Scientific Publications Compendium

2018·**2019**·2020

Nestlé HealthScience

Vitaflo®

Innovation in Nutrition

Prologue

Dear Reader,

Since its creation Nestlé Health Sciences has solid scientific contributions. Over the successive scientific compendium issues, we have continuously progressed in the scientific output which reflects a sustained scientific performance. I am pleased to share with you the 3rd issue of the Nestlé Health Science scientific publications compendium.

In 2019, Nestlé Health Science contributed to and / or supported a number of scientific publications covering a broad spectrum of clinical conditions. The present booklet summarizes these publications as well as those contributed by the worldwide scientific community.

As an innovative health science company, we strongly believe in leveraging and investing in leading-edge science in order to improve quality of life and provide clinical and health economic value. Our aim is to maximize the role of nutrition in empowering healthier lives. I also take this opportunity to thank all the experts involved in this work, namely Healthcare Professionals, Institutions and Nestlé Health Science colleagues. Our meaningful scientific partnership will positively impact patients and consumers' lives.

I hope you will enjoy the read.

Best regards,

Moreno Perugini, MBA, MHE
Global Head of Medical Affairs and Market Access
Nestlé Health Science

Inherited Metabolic Disorders & Ketogenic Diets

Investigation of paediatric PKU breath malodour, comparing glycomacropeptide with phenylalanine free L-amino acid supplements

Tiele A, Daly A, Hattersley J, Pinto A, Evans S, Ashmore C, MacDonald A, Covington JA

Journal of Breath Research. 2019 Oct 21;14(1):016001

https://www.ncbi.nlm.nih.gov/pubmed/31476741

• Background

Phenylketonuria (PKU) is an inherited metabolic disorder that causes Phe levels to accumulate in blood, potentially causing severe and irreversible neurological impairments. Effective management of the condition is achieved through dietary restriction of Phe and supplementation with Phe-free protein substitutes (PS). Patients and caregivers often associate intake of PS with bad breath and this can result in psychological distress, interfere with social interactions, lower self-esteem and body-image. Breath malodor in PKU has received little clinical or research attention, and it is unknown if this is an issue more common in PKU than a healthy population. This study focuses on two types of PS; Phe-free L-amino acids (L-AA) and low-Phe casein glycomacropeptide (CGMP-AA) to determine if there is any difference in breath malodour.

• Methods

40 children (20 PKU, 20 controls) were recruited. PKU individuals with good adherence to diet were recruited. All participants completed a questionnaire at baseline and consumed the same diet throughout the study period. Intake was recorded via food diaries. Subjects with PKU took all their PS requirement from either L-AA or CGMP-AA exclusively for 7 days, in a randomised order. Each participant with PKU then switched to consuming the other PS for a 7-day period. On the 7th day of each week taking L-AA or CGMP-AA, 7 breath samples were collected over a 10 h period. In the PKU group, the aim was to collect samples 30 min after consuming the PS to allow subjects to digest and metabolize their meals and PS. Breath malodour was measured as exhaled volatile compounds (VOCs) and analyzed using as chromatography-ion mobility spectrometry (GC-IMS technology).

• Results

Control subjects had less concern about breath malodor, but subjects with PKU were concerned about breath odor and associated this with PS. Study results from the questionnaire suggests that the effects of L-AA and CGMP-AA on exhaled breath are likely to be different, immediately post-consumption. Breath analyzed immediately after consumption of both L-AA and CGMP-AA PS showed an immediate increase in the number of VOC peaks, but these were no longer detectable at 30 min post-consumption.

• Conclusions

Longitudinal breath testing showed that there were no significant differences in the number and types of exhaled VOCs compared to controls or between PS. PS are thus shown to have a transient effect on exhaled breath. The timing of PS consumption with other foods or drinks may help to eliminate PS-related unpleasant breath odour.

Early feeding practices in infants with phenylketonuria across Europe

Pinto A, Adams S, Ahring K, Allen H, Almeida MF, Garcia-Arenas D, Arslan N, Assoun M, Atik Altınok Y, Barrio-Carreras D, Belanger Quintana A, Bernabei SM, Bontemps C, Boyle F, Bruni G, Bueno-Delgado M, Caine G, Carvalho R, Chrobot A, Chyż K, Cochrane B, Correia C, Corthouts K, Daly A, De Leo S, Desloovere A, De Meyer A, De Theux A, Didycz B, Dijsselhof ME, Dokoupil K, Drabik J, Dunlop C, Eberle-Pelloth W, Eftring K, Ekengren J, Errekalde I, Evans S, Foucart A, Fokkema L, François L, French M, Forssell E, Gingell C, Gonçalves C, Gökmen Özel H, Grimsley A, Gugelmo G, Gyüre E, Heller C, Hensler R, Jardim I, Joost C, Jörg-Streller M, Jouault C, Jung A, Kanthe M, Koç N, Kok IL, Kozanoğlu T, Kumru B, Lang F, Lang K, Liegeois I, Liguori A, Lilje R, Ļubina O, Manta-Vogli P, Mayr D, Meneses C, Newby C, Meyer U, Mexia S, Nicol C, Och U, Olivas SM, Pedrón-Giner C, Pereira R, Plutowska-Hoffmann K, Purves J, Re Dionigi A, Reinson K, Robert M, Robertson L, Rocha JC, Rohde C, Rosenbaum-Fabian S, Rossi A, Ruiz M, Saligova J, Gutiérrez-Sánchez A, Schlune A, Schulpis K, Serrano-Nieto J, Skarpalezou A, Skeath R, Slabbert A, Straczek K, Giżewska M, Terry A, Thom R, Tooke A, Tuokkola J, van Dam E, van den Hurk TAM, van der Ploeg EMC, Vande Kerckhove K, Van Driessche M, van Wegberg AMJ, van Wyk K, Vasconcelos C, Velez García V, Wildgoose J, Winkler T, Żółkowska J, Zuvadelli J, MacDonald A

Molecular Genetics and Metabolism Reports. 2018 Aug 8;16:82-89

https://www.ncbi.nlm.nih.gov/pubmed/30101073

• Background

Infants with phenylketonuria (PKU) are managed with a low phenylalanine (Phe) diet, that involves restricting natural protein intake. This is accomplished by lowering and balancing the amount of breast milk or standard infant formula, given in conjunction with a protein substitute (Phe-free infant formula). There is no universal approach to feeding infants with PKU, with health professionals adopting many different practices. In our survey, we aimed to collect information on the variety of dietary management methods used across Europe.

• Methods

A cross sectional, survey monkey questionnaire was sent to European IMD health professionals (dietitians, nutritionists and medical doctors). The questionnaire was composed of 31 open and multiple-choice questions about the infant age at newborn screening and dietary feeding practices at diagnosis and during the first 12 months of life.

• Results

Ninety-five centers from 21 countries responded. Methods used to feed infants with PKU varied widely across centres. Over 60% of centres had initiated dietary management by the time infants were 10 days of age. Prevalence of breastfeeding was highly variable between regions and only 30% of mums continued to breast feed beyond 6 months. The most common practice was to administer a pre-measured amount of Phe-free formula prior to breast-feeds, reported in 53% of centres. Alternating feeds of breast milk and Phe-free infant formula was practiced in 23% of centres. For infants who were given standard infant formula, the most popular method was mixing standard infant formula together with Phe-free infant formula which was described in 44% of centres. 37% of centres advised measured amounts of standard infant formula followed by phe-free infant formula to satiety. The amount of total protein prescribed was higher than the European guidelines (97% of centers prescribed ≥2 g/kg/day).

• Conclusions

Despite PKU being the most studied inherited metabolic disorder, infant feeding practices varied widely across Europe. There are few reports comparing different feeding techniques with blood Phe control, stability of blood Phe levels, long term feeding development and growth. Controlled prospective studies are needed to assess how different practices influence these outcomes, in order to define the optimal infant feeding practices in PKU.

The effect of glycomacropeptide versus amino acids on phenylalanine and tyrosine variability over 24 hours in children with PKU: a randomized controlled trial

Daly A, Evans S, Chahal S, Santra S, Pinto A, Gingell C, Rocha J, Spronsen F, Jackson R, MacDonald A

Nutrients. 2019 Feb 28;11(3).

https://www.ncbi.nlm.nih.gov/pubmed/30823411

• Background

Studies suggest that casein glycomacropeptide supplemented with rate-limiting amino acids (CGMP-AA) is related with better protein utilization and less blood Phe variability. The objective of this study was to assess the impact of CGMP-AA on blood Phe variability using 3 different dietary regimens in children with PKU.

• Methods

This was a 6-week randomized controlled cross-over study that included 19 children with PKU, with a median age of 10 years old. They were randomized to 3 different dietary regimens for 14 days: R1 (CGMP-AA only as their protein substitute and usual dietary Phe), R2 (CGMP-AA only but the amount of Phe contained in the CGMP-AA was deducted from usual diet) and R3 (children took Phe-free L-AA with their usual dietary Phe allowance). Over the last 48 h on days 13 and 14, blood spots were collected every 4 hours.

• Results

Eighteen children completed the study.

	Median Phe over 24 h (mol/L)	Tyr (mol/L)
R1 (CGMP-AA+Phe)	290 (30-580)	70 (20-240)
R2 (CGMP-AA-Phe)	220 (10-670)	70 (20-240)
R3 (Phe-free L-AA)	165 (10-640)	60 (10-200)

There was a significant difference in median Phe at each time point between R1 vs. R2 and R1 vs. R3, but not for R2 vs. R3. Blood Phe remained in the target range (120-360 mol/L) over 24h in children < 12 years, for 75% of the time in R1, 72% in R2 and 64% in R3. Older children had their blood Phe in the target range in R1 and R2 for 100% of the time, but 64% in R3. Tyrosine levels were significantly higher in both the CGMP groups compared the AA group.

• Conclusions

Blood Phe concentration was increased by residual Phe in CGMP-AA. There may be less blood Phe variability with CGMP-AA when compared to L-AA, but this effect may be masked by the increased blood Phe concentrations. Reducing dietary Phe intake may help compensate for CGMP-AA Phe content.

Phenylalanine free infant formula in the dietary management of phenylketonuria: acceptability and tolerance

Yilmaz O, Cochrane B, Wildgoose J, Pinto A, Evans S, Daly A, MacDonald A

Congress Abstract: Annual Symposium of the Society for the Study of Inborn Errors of Metabolism (SSIEM): JIMD P-116

https://onlinelibrary.wiley.com/toc/15732665/2019/42/S1

• Background

Phenylketonuria (PKU) is an inherited metabolic disorder that causes Phenylalanine (Phe) levels to accumulate in blood. Effective management of the condition is achieved through dietary restriction of Phe and a phenylalanine free infant formula is a key component of this diet in the first year of life. The acceptance and tolerance to these formulas is not well reported and the study aim was to assess gastrointestinal tolerance, efficacy and acceptance of a new Phe-free infant formula, PKU start™, in a group of infants with PKU.

• Methods

This open prospective study was conducted in UK centres and 10 infants diagnosed with PKU were recruited (medium age 3.4) Anthropometric measurements and medication intake was recorded at baseline and after 31 days on PKU start. Blood Phe levels were tested weekly and daily data collected on gastrointestinal tolerance, feed volume consumed, and formula acceptability.

• Results

Infants accepted and tolerated the study formula, satisfactory weight and height was reported and blood Phe levels remained within the target treatment range. Prior to the study, common challenges were poor feeding (n = 4), reflux (n = 3), constipation (n = 3), colic (n = 3), and flatulence (n = 2). Vomiting and straining with defecation were slightly improved, however, there was no statistically significant difference due to the small study size.

• Discussion

The new formula was well accepted and tolerated and was associated with appropriate growth and blood Phe control. Minor gastrointestinal intolerance was observed. Adding a new option for dietary management of infants with PKU is a great advantage, as it minimizes the risk of supply issues and offers a choice that was not available to the dietary management of this vulnerable group.

Body composition and bone mineral density in PKU children- interim results from a 3 year study

Daly A, Pinto A, Evans S, Rocha J C, Jackson R, MacDonald A

Congress Abstract: Annual Symposium of the Society for the Study of Inborn Errors of Metabolism (SSIEM): Nutrients P-117

https://onlinelibrary.wiley.com/toc/15732665/2019/42/S1

• Background

Diets severely restrictive in natural protein are a necessity in classical phenylketonuria (PKU), however may impair normal growth and bone mineralization. Protein substitutes provide amino acids, vitamins and minerals to help promote growth and bone development. The aim of this study was to compare the effects of the bioactive peptide glycomacropeptide (CGMP-AA) and synthetic amino acids (L-AA) on growth, body composition and bone mineral density (BMD) in children with PKU.

• Methods

This 3-year study included 28 children: 18 on CGMP-AA (9 boys) and 10 on L-AA (7 boys). Median age at the end of the study was 11.2 y (range 8-19) for CGMP-AA and 15.9 y (range 9-18) for L-AA. Baseline measurements were taken as part of the BEX assessment, when all participants were on L-AA, they included weight (kg), height (cm), body mass index (kg/m^2), fat free mass (g), % total fat, lean mass (LM), bone mineral content (g), BMD (g/cm^2), bone mineral apparent density (g/cm^2) and total body less head (g/cm^2). These measures were also registered at 36 months.

• Results

There were no significant differences between treatment group scores 36 months, however, fat-free mass was greater in the CGMP-AA than in for L-AA group at the end of the 36 months ($p=0.01$). Between genders, changes were observed in body mass index and bone mineral apparent density. At the end of the study, 7 children in the CGMP-AA group and 1 in the L-AA group were prepubertal.

• Conclusions

The fact that some children were already on a prepubertal status may reflect the difference in fat free mass between groups. This study comes to no advantage of using CGMP-AA compared to L-AA in enhancing bone formation and measurements are relative to normal population standards. Further data is required.

Over restriction of dietary protein allowance: the importance of ongoing reassessment of natural protein tolerance in phenylketonuria

Pinto A, Ferreira Almeida M, MacDonald A, Ramos P, Rocha S, GuimasA , Ribeiro R, Martins E, Bandeira A, Jackson R, Spronsen F, Payne A, Rocha J

Nutrients.2019 Apr 30;11(5)

https://www.ncbi.nlm.nih.gov/pubmed/31052331

• Background

Phenylketonuria is an autosomal recessive disorder defined by a complete or partial inability to convert phenylalanine (Phe) into tyrosine. The management of PKU is based on a low-Phe diet supplemented with a low-Phe/Phe-free protein substitute. Phe tolerance has been defined as the amount of Phe a patient can tolerate whilst maintaining blood Phe concentrations within a target range. In PKU, lifetime natural protein (NP) tolerance is neither defined nor described. Maximizing NP intake is essential. The aim of this study was to assess any changes in NP intake, when challenged systematically, in a group of well-controlled patients with PKU on diet treatment only above 12 years of age.

• Methods

This group performed a retrospective longitudinal study examining NP tolerance at baseline and at a median of 6 months after systematic challenge with extra NP between assessments, maintaining blood Phe ≤ 480 µmol/L. Data was collected on 40 patients with PKU with age range 12–29y. All participants were diagnosed at newborn screening and continuously treated with a low-Phe diet following diagnosis. They were treated with a low-Phe diet together with a Phe-free L-amino acid supplement or a low-Phe glycomacropeptide-based protein substitute (CGMP-AA).

• Results

Data was collected for anthropometric measurements (weight, height, BMI), dietary intake, protein equivalent intake from protein substitute and total protein intake, at each assessment. Phe levels were collected for a median of 6 months before the first and second dietary assessment. Median daily NP intake significantly increased between assessments (35 vs. 40 g/day, p = 0.01). Twenty-six patients (65%) were able to increase their median NP intake by a median 12 g/day (2–42 g)/day and still maintain blood Phe within target range.

• Conclusions

The main finding of this study was that 65% of patients with PKU aged ≥12 years were able to tolerate more NP than prescribed, when challenged. Most patients were adolescents, and 50% of all the patients were able to increase NP intake by a minimum of 20%. Most of the patients were over restricting NP allowance. This extra NP may positively influence a patient's nutritional status and quality of life. More data is important to clearly show how NP tolerance changes from childhood until adulthood.

A systematic review of cognitive functioning in early treated adults with phenylketonuria

Leonne-Hofman D, Champ CL, Lawton CL, Henderson M, Dye L

Orphanet Journal of Rare Diseases. 2018 Aug 30;13(1):150
https://www.ncbi.nlm.nih.gov/pubmed/30165883

• Background

Phenylketonuria (PKU) is a rare inborn error of metabolism. Since its discovery, research into PKU has improved diagnosis and management. Treatment is aimed at keeping Phe levels low. With dietary management severe cognitive impairments are prevented, but deficits in cognitive functioning are still observed in executive functions such as working memory, reasoning/planning, attention, and processing speed. Other cognitive functions have received less attention. There is a lack of a comprehensive and systematic overview of cognitive functioning across different cognitive domains in early treated adults with PKU (ET AwPKU). The objective of this study was to provide an overview of cognitive functioning across domains examined in ET AwPKU.

• Methods

This systematic review followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) 2009 checklist. Searches of electronic databases were carried out on several databases, following specific terms. A total of twenty two peer-reviewed publications, reporting on outcomes from 16 studies were reviewed and included. The Cochrane data extraction form was modified for these purposes. Data were extracted into the standardized form by two researchers.

• Results

Despite early treatment, ET AwPKU have deficits in vigilance, weight management, and motor skills compared to healthy controls. Long-term cognitive outcomes of ET AwPKU remain unclear. Several associations between cognitive performance and metabolic control throughout life were observed. However, these findings were inconsistent, and it is difficult to determine the long-term effects of poor metabolic control, at different stages in life, on cognitive function in AwPKU.

• Conclusions

A better understanding of cognitive functioning and cognitive deficits in ET AwPKU is required. To achieve this, future studies should include (inter)national multicentre-studies and consider other nutritional measures that may impact on cognitive functioning, as well as avoid using heterogeneous samples. Careful attention to cognitive test selection and statistical analysis is required.

The effect of various doses of phenylalanine supplementation on blood phenylalanine and tyrosine concentrations in tyrosinemia type 1 patients

van Ginkel WG, van Reemst HE, Kienstra N, Daly A, Rodenburg I, MacDonald A, Burgerhof J, Blaauw P, van de Krogt J, Santra S, Heiner-Fokkema MR, van Spronsen FJ

Nutrients. 2019 Nov 18;11(11).

https://www.ncbi.nlm.nih.gov/pubmed/31752110

• Background

Tyrosinemia type 1 (TT1) is a rare, autosomal recessive disorder of tyrosine metabolism. Combined medical management with 2-(2-nitro-4-trifluormethyl-benzyl)-1,3-cyclohexanedione (NTBC) and a low protein diet can result in phenylalanine concentrations within target range. This study aimed at investigating the biochemical effect of different amounts of phenylalanine supplementation on metabolic control.

• Methods

In total, 11 TT1 patients were studied. All patients received NTBC and a protein restricted diet with phenylalanine and tyrosine-free L-amino acids supplements. The dietary prescription and NTBC dose remained unchanged during the study. There were three different study periods in which three blood spots a day were taken in each, before breakfast, lunch and dinner. The first period consisted of two days without supplementation. In the second period, 20 mg/kg/day phenylalanine supplementation was given for 5 days. During the third period, 40 mg/kg/day was given for 5 days.

• Results

No patients reported any new or exacerbation of pre-existing clinical problems. The supplementation prevented the decrease in blood phenylalanine concentrations during the day, while it induced an increase in blood tyrosine concentrations. It did not affect blood SA (and NTBC) concentrations. With no phenylalanine supplementation, mean phenylalanine levels dropped from 50 (+/-21) µmol/l at breakfast to 37 (+/-14) µmol/l before the midday meal. There were significantly higher blood phenylalanine concentrations when 40mg/kg/d was given compared to no supplementation ($p = 0.001$) and 20 mg /kg/d ($p = 0.005$). There was a significant increase in tyrosine levels, but this was less pronounced when 20mg/kg/d was provided compared with 40 mg/kg/day.

• Conclusions

This study substantiates that the combined NTBC and dietary treatment regimen with phenylalanine supplementation may prevent low phenylalanine concentrations. 20 mg/kg/day phenylalanine supplementation could avert most of the low blood phenylalanine concentrations during the day. 40mg/kg/day phenylalanine supplementation led to a further decrease of low phenylalanine levels, but detrimentally increased tyrosine concentrations above the upper target range. It was concluded that the effects of phenylalanine supplementation should be analyzed using pre-midday meal blood samples which could be combined with an overnight fasted blood sample of the same day when in doubt.

Glycomacropeptide: long-term use and impact on blood phenylalanine, growth and nutritional status in children with PKU

Daly A, Evans S, Chahal S, Santra S, Pinto A, Jackson R, Gingell C, Rocha J, Van Spronsen FJ, MacDonald A

Orphanet Journal of Rare Diseases. 2019 Feb 15;14(1):44.
https://www.ncbi.nlm.nih.gov/pubmed/30770754

• Background

The amino acid profile of protein substitutes (including amino acids ratio) requires further study, especially when based on casein glycomacropeptide (CGMP). In this 12-month longitudinal, prospective study, the impact of using a modified CGMP-AA protein substitute (CGMP-AA2) is described and compared with a control group of children taking conventional Phe-free L-AA supplements only. The aim of this study was to evaluate a CGMP-AA2 formulation compared with phenylalanine-free L-amino acid supplements (L-AA) on blood Phe, Tyr, Phe:Tyr ratio, biochemical nutritional status and growth in children with PKU.

• Methods

CGMP-AA2 is a flavoured powdered protein substitute containing 20 g of protein equivalent, and 36 mg of Phe per 35 g sachet. Additional essential amino acids were added to provide a similar AA profile to conventional Phe-free L-AA supplements. Fifty children diagnosed by newborn screening with PKU were recruited. At baseline and 26 weeks, morning fasted pre-prandial venous samples were collected for nutritional markers. Anthropometry, height and weight, together with a stock check of protein substitute usage, diet history, and food frequency questionnaire were collected monthly.

• Results

At the end of 52 weeks only 48% of subjects were able to completely use CGMP-AA2 as their single source of protein substitute, without affecting blood phe control At 52 weeks CGMP-AA2 provided a median of 75% of the total protein substitute with the remainder being given as L-AA. Within the CGMP-AA2 group, blood Phe increased significantly between baseline and 52 weeks. There were no differences for Phe, Tyr, Phe:Tyr ratio and anthropometry when comparing the control group using L-AA and the CGMP-AA2 group. However, in the same period within the CGMP-AA2 group, blood Phe concentrations, weight and BMI z significantly increased. The median values for all nutritional parameters, measured at baseline and 26 weeks, were all within the reference ranges.

• Conclusions

CGMP can impact blood Phe concentrations so should be used with care in young children. On introducing CGMP, especially in young children, blood Phe levels should be closely monitored and it may be that in young children CGMP can only be partially used to meet protein requirements.

Sleep and quality of life of patients with glycogen storage disease on standard and modified uncooked cornstarch

Rousseau-Nepton I, Huot C, Laforte D, Mok E, Fenyves D, Constantin E, Mitchell J

Molecular Genetics and Metabolism. 2018 Mar;123(3):326-330.
https://www.ncbi.nlm.nih.gov/pubmed/29223626

• Background

Glycogen storage diseases (GSDs) are rare autosomal recessive disorders of glycogen synthesis or degradation. Dietary management of GSD requires a regular supply of exogenous carbohydrate to prevent hypoglycaemia. Uncooked cornstarch (UCCS) or a continuous glucose infusion/tube feeding are used to supply this carbohydrate source. However, use of UCCS leads to interrupted sleep for individuals, resulting in exhaustion, anxiety and possible delays in administration of the starch. To overcome these problems, a modified form of UCCS (Glycosade™) has been launched. The objectives of this study were to determine if, use of Glycosade™, improves sleep and quality of life, in addition to determining fasting duration using continuous glucose monitoring (CGM).

• Methods

A single centre prospective study of 9 adult patients with hepatic GSD type Ia, taking UCCS overnight, and with a documented history of hypoglycemia was conducted. The patients were evaluated during hospital admissions for sleep and QoL using validated questionnaires, sleep diaries and actigraphy. Fasting duration and glucose variability were also determined using CGM.

• Results

There was a statistically significant improvement in sleep quality ($p<0.05$) and duration of fasting with the introduction of Glycosade, compared to data when taking UCCS. QoL, which was normal pre-Glycosade, remained unchanged.

• Conclusions

The cost-benefit ratio of Glycosade™ use is promising in terms of possible improvement in compliance to therapy, decreased risk of hypoglycemia at nighttime and its potential impact on sleep quality. As this was a short-term study, greater differences in sleep and QoL may be seen with longer term use of Glycosade™.

Nice to know: impact of NICE guidelines on ketogenic diet services nationwide

Whiteley VJ, Martin-McGill KJ, Carroll JH, Taylor H, Schoeler NE on behalf of The Ketogenic Dietitians Research Network (KDRN)

Journal of Human Nutrition and Dietetics. 2020 Feb;33(1):98-105.
https://www.ncbi.nlm.nih.gov/pubmed/31429508

• Background

Ketogenic diets (KDs) are high-fat, restricted carbohydrate diets that are used for the dietary management of drug-resistant paediatric epilepsy. In 2012 the National Institute for Health and Care Excellence (NICE) published 'Clinical Guidelines for Epilepsies: Diagnosis and Management', in which the use of the KD in this group was mentioned for the first time. The aim of this study was to evaluate the impact of this guidance on the use of KDs in children and young people with epilepsy whose seizures did not respond to anti-epileptic drugs and who were referred to a tertiary paediatric epilepsy specialist for consideration of the use of KDs.

• Methods

Ketogenic dietitians from UK and Ireland received an online survey. Results were compared with similar surveys published in 2000 and 2010.

• Results

Since 2000 there has been a 77% overall increase in the number of centers offering KDs for treatment of epilepsy (from 22 in 2000 to 39 in 2017), which reflects the increase in patient numbers, from 101 in 2000 to 754 in 2017. Seven centers (previously two) now accept KD referral for adults. At the time of the study, 267 patients were waiting to start a KD amongst the 31 centers that replied.

• Conclusions

Despite the rapid growth both in centers and number of patients, there is an ongoing demand for patients to be considered for dietary therapy, highlighting the need for continued expansion of services. New models of service delivery and funding are needed to be found to ensure that patients can access an effective treatment in a timely manner.

Understanding the core principles of a 'modified ketogenic diet': a UK and Ireland perspective

Martin-McGill KJ, Lambert B, Whiteley V, Wood S, Neal E, Simpson ZR, Schoeler NE

Journal of Human Nutrition and Dietetics. 2019 Jun;32(3):385-390.
https://www.ncbi.nlm.nih.gov/pubmed/30859652

• Background

Ketogenic diets (KDs) have confirmed degrees of efficacy for the dietary management of epilepsy and neurometabolic conditions. Centres across the UK and Ireland have been using a modified ketogenic diet (MKD) for refractory epilepsy. The practice of KDs is apparently evolving and it is important to gain an insight into the MKD, as practiced in these centres, to advance and facilitate dietary interventions in the future.

• Methods

A group of ketogenic dietitians designed a survey with 35 questions regarding service demographics, dietary preparation and education, initiation of the diet, 'fine-tuning', monitoring and dietary discontinuation related to the use of MKD protocol in clinical practice. The survey was released to all KD centres across the UK and Ireland.

• Results

Eighteen centres returned the questionnaire. The results indicated the MKD is used widely across the UK and Ireland, in both adult and paediatric populations. A period of pre diet education and preparation is key for implementation. An estimation of total energy requirements is the basis for establishing macronutrient requirements. Fat was dimensioned to provide 65–80% of estimated total energy requirements. Ketogenic nutritional products available on prescription were used on dietary initiation and 'fine-tuning'.

• Conclusions

Prior to the present study, little was known about the clinical implementation of MKD in the UK and Ireland, or the differences between MKD and these other KDs. MKD is a hybrid KD, adopting principles from other established KD protocols whilst defining its own unique elements, with the aim of making KDs simpler and more accessible for patients and their families. Further research into the implementation of the MKD in a clinical trial setting is warranted.

Mechanisms of action for the medium-chain triglyceride ketogenic diet in neurological and metabolic disorders

Augustin K, Khabbush A, Williams S, Eaton S, Orford M, Cross J-H, Heales S, Walker M, Williams R

Lancet Neurology. 2018 Jan;17(1):84-93.
https://www.ncbi.nlm.nih.gov/pubmed/29263011

• Background

The ketogenic diet is a high-fat, low-carbohydrate diet, used since the early 1970's as a non-pharmacological treatment for drug-resistant epilepsy. Despite its common use, the mechanisms underlying its efficacy have remained unclear. Under fasting conditions, ketones can provide the energy source for cells, and have been thought to be the key mechanism of action in controlling seizure frequency in patients with epilepsy. Advances in the understanding of medium-chain fatty acids has resulted in a paradigm shift in the hypothesis behind the mechanisms of the diet, away from ketones and focusing on fatty acids instead. Several studies have indicated that medium-chain fatty acids can have a direct action on seizure activity and mitochondrial function. The aim of this review was to assess the mechanisms of action of the medium-chain triglyceride (MCT) ketogenic diet in relation to epilepsy and other disorders, including, Alzheimer's disease, cancer, and diabetes.

• Discussion

Dietary triglycerides are provided as a supplement in the MCT ketogenic diet. These are hydrolyzed to medium-chain fatty acids (e.g., decanoic acid and octanoic acid) and its metabolism results in the generation of ketone bodies: β-hydroxybutyrate, acetoacetate, and acetone Evidence that ketones can have an effect on seizure control is mixed, and reduced seizure activity probably occurs through indirect metabolic effects. The efficacy of decanoic acid in seizure control has been shown in animal models are likely to be a direct result of AMPA-receptor inhibition. It is therefore likely that, in patients with epilepsy on the MCT ketogenic diet, decanoic acid would reach enough concentrations in the brain to reduce excitation and thereby provide reduced seizure frequency. An alternative mechanism for the effect of the MCT ketogenic diet on epilepsy arises from beneficial effects on brain energy metabolism.

• Conclusions

Evidence suggests that medium-chain fatty acids have direct and differing effects on brain cell energy metabolism. The effect of ketones on metabolic activity in the brain highlights the potential of the ketogenic diet as a treatment for metabolic changes underlying Alzheimer's disease. The commonly accepted mechanism by which the ketogenic diet might aid in cancer therapy is that the decrease in circulating blood glucose, and the inability of tumors to use ketone bodies, result in reduced tumor growth or tumor regression. Studies suggest a beneficial role of MCTs in the treatment of type 2 diabetes and associated glucose-sensitive metabolic disorders. Analyzing medium-chain fatty acids in future ketogenic diet studies will provide further insights into their importance in modified forms of the diet.

Biochemical assessment of patients following ketogenic diets for epilepsy: current practice in the UK and Ireland

Schoeler NE, Simpson Z, Whiteley VJ, Nguyen P, Meskell R, Lightfoot K, Martin-McGill KJ, Olpin S, Ivison F on behalf of the Ketogenic Dietitians Research Network (KDRN)

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• Background

Ketogenic diets (KDs) are high-fat, low-carbohydrate, moderate protein diets used as a treatment option for drug-resistant epilepsy. However, KDs are inappropriate for some individuals and thus screening biochemical tests to rule out such disorders are a crucial part of pre-diet assessment. The objective of this study was to investigate current practice in the UK and Ireland in comparison to international guidelines, to determine approximate costs of screening in patients and to promote greater consistency in KD services.

• Methods

A survey was disseminated via email to 39 services in the UK and Ireland. Following the initial email, two follow-up emails were sent to obtain more responses on how to identify biochemical tests requested in patients commencing and following a KD for epilepsy and metabolic disorders at baseline, 3-, 6-, 12-, 18- and 24-months post diet initiation.

• Results

The survey was completed by 16 centres. All requested full blood count, electrolytes, calcium, liver function tests (LFTs), lipid profile and vitamin D at baseline, according to international guidelines. Although not recommended on international guidelines, all centres requested Magnesium and Zinc at baseline. Other less requested tests included bicarbonate, total protein and urianalysis. Follow-up request included urea and electrolyte profiles and some LFTs, keeping with international guidelines. Other less requested tests at follow-up included other LFTs and renal tests, full blood count, lipid profile, acylcarnitine profile, selenium, vitamin D and urinalysis. Lowest mean cost was £167.54 and highest £501.93. The mean costs of 3-month follow up tests was £19.17 and £450.06 for the lowest and highest, respectively.

• Conclusions

Practice in the UK and Ireland varies and does not fully correspond to international best practice guidelines. Further work is needed to harmonize cost-effectiveness within healthcare.

The modified ketogenic diet for adults with refractory epilepsy: an evaluation of a set up service

Martin-McGill KJ, Jenkinsona MD, Tudur-Smith C, Marsona AG

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https://www.ncbi.nlm.nih.gov/pubmed/28915401

• Background

The ketogenic diet (KD) is not recommended as an NHS routine treatment for adults with refractory epilepsy in EU countries, despite having proven effectiveness in children suffering from this condition and being recommended by the National Institute of Health and Care Excellence (NICE). To support a randomized control trial (RCT) and to choose and deliver the most appropriate type of KD to adults with refractory epilepsy in the NHS, evidence about feasibility and costs is needed. The MKD is the least restrictive KD and induces ketosis through encouraging a high fat and low carbohydrate intake, without the requirement to limit protein, fluid or energy intakes. There is no need for a fasting start or hospitalization to commence the diet, promoting ease of use and reducing costs. The diet is tolerated, with limited side effects.

• Methods

A multidisciplinary team proposed a questionnaire to collect data regarding demographics, attitudes towards the use of the MKD in refractory epilepsy, willingness to try the diet and willingness to participate in a RCT. The questionnaire was distributed to patients attending epilepsy clinics. The feasibility of delivering a KD service in a unit with no prior service was also subject of study.

• Results

102 questionnaires were completed. For 50 patients, MKD should be offered to patients with refractory epilepsy, within an NHS setting. 51 reported wanting to try the MKD for 3 months. 43 indicated that they would participate in a clinical trial to investigate deliverability, efficacy and tolerability. 37 were willing to participate in a randomized trial.

• Conclusions

Adults with refractory epilepsy are interested in accessing KD services, participating in RCT, and being allocated to the diet. Patient's key motivators to clinical trial participation include improved seizure control, quality of life and helping other patients with epilepsy. Barriers to participation included burden of dietetic visits, time commitment, expense of travel and expense of the diet. A further cost to consider is the biochemical screening and monitoring that is required, but screening costs could be kept to a minimum in selected adult cases.

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