their child in a correct manner, compared to the child itself. As for our study, the overall impression was that the diet was mostly registered by one of the parents and usually the mother.

The present study used different interviewers as part of the consultation. This might have affected how much information one got out of each subject in regards to their dietary registration that were supposed to be investigated during the consultation. As the main questions were agreed upon beforehand, the bias might have been each interviewer's way of asking questions or the chemistry between the subjects and the interviewer.

The use of a picture booklet in our study was to help the subjects in estimating the right portion size. The picture-booklet from Norkost 3 (98) has been validated in the adult population (99). As our study included children and adolescents, the amounts estimated in the picture-booklet might have been unsuitable for the use in our study population. Although the impression was that the majority of the population used a varied range of the different portion sizes established in the picture-booklet. Picture booklets has been shown to decrease the burden of the dietary registration for children up to 10 years of age due to their lack of recognizable skills related to food items (143, 144).

5.1.6 Physical activity

GENEActiv accelerometer

In present study, the GENEActiv accelerometer (GENEA) were selected due to its ability to collect raw accelerometer data, its availability and easy to use. The participants got instructions on using the GENEA on the non-dominant wrist and to wear it throughout the day. There are no clear guidelines on which arm is preferred in the PA-registration of children and adolescents. The GENEA has been validated for placement on the non-dominant wrist (111) of children 5 to 8 years. There might have been a difference in using either the non-dominant arm or the dominant arm, as pointed out by Crouter et al. (145). The dominant arm might have participated increasingly in everyday activities compared to the non-dominant arm. There are found potential differences in regards to location of the accelerometer and thereby different measurements, as pointed out by Kim et al. (146). The level of PA, especially weight-bearing PA, might have been underestimated due to location. Although these potential effects has to be investigated further.

As children has a higher resting metabolic rate than adults, the use of the MET cut-points from Shaefer et al. (116) and van Loo et al. (117) might have misclassified the intensity of the PA. A study by Troiano et al. (109) suggested using a cut-point of 4 MET and 7 MET in categorizing moderate PA and vigorous PA in children, rather than 3 MET and 6 MET used by Shaefer et al. and van Loo et al., respectively. In our study it might have affected some of the light PA being categorized as moderate PA or moderate being categorized as vigorous PA. This could have affected the amount of MVPA established in both the HPN-group and the reference-group, where both groups might have appeared as more active than what was the

case. As shown in a study by Kozey et al. (147), the MET values for each common PA varies substantially, which increases the risk of misclassification of the intensity-level of an activity. There is need for standardized guidelines in relation to the MET cut-points for all age-groups.

The use of a 60 second bout when reading the raw data from the accelerometer into epoch files might have decreased the accumulated minutes spent in MVPA. As children are active in a more sporadically fashion (108, 148, 149), it might have been more appropriate to use an epoch file with readings per second or per 5 second, also suggested in the review by Loprinzi et al. (122). An increased number of seconds used in the epoch files (from 1 second readings to 60 second readings), a decrease in the total amount of minutes per category of intensity has been observed (116).

Although there are no established guidelines on this methodological procedure. The findings from our study suggests the need for standardized guidelines for establishing cut-points for intensity, classification of PA, and quantifying the duration of each bout used in the epoch-files.

Physical activity – questionnaire

In present study, the questionnaires on type, frequency and intensity of PA was meant to be a supplement to the objectively measured PA by the accelerometer. The use of these types of questions is common in epidemiological studies (121-123) and were evaluated to cover the necessary supplementary information needed in our study.

The use of self-administered questions on PA might have been prone to a social desirability effect or an overestimation of PA by the child/parents. In our study the parents in both the HPN-group and the reference-group were often the ones who filled out the questionnaires. As seen in a study by Bringolf-Isler et al. (150), the parents tend to both over – and underestimate certain PA for their children. They also found an age-related difference in reporting PA. As the questionnaires were not costume made for the HPN-group, who had several subjects with different disabilities, this might have affected the level of response in that group. The questionnaires were not adapted to each age-group either.

As the self-reported amount of PA is generally at risk of bias (120), the use of an accelerometer alongside the questionnaire made the estimation of PA more reliable.

5.2 Interpretations of results

5.2.1 Dietary assessments

Total dietary intake in the study population

The nutritional intake within the HPN-group was in accordance with the EPSGHAN 2005-guidelines (6). The total energy intake (kcal/kg/day) was non-significantly higher in the HPN-group compared to the reference-group. In accordance with these findings, a population based cohort by Mutanen et al. (26) in 41 Finnish pediatric patients with IF found that the total energy intake (kcal/kg/day) were higher in the patient-group (76 kcal/kg/day) compared to healthy controls (62 kcal/kg/day). Their study were conducted in patients who were in similar age-group as our study.

The HPN-group were in average above RDI, while the reference-group was below RDI of energy needs per day (58). Within the HPN-group, the true energy needs might have been increased due to the neurological diseases (78). Using the RDI in this patient-group should be done with caution.

As pediatric patients with IF who receives PN was more closely monitored due to their special nutritional composition, they were less likely to misreport nutritional intake. The dietary registration in the reference-group was prone to misreporting because they had no specific restriction or monitoring regarding their daily nutritional daily intake. An exact calculation of misreporting were not conducted in present study, but the results from the average % of RDI might indicate that misreporting has occurred, especially in the reference-group.

A review on misreporting energy intake by Forrestal et al. (151) found that children and adolescents was especially prone to misreporting due to still development of social and congenital skills among other factors. A study by Murakami et al.(152) of children and adolescents aged 2 – 19 years, based on the National Health and Nutrition Examination Survey (NHANES) 2003–2012 data, found that older age were correlated with under-reporting and over-reporting were associated with a younger age.

Most of the HPN-patients were unable to register their diet themselves due to different disabilities and many of the children in the reference-group were too young (<12 years of age) to register diet themselves. The diet registration were then conducted by their parents. As mentioned earlier, the tendency to misreport might have been of a bigger problem in the reference-group compared to the HPN-group due to the HPN-patient's closely monitored nutritional regime.

The study by Burrows et al. (142) found mothers to be the most inaccurate family-member to register their children's diet. As most of the parents involved in our study were the mothers, this might have affected the dietary registration. In Ungkost 3 (153), a population-based study which included children and adolescents in the age of 9 and 13 years, there was a substantial amount of underreporting in the adolescent-group. This supports the findings from the study by Murakami et al.(152) related to age being a factor. The potential underreporting in the reference-group might have been because of the high burden of diet-registration or due to a social desirability bias.

The total daily intake of all the macronutrients were within the RDI (58) for both the HPN-group and the reference-group. The total daily intake of protein and fat were significantly lower in the HPN-group compared to the reference-group in our study. This was partly in accordance with the study by Mutanen et al. (26), where the patient-group received less protein, but more fat compared to the control-group. In our study, the fat-content from PN and EN varied greatly. Some received a fat-free PN and some might have had a higher fat-restriction compared to those in the study by Mutanen et al. (26). The patient-group was half the size of the study sample in the Mutanen et al.-study which itself could explain why those ingesting a low-fat diet in our study could have affected the results to a greater extent than in their study. The lower amount of fat and protein in the HPN-group compared to the reference-group in our study might have been because of restrictions in infusion-rate of the PN.

However, the reference-group had no restriction in either fat or protein and as both nutrients are easy to obtain by a normal and varied diet, they had unlimited access. The intake of macronutrients (E %) in the reference-group found in our study was in accordance with both the Ungkost 3 study for 4 year olds (154) and Ungkost 3 for 9 and 13 year olds (153) conducted during the year of 2015 and 2016. This suggest that despite the small sample size and inclusion of subjects from only the eastern part of Norway, our study reflected the

nutritional intake of children and adolescents similar to what was found in larger, population-based studies.

For total daily intake of the micronutrients vitamin D, calcium and phosphorus, there were significant differences between the HPN-group and reference-group. Although a direct comparison of these micronutrients across the HPN-group and the reference-group should be done with caution. This because the micronutrients given to the HPN-group was based on two different routes of administration (via EN and PN) which made it difficult to directly compare findings in the diet of the HPN-patients with the diet in the reference-group. This is especially important to have in mind when interpreting the results due to the great span of IF-diagnosis within this HPN-group, which is the main cause of poor nutrition in this patient group (76, 77). The food sources from EN may not have been fully utilized due to poor intestinal absorption. The food sources from PN could have been utilized to a greater extent due to its passage directly through the blood stream and avoiding the metabolism in the liver.

But having these different routes of administration in mind, our study found that both with and without supplements, the HPN-groups achieved RDI of both vitamin D and phosphorus, but not calcium. Similar results for vitamin D were found in the study by Mutanen et al. (26) where the dietary intake of vitamin D was covered by 130 % of RDI in their patient-group and 65 % of RDI in their control-group. Mutanen et al. did not report RDI-results for phosphorous and calcium like present study did.

A study by Sentongo et al. (155) in a group of 112 pediatric patients with Crohn disease found an average dietary intake of vitamin D of 5 µg/day. The study by Sentongo et al. used the old RDI and was conducted on patients with Crohn's disease, but could reflect the challenges with absorption from the gut when having gastrointestinal diseases and at the same time only rely on dietary intake per os.

The dietary intake of vitamin D was above RDI in both our study and the study by Mutanen et al (26), while below RDI in the study by Sentongo et al.(155). The main sources of dietary vitamin D for the HPN-patients in our study were PN. This suggests that the use of PN could secure sufficient amounts of dietary vitamin D in patient-groups with malabsorption diseases and that the PN-composition is of upmost importance in this patient-group. Most studies conducted in the pediatric patient-population both with and without PN, has investigated

vitamin D-status by using 25(OH)D, while not reporting the dietary intake of vitamin D alongside. This makes the comparison difficult in regards to findings in our study.

In the reference-group, the total daily intake of vitamin D, calcium and phosphorus, were found to be almost the opposite of the HPN-group's intake of micronutrients. In the reference-group, the daily intake of vitamin D was in average only 75 % of RDI. This result was not surprising due to findings in the two "Ungkost 3" – reports (153, 154) which showed that vitamin D still is a problem in the young Norwegian population. In accordance with our study, low dietary intake of vitamin D has also been shown in the general European adolescent-population (156, 157).

In present study there were only 14 subjects who took vitamin D supplements. This is important to have in mind when evaluating their main sources of vitamin D. However, when evaluating the food sources of vitamin the main source was fish (26 %). This in accordance to what is found in other studies (158, 159).

The calcium – and phosphorus were in average 114 % and 148 % of RDI in the reference-group, respectively. When evaluating the potential sources of calcium, the consumption of dairy-products were found to be the main source. Other sources like vegetables, legumes and nuts contributed in just a small amount. These findings were in accordance with other studies (158, 159). The findings were also in accordance with Ungkost 3, where the level of micronutrients was satisfactory, except vitamin D.

The use of vitamin D- supplements might be seen as trivial in our study as just 5 of the 19 HPN-patients and 14 of 50 in the reference-group registered using it. Several other studies (160-164) has investigated the effects of vitamin D-supplements to maintain 25(OH)D within a sufficient level. Two studies (160, 164) found a dietary supplement of 10 – 30 µg/day to be sufficient. Other studies (161-163) found 6 – 39 µg/day to be sufficient, depending upon skin-color.

5.2.2 Bone and body composition

The distribution of gender was significantly different between HPN-group and the reference-group. There was a majority of boys in the HPN-group and a majority of girls in the reference-group. The development of boys and girls are different during childhood and

adolescence (18, 23). This could have affected the interpretations of bone and body composition due to the wide range in age within the HPN-group (4.1 – 16.4 years) and the reference-group (3.7 – 16.8 years) of present study. Some of the subjects were pre-pubertal and some pubertal, which could the distribution of LM and FM.

The Z-scores of height-for-age and weight-for-age was significantly lower in the HPN-group compared to the reference-group, similar to what was found in other studies (15, 26, 27, 38). Children with disabilities, either physical and/or neurological, has been shown to be at risk for a negatively associated bone composition due to potential negative effects of medications, poor nutrition and a low activity level (29, 30). The HPN-patients in our study had various degrees of disabilities and a heterogenic variation of IF-diagnosis which might have a negative impact on their nutritional intake. These factors might then have contributed to the patients being at risk of growth retardation. Although further research has to be made in this matter.

In our study the HPN-group had a significantly lower total body BMD than the reference-group. These findings are supported by other studies, (14, 27, 31). The study by Pichler et al. (27), found 19 of 45 pediatric patients with IF having a low BMD. In our study, 1 out of 12 HPN-patients were categorized as having a low a total body BMD, and 4 out of 12 HPN-patients were categorized as having decreased BMD ,

Another study, by Neelis et al. (14), found that out of the 46 pediatric patients with IF, 16.2 % of them had a low BMD Z-score for total body at first DXA-scan. They also related age, PN-duration and surgical IF to their results of low BMD Z-score. Associations between these factors were not investigated in our study. Their study design was retrospective and current study had a cross-sectional study design, therefore directly comparison was not easily made, but nevertheless could assumptions be made as the results pointed in the same direction.

The spine BMD Z-score in present study were also found to be significantly lower in the HPN-group than in the reference-group. A study by Demehri et al. (31), screened 36 pediatric patients with IF, mean age of 9.9 years, for the risk of developing metabolic bone disease. They found a spine BMD Z-score < -1 SD for 50 % of the subjects. In our study 33 % of the HPN-patients and 25 % of the reference-group was categorized with a decreased BMD Z-score. Having in mind that measurements of the spine in our study were in the L2-L4-area in contrast to their study (L1-L4 area). Although the exclusion of L1 in our study should not

have made a great difference due to the increased BMC (g) from L1 – L5 (23). Demehri et al. conducted a retrospective single-centered study and evaluated the bone composition several times. This makes the possibility of finding stronger associations of potential factors affecting the bone composition compared to our study.

The study by Mutanen et al. (26), included 41 pediatric patients with IF. They found that 33 % of their patients had a decreased BMD Z-score and 33 % had a low BMD in the spine. In our study there were 17 % having a decreased BMD and 33 % having a low BMD in the spine. Even though our HPN-group were half the size, the results from our study pointed in the same direction as the study by Mutanen et al. Their study was a cohort-study and had several strengths compared to our cross-sectional study. Despite different study designs, it was possible to make associations between the heterogenic nature of IF and how it negatively affected the BMD Z-score.

Another study found to be in accordance with our results was the study by Schmidt et al. (28), with a population of 144 Swedish children with inflammatory bowel disease. They found that 47 % of the patients had a decreased spine (L2-L4) BMD.

A longitudinal study by Diamanti et al. (25), included 24 pediatric patients with IF and median age of 6.7 years. They found a significantly lower spine (L1-L4) BMD Z-score in the patient-group than in the control-group. Their patients received similar amounts of vitamin D, calcium and phosphorous as the HPN-patients in our study. Although their study was longitudinal and included a 1 year follow-up, their findings were similar to the present study. Diamanti et al. divided the group into subgroups and then performed analysis in relation to their different IF-diagnosis, age and use of PN. In our study, separation into subgroups were not conducted due to the possibility of increasing the risk of type II error because of an even smaller sample size.

As the results from our study was in accordance with all the studies above, it gives reason to think that by only conducting a cross-sectional study in a group of pediatric patients with IF, one might still be able to detect the well-known problem of a lower BMD Z-score compared to a healthy population.

The reference-data for children and adolescents used in the DXA-software was based on measurements from the population-based study called National Health and Nutrition

Examination Survey, (NHANES) (165), conducted between the year of 1999 and 2006 in the United States. Measurements of total body and spine BMD (g/cm2) in the reference-group of present study were in accordance with the findings from the NHANES-study. Although the NHANES-study separated on gender and age-groups, our findings suggest that Norwegian healthy children and adolescents had a similar bone composition as found in the general population in the United States.

The results of total body and spine BMD (g/cm2) within the HPN-group in present study should not be directly compared to the NHANES-results and therefore evaluated with caution. The HPN-patients were found to have lower BMD (g/cm2) compared to the healthy individuals in NHANES. This might have reflected the potential growth-retardation in the HPN-group compared to healthy children and adolescents in the same age-category.

A cross-sectional study, by Torres-Costoso et al. (166) investigated bone and body composition in a group of 132 healthy schoolchildren from Spain, with a mean age of 9.4 years. Their study found mean total body BMD to be 0.844 g/cm2 and mean spine (L1-L4) BMD to be 0.698 g/cm2. As their study was conducted with healthy subjects in the same age-group as our study, the results could be compared to some extent. In present study, total body and spine BMD (g/cm2) within the reference-group were similar to findings in the study by Torres-Costoso et al. The results of total body and spine BMD (g/cm2) in the HPN-group of our study were however lower than in the Torres-Costoso-study. This also supports the associations between HPN-patients and a possible growth retardation.

When evaluating body composition, a significantly higher percentage of FM and a lower percentage of LM were found in the HPN-group compared to the reference-group. Similar to our results was found in a study by Pichler et al. (38), investigated a potential growth failure in 34 pediatric patients with IF receiving long-term PN. A difference between our study and the Pichler et al.-study were their separation of the group into fully or partially dependent upon PN. In present study such separations were not made and the HPN-group were analyzed as a whole group.

Another study by Pichler et al.(27), also found results similar to our study in a group of 45 pediatric patients with IF. Their study found that the pediatric patients with IF were both lower and weighed less compared to the control-group. The study by Mutanen et al. (26)

showed similar results, with their patient-group having a lower mean height-for-age and a lower mean weight-for-age compared to the normal population.

In our study, one subject in the HPN-group and one subject in the reference-group were registered as non-Caucasian. This was non-significant for both total body and spine measurements in present study. The relationship between LM and bone composition has been found to be affected by a genetic and racial factor. This has been shown in a study by Cardel et al. (167), where bone and body composition were measured in a group of children with either African ancestry or European ancestry. The children with an African genetic composition was associated with higher total body BMC and lower FM compared to the group of children with European ancestry. Associations between ethnics and bone and body composition were not investigated in current study, but as both the HPN-group and the reference-group had a majority of Caucasian subjects, such differences would possibly not have been detected anyway.

5.2.3 Serum-level of 25(OH)D

No significant differences in 25(OH)D between the HPN-group and the reference-group were found in our study. The median 25(OH)D was well above the sufficiency-level of 50 nmol/l (58) in both groups.

A 2-years retrospective study by Wozniak et al. (64) investigated 25(OH)D in 27 pediatric patients with IF, receiving HPN for more than 6 months. Almost half (41 %) of the subjects in the study was categorized as insufficient of 25(OH)D (50 – 72.5 nmol/l) and 1 subject categorized as 25(OH)D-deficient (<50 nmol/l). They concluded that in regards to 25(OH)D, the pediatric patients with dysmotility or malabsorption syndromes were more likely to have low 25(OH)D compared to those with short bowel syndrome. In our study, the one subject categorized as deficient (< 30 nmol/l) in the HPN-group was within the diagnosis-category of severe dysmotility disorders. No further investigation were made in our study in regards to type of IF-diagnosis and its potential effect on 25(OH)D. The potential relationship between these two factors was therefore impossible to establish.

In contrast to the study by Wozniak et al. (64), the diagnosis-category of severe dysmotility-disorders in our study also included subjects who were found to be sufficient of 25(OH)D (> 50 nmol/l). Having in mind the different cut-offs in evaluation of 25(OH)D-deficiency used in

their study and our study, there might be other reason for why only one subject were found to have such a severe degree of deficiency in our study. Although it is not possible to conclude to anything in our study, the reasons might have had something to do with dependency of PN, dietary supplements, additional medications or a minimum of sun exposure due to disabilities.

A retrospective study by Namjoshi et al. (168) included 60 pediatric patients with IF receiving HPN, with a median age of 3.3 years where 77 % were non-white. They found 67 % with deficiency (< 75 nmol/l). In our study, a cut off by 50 nmol/l (58) were set to establish sufficiency of 25(OH)D. This might then suggest that more subjects could have been deficient in the study by Namjoshi by using the same cut-off as present study. The presence of ethnic diversity in their study is different from our study, where one HPN-patient and one subject in the reference-group were non-Caucasian. Non-Caucasian children and adolescents (169) has been found to have a lower 25(OH)D compared to the Caucasian population. This might then have increased the possibility of finding deficient subjects in the study by Namjoshi et al. (168) compared to our study.

Another study, by Ubesie et al. (79), investigated 123 pediatric patients with IF and a median age of 4.4 years. They found a 25(OH)D-deficiency in 40 % of the subjects when a cut-off by 50 nmol/l were used. They linked the deficiency to whether the patients received supplementations or not. In our study this association was not made due to few having reported the use of vitamin D supplements outside the additives in PN. Ubesie et al. also included analysis of 25(OH)D related to age-groups, which were not conducted in present study due to an already small sample size. In contrast to our study, Ubesie et al. had a longitudinal study design with a greater sample size and their findings were based on a 5 year follow-up.

The cohort by Yang et al. (77), included 30 pediatric patients with IF, with a mean age of 5 years. They investigated the prevalence of micronutrient deficiencies when decreasing PN and increasing EN in a transitional period. Deficiency of 25(OH)D were established by a cut-off of < 75 nmol/l. They found the prevalence of 25(OH)D-deficiency to be 20 % in the transition period and a prevalence of 25(OH)D-deficiency of 68 % when full EN were initiated. Our study had the disadvantage of both being a cross-sectional study and having a small study sample. Even so, the presence of 25(OH)D-deficiency in the HPN-group versus none in the reference-group might indicate that the pediatric patients are at higher risk of developing deficiency compared to the healthy population.

Similar results of both 25(OH)D-deficiency and insufficiency has also been shown in pediatric populations with irritable bowel syndrome (IBS) (61) and irritable bowel disease (IBD) (63). In the study by Sohn et al. (63), the presence of Crohn's disease seemed to be associated with a higher risk of an suboptimal 25(OH)D compared to other IBD-related diseases. Which were also found in the study by Sentongo et al. (155).

In the study by Pekkinen et.al (62), 195 healthy Finnish school-children, age 7 – 19 years, were included to investigate the potential associations between bone composition and vitamin D (both dietary intake and 25(OH)D). They found 71 % of the subjects having insufficient 25(OH)D, with a median of 41 nmol/l for girls and 45 nmol/l for boys. The dietary intake of vitamin D in their study were 10.4 µg/day, which were in accordance with NNR 2012 (58). Their findings is in contrast to our study where 4 % of the reference-group were found to be insufficient of 25(OH)D and the dietary intake of vitamin D were in average only 75% of RDI. Our study included a reference-group comprised of only one-fourth of the study sample in the Pekkinen et al.-study (62). This might have increased the risk of type II error and thereby the inability to detect potential subjects at risk for insufficiency in our study.

The study by van der Gaag et al. (170), included 174 healthy children from the Netherlands, with a median age of 8.5 years. They found 51 % of the children being insufficient of 25(OH)D (<50 nmol/l), while 9 % were deficient of 25(OH)D (<30 nmol/l). As their study were conducted between October and April and our study between March and September, it's possible that our study had the benefit of the summer-months and thereby increased sun exposure.

The findings of our study suggest the continued need for close monitoring of 25(OH)D in these pediatric patients. It is also important to establish international, standardized guideline on which cut-off of 25(OH)D to use when establishing deficiency. This should be emphasized to avoid deficiency and higher risk of bone-related diseases (2, 31, 77).

5.2.4 Physical activity

There were no significant differences in minutes of MVPA between the HPN-group and the reference-group. However, the HPN-group had a lower counts of minutes compared to the reference-group. Both groups were within the recommendations of >60 minutes of MPVA per day by WHO (85).

The use of an accelerometer has been found to be a reliable tool when objectively measuring the amount of PA in different age-groups (109, 113, 114), but the non-use in relation to different activities should be kept in mind when interpreting these findings. As some of the subjects in the reference-group participated in activities such as football, handball and martial arts, that allowed no jewelry, the most intense sessions of football, handball or martial arts would not be registered. Therefore, the differences in the MVPA between the HPN-group and the reference-group in our study might have been even greater than these findings suggested. The range of minutes in MVPA was found to be of a greater width in the HPN-group than in the reference-group. This might be due to some of the HPN-patients being disabled and mostly bedridden, and therefore had a minimum of MVPA during the day.

As there was few studies conducted on PA in pediatric patients receiving HPN and the studies found was over 15 years old, it made the comparison between present study and updated literature difficult. However, a study by Beghin et al. (171) investigated the total energy expenditure and the level of PA by using an accelerometer in a group of 11 pediatric patients with HPN compared to a group of 11 healthy children. Both groups had a median age of 6 years. In accordance with present study, no significant differences were found between the patient-group and the control-group. Even though similarities were found between ours and their study, there were several differences which might make the comparison invalid to a full extent. Beghin et al. used kilo counts per minute/day and current study used minutes/day to evaluate the amount of PA measured by accelerometer, which makes the comparison possible, but should be interpreted with caution due to potential use of different cut-points (172).

Besides using a different accelerometer, which itself might cause differences in the raw-data, the study by Beghin et al. (171) also used the hip as location for their accelerometer. Our study used the non-dominant wrist as location, which might have led to a misinterpretation of the registered raw-data. Different locations on the body as shown to be inconsistence in detection of PA (146, 172).

Beghin et al. (171) also included only one day of PA-registration with no additional after-school activities. This is in contrast to present study where 4 days of PA-registration were included. Both the study by Beghin and our study included a small sample size, which might have made the results at risk for type II errors and thereby false negative due to lack of power.

The review on physical activity in children with disabilities measured by accelerometers, by Lobenius-Palmer et al. (110), concluded that children and adolescents with different disabilities were insufficiently active and were more prone to SLPA rather than MVPA compared to the healthy population. The HPN-group in our study showed no significantly lower MVPA compared to the reference-group, which were inconsistence with the review by Lobenius-Palmer. However, the lower range of MVPA found in the HPN-group compared to the reference-group might indicate that some subjects in the HPN-group could be at risk of not meeting the WHO-recommendations of >60 minutes per day of MVPA. These findings may therefore point in a similar direction as the review by Lobenius-Palmer et al. As concluded in the review by Ross et al. (88), the definition of PA and measuring-methods should be standardized and adapted according to age, gender, type and degree of disability. Therefore, the results from our study should be interpreted with caution as these adaptations were not made.

The present study found significant differences in type, frequency and intensity of PA measured by a questionnaire between the HPN-group and the reference-group. As many of the children in our study had several disabilities, it might have affected their possibilities of being as active as their peers. Many children with disabilities need extra supervision and encouragement to obtain the same amounts of PA as the healthy population (92, 173). The importance of facilitated activities should therefore be empathized both at home and at school (89, 91). It might increase the ability of children to be more physically active despite their disabilities and thereby becoming a facilitating factor to good health.

PA has also been linked to an increased bone mass accrual in studies conducted in children with cerebral palsy (CP) (90, 93) and pediatric bone tumor patients (174). As pediatric patients with IF are found to be at great risk of developing bone-related diseases, the impact of PA should also be emphasized in this heterogenic group of patients.

The health benefits of maintaining the recommended level of MVPA (85) has been shown to be several in the healthy population of children and adolescents (175). As in contrast to sedentary time which has been found to have a negative impact on health, especially bone health (34).

In our study, the amount of MVPA were found to be within the recommendations, which are in contrast to other studies conducted in the European population of children and adolescents

(108, 149) and in the United States (109), suggesting a MVPA below recommendations in children and adolescents.

The cross-sectional study by Nilsson et al. (149) included 1954 European children and adolescents between 9 and 15 years. They found time spent in MVPA to be higher during the weekdays compared to the weekend days across both age-groups and countries. This was also found in SLPA and differences between weekdays and weekend days. Their findings also suggest the 9 and 15 year olds from Norway to have the highest amount subjects (%) reaching the recommendations of MVPA compared to the other participating countries.

The cross-sectional study by Ruiz et al. (108) included 2200 adolescents from Europe, median age of 14.9 years, and investigated time spent in SLPA and MVPA by using an accelerometer. They found 53.7 – 58.6 % of the boys in Southern and Central Europe to meet the recommendations of MVPA daily. The percentage of girls was lower, with only 19.9 % in Southern Europe and 32.2 % in Central Europe meeting the recommendations of MVPA/day. The girls spent more time in SLPA compared to the boys, showing that boys were more active during the day.

The study by Troiano et al. (109) included 4880 children and adolescents from the population-based survey the National Health and Nutrition Examination Survey (NHANES) in the United States. Their findings suggested that the level of PA decreased markedly in the adolescent years. In the group of children up to 15 years of age, only 42 % met the recommended levels of MVPA/day.

In accordance to our study, time spent in SLPA were almost twice as high as time spent in MVPA in the studies by Nilsson et al. (149), Ruiz et al. (108) and Troiano et al. (109). In contrast to present study, total time spent in MVPA was considerably lower in their studies, even though Nilsson et al. (149) found Norwegian adolescents to be more active than adolescents from the other participating countries. This might be due to the use of different use of MET cut-points and thereby overestimating MVPA in our study. Or misinterpretation of what was registered as SLPA and MVPA and thereby getting a skewed impression.

As in our study, Nilsson et al. (149) conducted measurements of 4 days. Although they registered 2 + 2 rather than 3 + 1 of weekdays + weekend days as in present study, respectively. Nilsson et al. also investigated potential differences between weekdays and

weekend days, which were found to be significantly different. This procedure was not conducted in our study, which were mainly focused on registration of PA during the same period as the dietary registration were made. This might have increased differences between the individuals in regards to potentially different PA pattern during weekdays and weekend days.

Ruiz et al. (108) measured PA over 7 days, which therefore minimized potential differences between weekdays and weekend days. The study by Troiano et al. (109) also conducted their measurements over 7 days.

All three studies (108, 109, 149) also minimized any potential seasonal differences due to conducting measurements through 1 whole year. In present study, all measurements were conducted between March and September, which might have increased the MVPA due to potentially increased outdoor activities.

The studies by Nilsson et al. (149), Ruiz et al. (108) and Troiano et al. (109) also separated their groups by gender, which was a possibility due to their large sample sizes.

The locations of the accelerometers might also be of importance when evaluating PA (145, 146, 172). In the studies by Nilsson et al. (149), Ruiz et al. (108) and Troiano et al. (109), the subjects wore the accelerometers attached to their hip-area. This was in contrast to present study, where the accelerometers were worn at the non-dominant wrist. As many movements might have been underestimated by using the hip as location, many movements might also have been overestimated by using the wrist as location.

Findings in our study suggest that there are many errors related to the measurements and evaluation of PA in both the pediatric patient-population and in the population of healthy children and adolescents. These findings should therefore be interpreted with caution.

5.3 Strengths and limitations of the study

The strengths of this study were a 100 % participation rate in the HPN-group. Also, all the 19 subjects in the HPN-group and all the 50 subjects in the reference-group completed the 4 days diet registration. Another strength was the combined use of an objectively wrist-worn accelerometer and a questionnaire on type, frequency and intensity when measuring the physical activity in both groups. Although the use of a cross-sectional design had many

limitations, one strength was that it was possible to investigate several variables at the same time.

This study had several limiations. The cross-sectional design made it impossible to draw any conclusions related to what might have affected the low BMD in the patient-group. The design only made it possible to reflect upon whether our findings pointed in the same direction as other studies.

Although a high participation rate in both the HPN-group (100 %) and in the reference-group (86 %), the study sample was small in general. This could have resulted in an increased risk of type II error. Thereby hidden any potential significant differences between the HPN-group and the reference-group. This was also why separation into gender and age-group were avoided. As several studies has been conducted on the basis of gender- and age-differences, the comparison to other studies were not completely valid.

Although according to the ISCD 2013 (106), the recommended interpretation of total body DXA-scan should be done without head, the results from this study were interpreted as total body included head. This was decided because the reference-data used in the DXA-instruments were based on normativ data included head and most studies has either reported their findings as total body included head or not specified it at all. A significant difference between the HPN-group and the reference-group were however found in both total body and spine BMD when including and excluding the head. The including of the head in this study have therefore not affected the conclusion.

Another limitation to this study were a study sample with a majority of Caucasian subjects. As this was not an ethnically diverse group it might have had an impact on the evaluation of bone composition as anscertry has been found to play a potential role in accrual of bone mass.

The pubertal stages, included menstrual cycle were not registered in this study. As these two factors has been shown to have a potential impact on the BMD Z-score, this made the results in this study more difficult to interpret.

6. Conclusion

Based on the results from this study, these are the following conclusions.

The dietary assessment concluded with the nutritional intake from parenteral nutrition to be in accordance with the ESPGHAN 2005 – guidelines. The HPN-group had a higher intake of carbohydrate and a lower intake of fat and protein compared to the reference-group according to NNR 2012. The HPN-group had a higher dietary intake of vitamin D and a lower dietary intake of calcium and phosphorous than the reference-group according to NNR 2012. The low dietary intake of calcium in the HPN-group are worrisome and needs further attention.

BMD Z-scores for total body and spine were found to be significantly lower in the HPN-group compared to the reference-group. As much as 1/3 of the HPN patients had low spine BMD. The HPN-group also had lower height-for-age and higher fat mass compared to the reference group, and illustrates the importance of follow-up of these patients.

No differences between the two groups were found in vitamin D status, and only 5 % in the HPN-group were classified as deficient.

The amount of moderate-to-vigorous physical activity measured by an accelerometer was not significantly different between the HPN-group and the reference-group. However, both the frequency and intensity of physical activity were significantly lower in the HPN-group compared to the reference-group. Further research is however needed to investigate the longitudinal impact of nutritional status and physical activity on HPN children's growth and bone health.

The results from this study should be interpreted with caution due to its small sample size and due to it having a cross-sectional study design.

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8 Appendices

Appendix 1: Web-form for recruitment of healthy children and adolescents.

Kosthold og ernæringsstatus hos friske barn og unge

Vi søker friske barn og unge i alderen 2-18 år for å være med i en kostholdsundersøkelse

Hovedhensikten med prosjektet er å få mer kunnskap om ernæringssituasjonen til barn på sykehus. Til dette trenger vi en referansegruppe av frivillige, friske barn og ungdommer i alderen 2-18 år. Universitetet i Oslo er ansvarlig for forskningsprosjektet.

Du/barnet ditt kan være med i studien dersom:

- Barnet/ungdommen er i alderen 2-18 år
- Barnet/ungdommen tåler melk, fisk og gluten
- Dere har mindre enn en times reisevei til Universitetet i Oslo

Deltagelse i prosjektet innebærer at foreldre og barn blir invitert til en undersøkelse på Universitetet i Oslo, Senter for klinisk ernæring. Det blir gjort måling av vekt, høyde, måling av muskelmasse, samt tatt en urinprøve og blodprøve av barnet. Undersøkelsene tar ca 60 minutter. I tillegg skal dere svare på noen enkle spørsmål om blant annet livskvalitet, appetitt, smaksendringer og mage-tarm symptomer hos barnet. Dere skal også registrere barnets inntak av mat og drikke, samt bruke en klokke som registrerer aktivitetsnivået i 4 dager.

Måling av muskelmasse blir gjort ved en DXA-undersøkelse, som innebærer at barnet ligger rolig i omlag 5 minutter. DXA-maskinen gir en svak stråling, men nivået er svært lav sammenlignet med et vanlig røntgen-bilde. I tillegg måles muskelmasse ved hjelp av en bioimpedansmåler (elektroder som festes til armer og ben). Disse undersøkelsene er ikke vonde eller ubehagelige. Hvis vi oppdager uforutsette funn, enten som normalvariasjon eller som tegn til sykdom, vil barnet henvises videre og undersøkes av spesialister på de aktuelle feltene.

Blodprøven innebærer at barnet får et stikk i armen. Noen barn synes dette er ubehagelig, og de som ønsker det får bedøvelseskrem. Dersom det påvises tegn til feil-eller underernæring, vil dere få beskjed om dette og råd om hva som bør gjøres.

Høres dette interessant ut? Fyll ut skjemaet under, og vi tar kontakt med dere:

Barnet/ungdommens alder *

2-6 år

7-10 år

11-13 år

14-18 år

Barnet/ungdommens kjønn: *

- Gutt
- Jente
-
-

For oss passer det best å komme: *

På dagtid

Etter kl 16.00

Vennligst oppgi et mobilnummer som vi kan nå dere på:*

E-postadresse *

Appendix 2: Information-letter and written informed consent for participation in the study.

UiO : Universitetet i Oslo

Oslo universitetssykehus

Forespørsel om deltakelse i forskningsprosjektet

ERNÆRING TIL BARN PÅ SYKEHUS

Dette er et spørsmål til dere og ditt barn om å delta i et forskningsprosjekt for å få mer kunnskap om ernæringssituasjonen til barn på sykehus. I dette forskningsprosjektet ønsker vi å undersøke ernæring til barn som behandles med stamcelletransplantasjon, barn som bruker parenteral ernæring hjemme og en gruppe friske barn. Universitetet i Oslo er ansvarlig for forskningsprosjektet.

Hva innebærer PROSJEKTET?

Deltagelse i prosjektet innebærer at barnet ditt blir invitert til en undersøkelse på Oslo Universitetssykehus. Denne vil samkjøres med en av de faste kontrollene barnet har ved Oslo Universitetssykehus i forbindelse med at det får hjemme parenteral ernæring. I tillegg til de vanlige undersøkelsene av vekt og høyde, blir det også gjort en mer nøyaktig måling av muskelmasse og skjelettmasse (DXA-undersøkelse). Vi ber om å få bruke svarene fra de vanlige blodprøvene som tas ved HPN kontrollen. Vi ber også om at det samtidig tas en urinprøve og en ekstra blodprøve som brukes til spesifikke forskningsprøver. Dere skal svare på noen enkle spørsmål om blant annet livskvalitet, appetitt, smaksendringer og mage-tarm symptomer hos barnet. Vi vil be dere registrere barnets inntak av mat og drikke, inkludert tilførsel av parenteral ernæring, i 4 døgn. De samme dagene skal barnet bruke en klokke som registrerer fysisk aktivitetsnivå. Journalopplysninger om sykdom og behandling vil benyttes.

Mulige fordeler og ulemper

En fordel ved studien er en grundigere undersøkelse av barnets ernæringsstatus sammenlignet med det som gjøres rutinemessig.

Måling av muskelmasse/skjelettmasse blir gjort ved en DXA-undersøkelse, som innebærer at barnet ligger rolig på en åpen benk med vanlige klær (uten metalldeler) i omlag 5 minutter. DXA-maskinen gir en svak stråling, men nivået er svært lavt sammenlignet med et vanlig røntgen-bilde og mer likt det vi utsettes for til daglig. Hvis vi oppdager uforutsette funn, enten som normalvariasjon eller som tegn til sykdom, vil barnet henvises videre og undersøkes av spesialister på de aktuelle feltene.

Blodprøven innebærer at barnet får et stikk i armen. Noen barn synes dette er ubehagelig, og de som ønsker det får bedøvelseskrem. Dersom barnet vanligvis tar prøver fra sin sentrale veneport vil dette også gjøres ved denne undersøkelsen.

Dersom det påvises tegn til feil- og/eller underernæring, vil dere få beskjed om dette. Klinisk ernæringsfysiolog og barnelege som er ansvarlig for behandlingen til barnet vil få svarene på de ulike undersøkelsene, og kan ta hensyn til disse i videre behandling av barnet.

Frivillig deltakelse og mulighet for å trekke sitt samtykke

Det er frivillig å delta i prosjektet. Dersom dere ønsker å delta, undertegner dere samtykkeerklæringen på siste side. Dere kan når som helst, og uten å oppgi noen grunn, trekke samtykket. Dersom dere trekker dere fra prosjektet, kan dere kreve å få slettet innsamlede prøver og opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner. Dersom dere senere ønsker å trekke dere eller har spørsmål til prosjektet, kan dere kontakte: Christine Henriksen: tlf 22 85 13 80, epost christine.henriksen@medisin.uio.no.

Hva skjer med informasjonen om deg?

Informasjonen som registreres om barnet skal kun brukes slik som beskrevet i hensikten med studien. Dere har rett til innsyn i hvilke opplysninger som er registrert om barnet og rett til å få korrigert eventuelle feil i de opplysningene som er registrert.

Alle opplysningene som brukes i forskningen vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter barnet til hans/hennes opplysninger gjennom en navneliste.

Prosjektleder har ansvar for den daglige driften av forskningsprosjektet og at opplysninger om barnet blir behandlet på en sikker måte. Informasjon om barnet vil bli anonymisert eller slettet senest fem år etter prosjektslutt.

Hva skjer med prøver som blir tatt av deg?

Blodprøvene som tas av barnet skal oppbevares i en forskningsbiobank ved Avdeling for Ernæringsvitenskap, Universitetet i Oslo. Professor Jan Gunnar Bjålie er ansvarshavende for forskningsbiobanken. Biobanken planlegges å vare til 2020. Senest i 2024 vil materialet og opplysninger bli destruert og slettet etter interne retningslinjer. Biobanken opphører etter prosjektslutt.

Forsikring

Deltagerne er forsikret gjennom Norsk Pasientskadeerstatning.

OppfølgingsPROSJEKT

Hvis det blir aktuelt med oppfølgingsprosjekt, vil dere bli kontaktet på nytt ca 5 år etter avsluttet behandling.

Økonomi

Vi dekker kostnader til transport og parkering med kr. 500.-, men utover det gis det ingen økonomisk kompensasjon for deltagelse. Prosjektet er finansiert av Throne Holst Fondet og Universitetet i Oslo.

Godkjenning

Prosjektet er godkjent av Regional komite for medisinsk og helsefaglig forskningsetikk, (referansenr. 2016/391)

Samtykke til deltakelse i PROSJEKTET

For barn og ungdom under 16 år, skal i utgangspunktet begge foresatte undertegne. Ungdom over 16 år skal i tillegg underskrive selv.

Jeg er villig til å delta i prosjektet

Sted og dato	Deltakers signatur
	Deltakers navn med trykte bokstaver

Som foresatte til_ (Fullt navn) samtykker vi til at hun/han kan delta i prosjektet

Sted og dato

Foresattes signatur

Foresattes navn med trykte bokstaver

Sted og dato

Foresattes signatur

Foresattes navn med trykte bokstaver

Jeg bekrefter å ha gitt informasjon om prosjektet

Sted og dato

Signatur

Rolle i prosjektet

Appendix 3: Instructions on urine-collection and use of accelerometer.

Veiledning for innsamling av urinprøver og bruk av aktivitetsklokken

Innsamling av urinprøver:

Urinprøveglass

- Husk å ha rene hender når du håndterer prøveglassene.
- Obs! Det er viktig at urinprøvene ikke tas fra første morgenurin. Med unntak av den første morgenurinen, kan prøvene tas når som helst i løpet av dagen. Prøven kan samles i et rent beger før overføring til prøveglasset.
- Hvert glass må inneholde minimum 10 ml urin.
- Merk prøveglassene med navn, fødselsdato, samt dato og klokkeslett for prøvetaking.
- Husk at det skal gjøres to urinprøvetakinger.
- Urinprøvene oppbevares i kjøleskap frem til levering på timen du er satt opp til.
- Urinprøvene bør tas så nærme den oppsatte timen som mulig, og tidligst 5 døgn før oppsatt time.

Bruk av aktivitetsklokke:

Slik ser aktivitetsklokken ut

- Klokken måler nivå av fysisk aktivitet på en lignende måte som en skritt-teller.
- Klokken festes på venstre arm for høyrehendte, og på høyre arm for venstrehendte.
- Klokken startes ved å trykke på oversiden til det sees et grønt lysblink. Dette gjøres bare en gang, den første dagen. Når klokken først er startet, er det ikke mulig å re-starte den på et senere tidspunkt.
- Klokken skal bæres i 4 hele dager. Noter underveis dersom en eller flere av disse dagene var uvanlige i forhold til aktivitetsnivå, for eksempel ved sykdom.
- Klokken tåler vann og kan dermed også brukes ved dusjing og bading
- Det er greit å ta av klokken om natten dersom man vil det.

Appendix 4: Dietary registration booklet.

Kostregistreringskjema

ID-nummer: …….

Alt du spiser og drikker i fire dager registreres på skjemaet

Beskriv all mat og drikke, mengder og tidspunkt du inntar dette så nøyaktig som mulig. **Bruk vedlagt bildehefte fra NORKOST til hjelp for å beskrive porsjonsstørrelsene.** Beskriv;

- Type brød (f.eks loff). Angi mengde, fasong, tykkelse og grovhet (se side 5 til 9 i vedlagt hefte).
- Type smør/margarin (f.eks Meierismør), og mengde (f.eks bilde 10 B).
- Type pålegg, f eks: kaviar (Mills blå, bilde 10 D), 1 skive kokt skinke (Gilde).
- Middagsmat (f.eks 2 eggstore, kokte poteter uten skall, 3 kjøttkaker Gilde). På baksiden av arkene angis oppskriften på hjemmelagde retter. Salat kan angis som på bilde 34 eller gryterett bilde 25.
- Dersom det ble brukt salt i eller over mat oppgis type (f.eks jozo rød pakke).
- Tilberedning angis; kokt, stekt, grillet, panert (f.eks kokt fullkornpasta, grillet biff).
- Tilbehør angis som mengde og type (f.eks ½ dl Toro sjysaus eller bilde 33 B).
- F.eks 1 plomme, 4 Ritz kjeks, 4 seigmenn, 1 pose potetskruer med salt (100 g).
- Type og mengde kosttilskudd (f.eks 5 ml tran, 500 mg kalsiumtbl).
- Drikke (f.eks 2 glass vann eller bilde 3 B, til øverste streken), 1/2 krus kakao (bilde 4 J) - (hjemmelaget – se egen oppskrift), ½ L solo.
- Beskriv gjerne mengdene på de vanlige glassene/koppene du bruker, mål opp ved hjelp av dl mål hjemme:
    - 1 glass = _____dl
    - 1 kopp = _____ dl
    - 1 krus = _____dl
- Dersom du bruker sondeernæring noteres produktnavn, mengde pr måltid/døgn og tidspunkt for inntak (fra-til/infusjonshastighet).
- Dersom du bruker parenteral ernæring, oppgis produktnavn (f.eks egen blanding), mengde pr døgn og tidspunkt for tilførsel (fra-til/infusjonshastighet).

Husk:

- Spis som du pleier selv om du skal registrere!

- Noter det du spiser og drikker mellom måltidene.
- Registrer tre hverdager og en dag i helgen (lørdag-søndag).

Start på nytt ark for hver ny dag, og begynn på ny linje for hver matvare. Eksempel:

TIDSPUNKT	MENGDE	MAT OG DRIKKE	BESKRIVELSE, FOR EKSEMPEL TILBEREDNING, PRODUKTNAVN
8:00	2 skiver (*Bilde 8 B*)	**Kneippbrød**	*Bilde 6 B* (halvgrovt)
	1 ss (*Bilde 10 D*)	Lettmargarin på brødskivene	Soft margarin
	1	Stekt egg	Stekt i soft margarin (*Bilde 10 B*)
	Tynt lag (*Bilde 12 A*)	Leverpostei	Go og mager
	4 skiver	Sylteagurk	Nora
	4	Druer	
	1 glass (*Bilde 3 B til øverste strek*)	Lettmelk	Rosa, økologisk
	½ kopp (*Bilde 4 L*)	Kaffe	Traktet
	1 ss	Tran	Møllers med sitronsmak
10:30	2 dl	Vann	
12:15	1 porsjon (*Bilde 20 D*)	Lasagne	Toro, laget med karbonadedeig og Lett Synnøve Finden ost

DATO:……

TIDSPUNKT	MENGDE	MAT OG DRIKKE	BESKRIVELSE, FOR EKSEMPEL TILBEREDNING, PRODUKTNAVN

Egne oppskrifter:

Appendix 5: Questionnaire on background-information, included physical activity.

Fylles ut av deltaker og/eller foreldre
ID-nummer:_____

Dato for utfylling : _____

1. Alder: _____år **2. Kjønn:** Jente ☐
Gutt ☐

3. For barn i skolealder - hvilken utdanning er den høyeste du/deltaker har fullført? (Sett kun ett kryss)

Barneskole ☐

Ungdomsskole ☐

Videregående skole eller yrkesfag ☐

Spesialtilpasset opplæring/tilbud ☐

4. For barn i barnehagealder – går barnet i barnehage?

Ja ☐ Nei ☐

5. Hvilken utdanning er den høyeste fullførte hos	**mor**	**far**
Barneskole	☐	☐
Ungdomsskole	☐	☐
Videregående skole eller yrkesfag	☐	☐
Høyskole/universitet…….	☐	☐

6. Hvem bor du sammen med

Mor og far ☐

Mor ☐

Far ☐

Andre (beskriv):_____
_____

Hvis du bor flere steder beskriv gjerne hvordan fordelingen er:

_____
_____

ID-nummer:_____

7. Hvor ofte driver du mosjon/trening (gjennomsnittlig)

Aldri eller sjeldnere enn en gang pr uke ☐

1-3 ganger pr uke ☐

4 eller flere ganger i uke ☐

Dersom du driver mosjon/trening mer enn 1 gang pr uke, hvor hard mosjonerer du?

Tar det rolig uten å bli andpusten eller svett ☐

Jeg blir andpusten og svett ☐

Dersom du driver mosjon/trening beskriv aktiviteten(e) du driver med (f.eks svømming)

_____
_____

_____
_____

8. Har du fordøyelseplager?

Ja ☐ Nei ☐

Hvis ja, beskriv type og frekvens (du kan sette flere kryss);

	Daglig	**Ukentlig**
Magesmerter	☐	☐
Diare	☐	☐
Forstoppelse	☐	☐
Luft i magen	☐	☐

Oppkast ☐ ☐

Sure oppstøt ☐ ☐

9. Bruker du snus? Ja ☐ Nei ☐

10. Røyker du? Ja ☐ Nei ☐

Appendix 6: Case report form (CRF).

CRF ID-nummer:

	Dato:	**Hvor/hvordan:**	**Kommentar:**	**Prosjekt-medarbeider**
Informert om studien			Innlagt ☐ Telefon ☐ Poliklinisk kontroll ☐	
Sendt ut konvolutt med utstyr				
Deltakelse			Inkludert ☐ Ønsket ikke delta ☐ Ekskludert ☐ årsak: _____	
Henvist DXA				
Fått time for DXA us Rikshospitalet Parkering i parkerings- huset nærmest sykehuset		Kart/veibeskrivelse sendt hvis første us ☐ Sendt med hvis de kjører opp alene ☐	Transportbehov: Taxi ☐ følges av _____ ☐ Egen bil ☐ refundert parkeringsutgifter ☐ Prosjektmedarbeider som er med/møter dem på Rikshospitalet:	
DXA gjennomført				
DXA svar mottatt				
Samtykke foresatte mottatt og kopi			Journalfør deltakelse i studien i kef notatet	

levert			og hvem som har samtykket ☐	
Samtykke alder≥16 år mottatt og kopi levert (NB husk dette ved ktr 2 hvis fylt 16 år i mellomtiden)				
Urinprøver 2 stk mottatt			Husk å notere dato og klokkeslett på glassene + idnr	
Urin fordelt i 2+2 glass, og lagt i fryser				
Kreatinin-svar mottatt			Batch?	
Kostregistrering mottatt og kvalitetssikret				
Kostregistrering beregnet				
Fysisk aktivitet klokke mottatt				
Fys akt data lagt inn på pc				
Fys akt data beregnet				
QoL skjema fylt ut på sykehuset			Foreldre ☐ Barn ☐	
Vekt (undertøy)			Vekt:	
Lengde (stadiometer med fast plate)			Lengde:	
Bioimpedans undersøkelse				

Blodprøver		Noter metode (CVK, venøst) og hvor prøven ble tatt (UL/RH/ern.)		
Blodprøve levert biobank UiO				
Blodprøvesvar mottatt			Klinisk kjemisk ☐ Aker hormonlaboratoriet ☐	
Rtg skjelettalder gjennomført 1 års ktr				
Rtg skjelettalder svar mottatt 1 års ktr				
Journalført aktuelle data etter ktr sykehus				
Tilbakemelding om resultater				

ID-nummer:_____

Samtale med student/kef kl: _____

- Bioimpedans ☐
- QoL skjema foreldre + barn > 5 år☐
- Bakgrunnsinformasjon skjema☐
- Gjennomgang konvolutt og sjekk at alt er returnert (kostreg., fys akt klokke, urinprøve) ☐
    - Kostanamnese
    - Send med ny konvolutt hjem hvis mangler kostregistrering + returkonvolutt ☐

- Oversikt over TPN regimet ☐
    - Antall timer pr døgn_____
    - Antall døgn pr uke_____
    - Sondeernæring:
        - Produkt_____

        - Regime (PEG, ng-sonde, ventrikkel/jejunalt, kontinuerlig/måltider, volum pr måltid og totalvolum.
        - Skyllevæske, medikamentvæske. Mengde og produkt (GEM, vann, NaCl 9% etc).
    - Innhente info fra apoteket om blandingen hvis behov i etterkant ☐

- Tap (diare (frekvens, hvor løst), stomi-output, oppkast – hyppighet)

- Kosttilskudd/naturprepareter el? ☐

- Salt i matlaging/type? ☐

Appendix 7: Example of written feedback to the reference-group.

Tusen takk for deltakelsen i denne studien. Dette er en tilbakemelding på resultatene fra blodprøvene og det 4-dagers registrerte kostholdet ditt. Vi har oppsummert noen råd i forbindelse med dette, se under.

BLODPRØVER

Tabellen viser ditt barn sine verdier fra blodprøveanalysene og referanseverdier basert på alder og kjønn.
Verdier utenfor referanseområdet er merket med fet skrift under «Ditt analyseresultat».

	Ditt analyseresultat	**Referanseverdi**
Hemoglobin (g/dl)	13,9	(11,0 – 15,5)
Erytrocytter (10^{12}/L)	4,7	(3,9 – 5,3)
EVF	0,42	(0,30 – 0,40)
MCH (pg)	29	(23 – 31)
MCHC (g/dL)	33	(28 – 36)
MCV (fL)	88	(70 – 87)
Jern (umol/L)	14	(9 – 22)
Transferrin (g/L)	3,1	(2,0 – 3,3)
TIBC (umol/L)	78	(49 – 83)
Transferrinmetning	0,18	(0,10 – 0,50)
Ferritin (ug/L)	37	(10 – 140)
Transferrinreseptor (mg/L)	2,5	(1,9 – 4,4)
Vitamin B12 (pmol/L)	482	(150 – 650)
Folat (nmol/L)	16	(>7)
Kalsium (mmol/L)	2,27	(2,15 – 2,65)
Fritt kalsium (mmol/L)	1,23	(1,15 – 1,33)
ALP (U/L)	85	(<270)
PTH (pmol/L)	2,5	-
CRP (mg/L)	<0,6	(<4)
25-OH vitamin D (nmol/L)	79	(50-150)

1,25 OH Vitamin D (pmol/L)	151	(48-168)

Resultatene fra dine blodprøver er tilfredsstillende.

KOSTHOLDSDATA

Tabellen viser ditt gjennomsnittlige inntak i registreringsperioden og anbefalt daglig inntak av næringsstoffer.

Næringsstoff	Ditt gjennomsnittlige inntak		Anbefalt daglig inntak for jenter 14-18 år
	Med kosttilskudd	Uten kosttilskudd	
Energi (kcal)	**1956,3**	**1956,3**	**2180-2560 kcal/døgn**
Protein (%)	20,6	20,6	10-20 E%
Fett (%)	30,5	30,5	25-40E%
Karbohydrat (%)	46,5	46,5	45-60E%
Fiber (g)	24	24	25-35g
Vitamin C (mg)	89,3	89,3	75 mg
Jern (mg)	**10,1***	**10,1***	**15 mg**
Kalsium (mg)	1198,3	1198,3	900 mg
Vitamin A (RE)	938,6	938,6	700 RE
Vitamin D (ug)	**4,4***	**4,4***	**10 ug**
Vitamin E (mg)	7,4	7,4	8 mg
Tiamin (mg)	1,3	1,3	1,2 mg
Riboflavin (mg)	1,8	1,8	1,4 mg
Niacin (mg)	22,7	22,7	16 mg
Vitamin B6 (mg)	1,9	1,9	1,3 mg
Vitamin B12 (ug)	8,9	8,9	2,0 ug
Fosfat (mg)	1896,2	1896,2	700 mg
Magnesium (mg)	347,7	347,7	280 mg
Natrium (g)	**2,8***	**2,8***	**<2 g**
Kalium (g)	3,5	3,5	3,1 g

Sink (mg)	11,5	11,5	9 mg
Mettede fettsyrer (E%)	**12,9***	**12,9***	**<10 E%**
Enumettede fettsyrer (E%)	10,6	10,6	10 – 20 E%
Flerumettede fettsyrer (E%)	**3,7***	**3,7***	**5 – 10 E%**
Tilsatt sukker (E%)	6,4	6,4	<10 E%
Folat (ug)	**209,1***	**209,1***	**300 ug**
Selen (ug)	56	56	50 ug
Jod (ug)	173,7	173,7	150 ug
Kobber (mg)	1,2	1,2	0,9 mg

Kommentar til kostholdet som har blitt registrert:

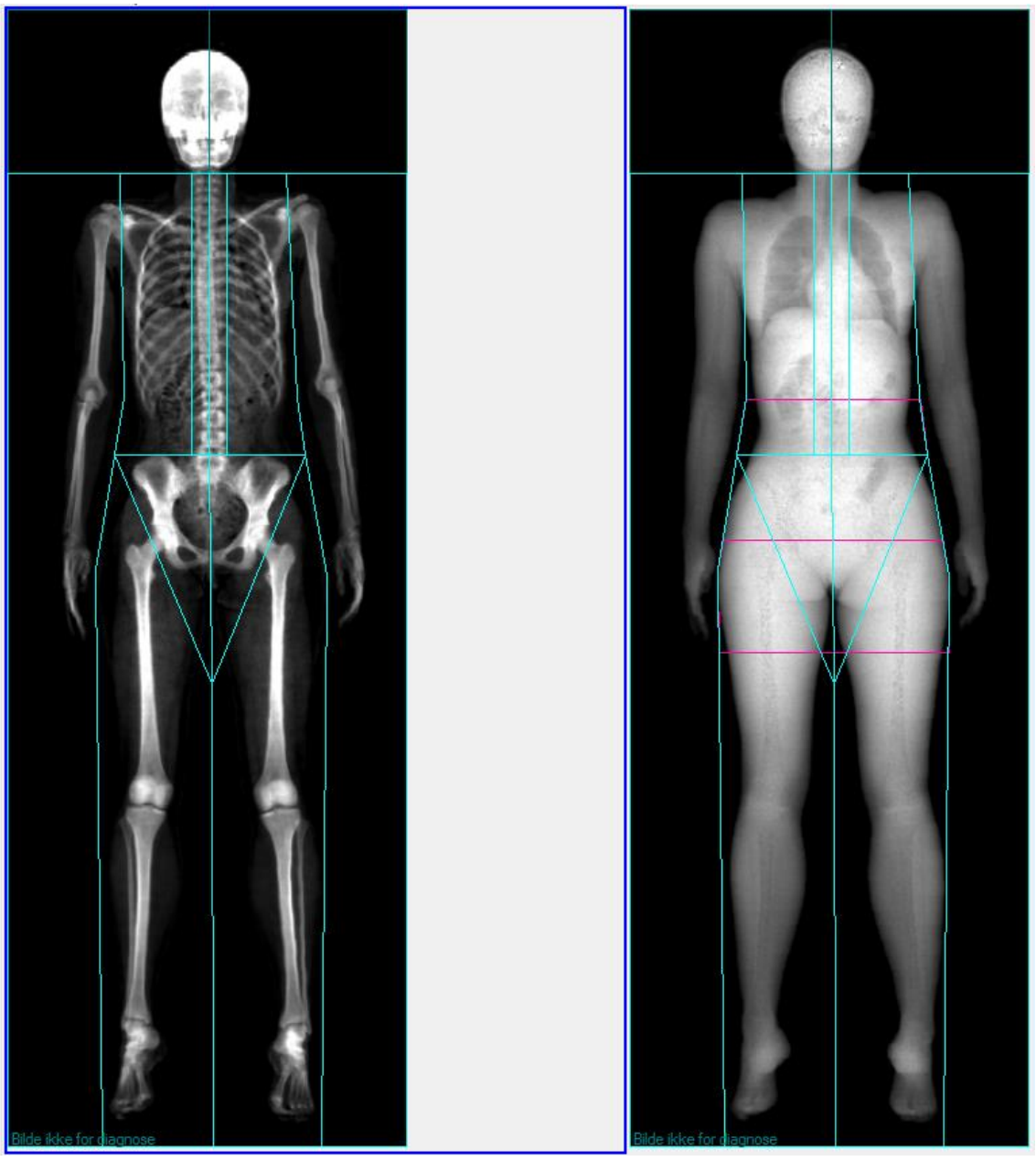
- I forhold til anbefalingene er jern noe for lavt.
    - Hvorfor er jern viktig for kroppen:
        - Jernets oppgave i hemoglobinet er å ta opp oksygen i lungene ved å binde oksygen til hemoglobin og frakte oksygenet med blodet til alle celler og vev i kroppen. Hvis man har jernmangel vil de røde blodlegemene transportere mindre oksygen.
        - I musklene bindes oksygenet til myoglobin som også inneholder jern.
        - Jern deltar også i omdannelsen av karbohydrat, fett og proteiner til energi som kroppen kan bruke.
    - Gode kilder til jern:
        - Kjøtt og kjøttpålegg, fisk og innmat, leverpostei, egg, grovt brød og grove kornprodukter, havregryn og hirse, mørkegrønne grønnsaker, erter, bønner og linser, tørket frukt som rosiner og aprikoser.
- Inntaket av vitamin D i denne registreringsperioden er svært lavt i forhold til anbefalingen.
    - Hvorfor er vitamin D viktig?
        - Styrker ditt skjelett. Viktig for å opprettholde normale nivå av kalsium og fosfor, som er med på å styrke skjelettet og tennene dine.
        - Stimulerer dannelsen av beinvev og kan redusere risikoen for beinskjørhet i senere alder.
        - Bidrar til et normalt immunforsvar.
        - Viktig for cellenes deling og funksjon i kroppen.
    - Gode kilder til vitamin D:
        - Tran og fet fisk. Eventuelt inntak av omega-3 kapsler som blant annet inneholder vitamin D i tillegg til vitamin A og K og sunne fettsyrer.
        - Uten tran i kosten vil det gjennomsnittlige inntaket av vitamin D være for lavt, så det er fint å inkludere dette i kostholdet.
    - Det anbefales å ta vitamin D-tilskudd daglig. 10 µg/dag.
- Saltinntaket er nokså høyt, og kan med fordel reduseres. Husk at hel- og halvfabrikata ofte er «usynlige» kilder til salt. For å smaksette hjemmelaget mat kan man forsøke å bruke mer urter og andre krydder.
- Mettet fett kan med fordel reduseres da det er noe høyt i forhold til anbefalingene. Magre kjøtt – og meieriprodukter kan for eksempel benyttes.

- Flerumettet fett er noe lavt i forhold til anbefalingene. Ved å bytte ut noe av kjøttproduktene med for eksempel fisk og erstatte sjokolade med nøtter som snacks kan mengden flerumettet fett i kosten lett økes og mengden mettet fett minkes.
- Folat var noe lavt i forhold til anbefalingene. Matvarer som inneholder mye folat, er grove kornprodukter, grønne grønnsaker som brokkoli, grønnkål, rosenkål og spinat, i tillegg til frukt som appelsin og bær.

BEINTETTHETSMÅLING

Bein er et levende vev der det skjer en kontinuerlig oppbygging og nedbrytning. Hos barn og ungdom vil det være en større oppbygging enn nedbrytning slik at man får en netto økning av beinmasse. Maksimal beinmasse nås en gang mellom 18 og 30 år. Beintetthetsmålingen er en røntgen undersøkelse som gir opplysninger om hvor godt beinvevet er mineralisert.

Din beintetthetsmåling viste tilfredsstillende resultat. Under kan du se bilde av ditt eget skjelett og kropp.



Dere er hjertelig velkomne til å ta kontakt dersom det er noen spørsmål.

Vi kan kontaktes per epost eller telefon:
Christina Kjeserud

- Tlf: 93424622
- Email: christina.kjeserud@studmed.uio.no

Camilla Sæland

- Tlf: 93257798
- Email: camilla.saland@studmed.uio.no

Mvh Camilla Sæland og Christina Kjeserud. Masterstudenter, klinisk ernæring, UiO

Appendix 8: Regional Committee for Research Ethics (REK) - approval (2016/391)

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Mariann Glenna Davidsen	22845526	19.05.2016	2016/391/REK sør-øst B
			Deres dato: 02.05.2016	**Deres referanse:**

Vår referanse må oppgis ved alle henvendelser

Christine Henriksen
Universitetet I Oslo

2016/391 Ernæringsstatus hos barn og ungdom som behandles med allogen stamcelletransplantasjon

Forskningsansvarlig: Universitetet I Oslo **Prosjektleder:** Christine Henriksen

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble første gang behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet 16.03.2016. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikkloven § 4.

Prosjektomtale

Det finnes lite kunnskap om ernæringsstatus til barn som gjennomgår allogen stamcelletransplantasjon (SCT). Vi ønsker å gjøre en prospektiv longitudinell studie, der en gruppe barn og unge i alderen 2-18 år følges det første året etter SCT. Hovedmålet med studien er å kartlegge ernæringsstatus før oppstart, samt 1, 3 og 12 måneder etter allogen SCT hos barn. Utvalget består av 25 pasienter som behandles med SCT og en referansegruppe på 25 pasienter som behandles med hjemmeparenteral ernæring (HPN) ved Oslo Universitetssykehus (OUS), samt 50 friske referansepersoner i samme alder. Metoden som benyttes er måling av ernæringsstatus ved hjelp av: Kroppssammensetning, blodprøver, kostregistrering, aktivitetsregistrering samt måling av livskvalitet. Disse målingene blir gjort ved tre anledninger for pasienter med SCT, og ved en anledning hos referansegruppene. Opplysninger om demografiske data og medisinsk behandling vil hentes fra journal.

Saksgang:
Søknaden ble behandlet første gang på komiteens møte den 16.03.2016. I vedtak sendt 15.04.2016, skrev komiteen at den ønsket prosjektleders tilbakemelding på flere punkter før den tar endelig stilling til søknaden. Prosjektleder har sendt inn en skriftlig tilbakemelding mottatt den 02.05.2016.

Ved komiteens første gangs behandling ble følgende tilbakemeldinger gitt:

«***Komiteens vurdering***:
Slik komiteen forstår det er dette et PhD prosjekt som utgår fra UiO, og skal undersøke ernæringsstatus hos barn og unge i alderen 2-18 år, før og etter (1, 3 og 12 mnd.) de har gjennomgått allogen stamcelletransplantasjon. Det skal måles kroppssammensetning, kartlegge kostholdet under innleggelse og barnas nivå av fysisk aktivitet. Det skal også gjøres undersøkelser med tanke på livskvalitet. Videre skal det tas blodprøver hvor man skal undersøke vitaminstatus, antioksidanter, oksidativt stress, benmarkører og inflammasjonsmarkører. For å vurdere barnets kroppssammensetning skal det benyttes DXA (liten stråledose) eller BIA (Bioimpedans) på de minste barna. For å måle fysisk aktivitet brukes et akselerometer (en klokke man har på armen), og denne sjekkes daglig gjennom en måned. For å undersøke kostholdet

bruker man til dels sykehistorikken, og til dels en billedbok med symboler for mengdeangivelser. Dersom det oppdages sykdommer/ernæringssvikt som ikke er kjent på forhånd, vil dette følges opp.

Forskningsbiobank: Det skal opprettes en ny forskningsbiobank; Ernæringsstatus hos barn etter SCT», ved « ansvarshavende Christine Henriksen. Det skal ikke gjøres genetiske undersøkelser av blodprøvene som blir tatt.

Deltakere/rekruttering: I tillegg til 25 pasienter som har gjennomgått allogen stamcelletransplantasjon, skal det inkluderes 25 pasienter som får hjemmeparenteralernæring (for andre sykdommer). Disse rekrutteres fra barnemedisinsk avdeling ved OUS. Det skal også inkluderes 50 friske alderstilpassede barn, disse skal rekrutteres fra skole og barnehage, i tillegg til poster og sosiale medier. Det fremkommer imidlertid ingen redegjørelse for hvordan barnehagene og skolene skal oppsøkes, og hvordan rekrutteringen derfra skal foregå. Dette må redegjøres nærmere.

Informasjons- og samtykkeskriv: Komiteen mener det foreligger tilfredsstillende informasjons – og samtykkeskriv til de barna som blir rekruttert fra sykehuset, og til deres foreldre. Det foreligger imidlertid ikke info- og samtykkeskriv til de friske barna som skal delta, eller deres foreldre. Dette må utarbeides.

Komiteen ber om at prosjektleder redegjør for hvordan rekrutteringen skal forgå ved skoler og barnehager, samt utarbeide informasjonsskriv til de friske barna og deres foreldre. Vi ber om at den etterspurte dokumentasjonen oversendes komiteen til godkjenning.

***Komiteens beslutning** Vedtak i saken utsettes. Komiteens leder vil ta stilling til prosjektet ved mottatt svar."*

Prosjektleders tilbakemelding

I tilbakemeldingsskjema har prosjektleder gjort rede for rekrutteringen ved skole og barnehager, og viser til at rekrutteringen av kontrollgruppen skjer gjennom plakater som henges opp på helsestasjoner, barnehager og skoler i nærheten av Universitetet og OUS, samt annonser på web som også kan spres via sosiale media. All rekruttering er rettet mot foreldrene. Forslag til annonsetekst er vedlagt tilbakemeldingsskjemaet. Det er også utarbeidet informasjonsskriv slik som komiteen ba om.

Tilbakemeldingen og alle vedlegg er gjennomgått av sekretariatet og komiteens leder.

Komiteens vurdering etter mottatt tilbakemelding

Komiteen, ved komiteens leder, anser at prosjektleder har gitt en fyllestgjørende tilbakemelding , og informasjonsskrivene synes tilfredstillende utarbeidet. Komiteen har ingen ytterligere innvendinger til at prosjektet gjennomføres slik det nå fremstilles.

Vedtak

Komiteen godkjenner prosjektet i henhold til helseforskningsloven § 9 og § 33 under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden.

Tillatelsen gjelder til 31.01.2019. Av dokumentasjonshensyn skal opplysningene likevel bevares inntil 31.01.2024. Opplysningene skal lagres avidentifisert, dvs. atskilt i en nøkkel- og en opplysningsfil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder "Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren"

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningslovens § 28 flg. Klagen sendes til REK sør-øst B. Klagefristen er tre uker fra du mottar dette brevet. Dersom vedtaket opprettholdes av REK sør-øst B, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Sluttmelding og søknad om prosjektendring

Prosjektleder skal sende sluttmelding til REK sør-øst på eget skjema senest 31.07.2019, jf. hfl. §
12. Prosjektleder skal sende søknad om prosjektendring til REK sør-øst dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Med vennlig hilsen

Grete Dyb førsteamanuensis dr. med.
leder REK sør-øst B

Mariann Glenna Davidsen rådgiver

Kopi til:
- *Universitetet i Oslo ved øverste administrative ledelse*