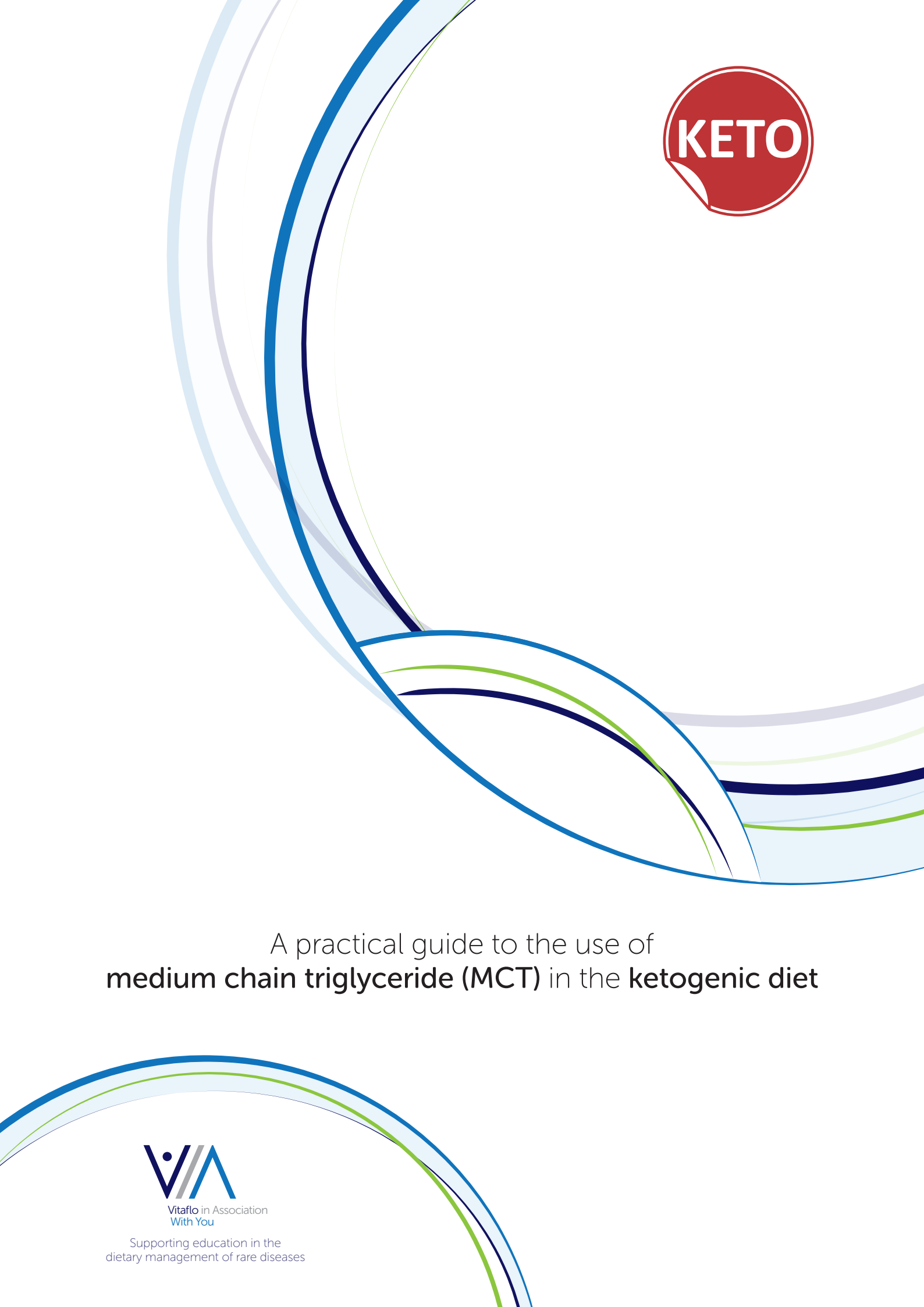


A practical guide to the use of **medium chain triglyceride (MCT)** in the **ketogenic diet**

Vitaflo in Association With You

Supporting education in the dietary management of rare diseases

Disclaimer

This resource:

- Is intended to provide information on the use of medium chain triglycerides (MCT) in the ketogenic diet (KD) in children aged over 1 year, adolescents and adults diagnosed with epilepsy or an inherited neurometabolic disorder, for example, Glut-1 Deficiency Syndrome (Glut-1 DS) or Pyruvate Dehydrogenase Deficiency (PDHD), where its use is indicated and evidence based.
- Is primarily focused on the dietetic application of the KD not the clinical management associated with its use.
- Does not relate to the challenge of KD implementation in infants i.e. those under 12 months of age. Further guidance from more specialist resources should be sought for this group.
- Is only to be used by qualified healthcare professionals.
- Is not for use by patients or their parents or caregivers.
- Is for general information only and must not be used as a substitute for professional medical advice or treatment.

The information, although accurate and based on current best practice in the UK at the time of publication, is subject to change as use of the KD evolves.

It is the sole responsibility of the Multi-Disciplinary Clinical Team (MDT), i.e. a dedicated '**keto-team**', to ensure patients managed on the KD are suitable to undergo this form of dietary therapy and they undertake and implement all the assessments, procedures, investigations and monitoring required in accordance with locally agreed procedures specific to the intervention. The term '**keto-team**' is a generic description for those healthcare professionals (for example, dietitians, clinicians, nurses) involved in the implementation, follow-up and care of patients on a KD.

We advise this guide is read in conjunction with your local and national protocols and general recommendations for the use of MCT and the KD in the dietary management of epilepsy and neurometabolic disease.

For allergens contained within products included in this guide, please refer to individual product labels.

Written by Bridget Lambert, Vitaflo dietitian, and Vitaflo dietitians, in collaboration with Elizabeth Neal MSc PhD RD, Specialist Ketogenic Dietitian - Matthew's Friends Clinics and Honorary Research Associate, UCL-Institute of Child Health, London, UK.

Abbreviations

CKD	Classical ketogenic diet
C8	Caprylic or octanoic acid; ketogenic medium chain fatty acid
C10	Capric or decanoic acid; ketogenic medium chain fatty acid
GI	Gastrointestinal
KD	Ketogenic diet
LCFA	Long chain fatty acid
LCT	Long chain triglyceride
LGIT	Low glycaemic index treatment
MAD	Modified Atkins diet
MCFA	Medium chain fatty acid
MCT	Medium chain triglyceride
MCTKD	Medium chain triglyceride ketogenic diet
MKD	Modified ketogenic diet

For information on the ketogenic diet, Vitaflo products for the use in ketogenic diet and recipes visit the Vitaflo websites:

www.vitafloweb.com
www.myketogenicdiet.com
www.myketogenicdiet.co.uk
www.myketogenicdiet.co.uk/de
www.myketogenicdiet.co.uk/ie
www.myketogenicdiet.co.uk/nl

Other Vitaflo resources for the KD can be accessed on the VIA website
www.nestlehealthscience.com/Vitaflo/VIA

Contents

Introduction

The ketogenic diet (KD) originally devised in the 1920's and 30's[1-3] and still in worldwide use today uses foods naturally rich in fat as long chain triglyceride (LCT) to provide an abundance of fatty acids for conversion to ketones. However, the diet is challenging to undertake, despite its proven success in the dietary management of drug resistant epilepsy and neurometabolic disorders[4].

In the 1960's, medium chain triglycerides (MCT) became available for clinical use[5]. Differences in molecular structure between MCT and LCT, and major dietary sources are outlined in Figure 1 and described in section 1.0. To take advantage of the observed greater ketogenic potential of fat comprised of medium chain fatty acids[6,7] and to try to improve patient acceptability and application of the ketogenic diet, an alternative to the original, Classical regime (CKD) was devised in the 1970's - the medium chain triglyceride KD (MCTKD). Inclusion of MCT oil retained clinical efficacy and importantly, enabled reduction in total fat content and more protein and carbohydrate foods, facilitating greater dietary palatability[8,9]. A randomised trial of the MCTKD and CKD in children with intractable epilepsy found them comparable in efficacy and tolerability, and concluded both had their place in the treatment of childhood drug resistant epilepsy[10].

Aside from heightened ketone production, a specific anti-epileptic effect of MCT and of the individual medium chain fatty acids octanoic (C8) and decanoic (C10) has been proposed, resulting from studies of children on the MCTKD[11,12]. More recently, research has emerged that reinforces and extends these observations[12, 13], so potentially meriting the inclusion of MCT in combination with LCT as a beneficial and advantageous constituent in all versions of the ketogenic diet in the dietary management of seizures[13-15].

The scientific, clinical and dietary aspects of the use of MCT in the KD are outlined in sections 2.0 and 3.0, and a time-line showing the history of use of MCT in the KD in 4.0.

1.0 Overview of MCT and LCT

1.1 Dietary sources of MCT and MCFA

Figure 1

MCT

A molecule of MCT consists of mixtures of three medium chain fatty acids (MCFA) of 6 - 10^ carbons attached to a glycerol backbone:

C6 (hexanoic or capronic acid)

C8 (octanoic or caprylic acid)
C10 (decanoic or capric acid)
} MCFA with ketogenic and antiepileptic effects

MCT is present naturally in only a few foods, in small amounts, e.g coconuts, animal milks. Proprietary products (oils, emulsions and powders) therefore typically supply MCT in the KD.

LCT

A molecule of LCT consists of mixtures of three long chain fatty acids (LCFA) of 14 carbons or more, attached to a glycerol backbone.

LCT is the predominant fat present in food. Concentrated animal and plant sources of LCT such as butter, oils and double cream, typically supply LCT in the KD.

*betaquik® and **MCTprocal® (Vitaflo® International Ltd) are foods for special medical purposes. Betaquik and MCTprocal are suitable from 3 years of age. Betaquik and MCTprocal are not for use as sole sources of nutrition and are for enteral use only.

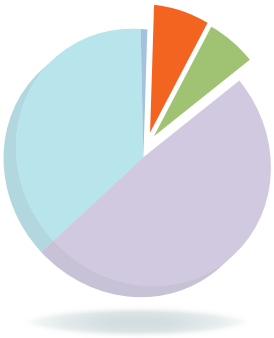
Note: ^C12 (dodecanoic or lauric acid) is sometimes classified as MCFA.

Foods - LCT is the main fat present in foods. Naturally occurring MCT is only found in small amounts in coconuts, palm kernels and animal milks and therefore normal dietary intakes are limited. In coconut and palm kernel oils, the proportions of C6, C8 and C10 in the triglycerides are low in comparison to C12, which is the main fatty acid present.

Proprietary MCT oils, emulsions and powders - MCT oils have been available for clinical use since the 1950's and contain predominantly C8 and C10 fatty acids. They are produced by hydrolysis of coconut or palm kernel oils followed by filtration to remove the C12 fatty acids. The remaining C8 and C10 are then re-esterified with glycerol back bone into triglycerides[4]. The proportions of C8 to C10 are defined during manufacture of the MCT oil and typically expressed as a ratio, e.g. 40:60, 50:50. MCT emulsions (e.g. betaquik®, Vitaflo® International Ltd) are made by combining these oils with water, and MCT powders (e.g. MCTprocal™, Vitaflo International Ltd) by the spray drying of MCT oils onto protein and carbohydrate. A comparison of the fatty acid profiles of coconut oil and an MCT oil with a 60:40 ratio of C8 to C10 MCFA is illustrated in Figure 2.

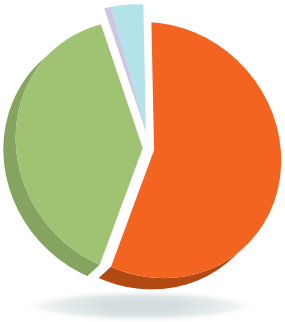
Figure 2

Typical fatty acid profile of **coconut oil** per 100g fatty acids[16].



0.7%	C6 Hexanoic	0%
4.6-10%	C8 Octanoic	56%
5-8%	C10 Decanoic	39%
45-53%	C12 Lauric	1%
28-45%	C14 - 20 (LCT)	4%

Example of the fatty acid profile of an **MCT oil** per 100g fatty acids[(Company data on file)].



1.2 Assimilation of MCT and LCT[17-21]

The process of assimilation i.e. the incorporation of nutrients into the body via digestion, absorption and transportation, is different for MCT compared to LCT. This is due to the specific physical structures and unique biological properties of the triglyceride molecules and their constituent fatty acids. When consumed as part of a KD, these features influence the availability of the fatty acids for beta-oxidation to acetyl-CoA and then onwards to ketogenesis. Essentially, due to their shorter carbon chain lengths, the MCFA go through the beta-oxidation pathway more quickly and undergo conversion to ketones more efficiently and rapidly than the LCFA (Figures 4 and 5, Appendices). C8 is thought to drive the ketogenic effect of MCT containing both C8 and C10. It has been shown that C8 is preferentially converted to acetyl-CoA compared to C10, hence it can undergo ketogenesis more rapidly[3].

1.3 MCT in the KD

MCT oils, emulsions and powders high in C8 and C10 MCFA have a history of safe and efficacious use in the KD (Section 4.0). They are primarily used for the ketogenic and anti-epileptic effects of these fatty acids. To provide MCT in the KD, it is preferable to use these proprietary products rather than coconut oil, as although it is a useful source of fat, it provides only small amounts of C8 and C10 due to its high C12 content.

Clinical, scientific and dietetic evidence, in combination with experience of use, suggests that inclusion of MCT as a source of fat in the KD may:

- Promote and enhance ketogenesis.
- Provide a potential anti-epileptic effect.
- Enhance dietary palatability and acceptability.
- Be helpful in the management of KD related side effects, e.g. dyslipidaemia, gastroesophageal reflux (GOR), constipation.

2.0 Scientific and clinical basis for the use of MCT in the KD

2.1 For ketogenesis

In the context of the KD, the faster route to ketogenesis of MCT and MCFA in comparison to LCT and LCFA is advantageous. Compared to LCFA, MCFA have been demonstrated to:

- Reach and enter the liver cell mitochondria faster and undergo a more prompt and extensive oxidation to acetyl-CoA via the β oxidation pathway, in particular, C8[17, 18, 22].
- Primarily undergo ketogenesis, instead of being stored in adipose tissue as an energy reserve[21, 23].
- Be converted to ketones in both regular and ketogenic diets, after oral administration of MCT[7, 24].
- Be rapidly converted to ketones within 30 minutes of ingestion of either MCT oil or emulsion, and for blood levels to remain elevated for around 4 hours, in comparison to LCT[7, 25].

2.2 For specific, anti-epileptic properties

Based on its ketogenic potential, in combination with LCT, MCT has a role in establishing and maintaining ketosis on the KD. However, degree of ketosis is known to be independent of successful seizure control *in vivo* as both high and low ketone levels (typically monitored on the KD and useful as a marker for dietary compliance), can be equally efficacious[26]. The observed antiepileptic effect of the KD therefore appears to be more than solely about the ketones produced by the systemic metabolic changeover from glycolysis to ketosis[27-29].

The potential of the MCFA to have antiepileptic properties, both individually and in combination, and hence a direct effect on the nervous system, was originally suggested by researchers in the 1970's and 80's based on their clinical observations of application of the MCTKD[8, 9, 11, 12, 30]. More recent and emerging research indicates biological processes manifesting as seizure reduction and control are induced by C8 and C10 (an isomer of the anticonvulsant valproic acid) when administered alone or in combination in specific ratios, or at concentrations equivalent to those achieved on the MCTKD. For example:

- C8 and C10, given separately or together raised drug induced seizure thresholds in mice[31, 32].
- Administration of MCFA to rats promoted seizure control[13], and interaction between MCFA and the amino acid tryptophan raised seizure threshold[33].
- In cell studies, C8 and C10 in differing combinations promoted mitochondrial proliferation, hence potentially increasing energy supplied from ATP to neurones[14].

3.0 Dietary attributes of MCT in the KD

3.1 To enhance dietary palatability and promote acceptability

The requisite high fat, low carbohydrate content of the KD limits the choice and variety of foods permitted. This can have a negative influence on the enjoyment of eating, contributing toward a high discontinuation rate, despite any initial success, especially in adolescents and adults[34]. Huttenlocher *et al.* developed the MCTKD as a modification of the CKD by replacing a proportion of the LCT content with MCT oil[7,8]. This enabled total fat content to reduce from 87-90% to around 75% of daily energy requirement yet still achieve adequate ketosis and dietary efficacy. In addition more protein and carbohydrate could be included which reportedly enhanced overall dietary palatability and acceptability[8,9].

The attribute of MCT that allows more carbohydrate in the MCTKD can be applied in all the LCT based versions of the KD - CKD, LGIT, MAD and MKD[35].

Inclusion of MCT, as an addition or substitution of a proportion of total LCT content in a KD may, therefore;

- Help preserve carbohydrate content or permit an additional amount to be included.
- Promote dietary acceptability, palatability and adherence.

3.2 To improve ketosis

- **In the CKD**

  Inclusion of MCT may be beneficial as an alternative to increasing the ketogenic ratio, e.g. from 3 to 1 up to 4 to 1 as this involves reducing the amount of carbohydrate and/or adding more LCT[35].

- **In the modified versions of the KD (LGIT, MAD, and MKD)**

  Adding in a measured daily quantity of MCT may avoid further carbohydrate restriction[35].

- **In neurometabolic conditions, e.g. Glut-1 DS**

  For those reliant on the KD to supply an alternative energy source to glucose, regular consumption of MCT at specific times during the day may help improve ketosis overall and ensure an adequate supply of ketones to meet energy needs[36].

3.3 For rapid ketone production at specific times

- MCT may 'boost' ketone production and energy supply at specific times, e.g. for those with Glut-1 DS before exercise.
- MCT taken at bedtime to help maintain ketosis overnight is linked to improved control of nocturnal seizures[11].

3.4 For the management of diet related side effects of the KD

- Evidence suggests that in normal human diets, MCT is beneficial in the context of cardiovascular risk factors and health[17, 37]. On the KD, **dyslipidaemia** is common, and, although typically self-resolving with time, can be of concern, and warrant manipulation of dietary fat sources. In studies, use of MCT in the KD is associated with more favourable lipid levels, and therefore its inclusion may be helpful in the prevention or management of this condition[38-41].
- MCT may help manage **GOR**. In those with drug resistant epilepsy, when especially in combination with neurological impairment, there is a high incidence of GOR. This condition is often aggravated by a high fat diet[42]. Use of MCT to promote stomach emptying[43] and/or as an adjunt to lowering total fat content, may help application and tolerance of the KD in this situation, or if GOR symptoms related to high fat intake manifest once on diet.
- MCT may be helpful in the management of **constipation**, a common side effect of the KD[44]. However, care is advised when MCT is given for this (or any other reason) as it can induce diarrhoea and gastrointestinal disturbance in some individuals[45] (See also the Vitaflo resource 'A practical guide to establishing gastrointestinal tolerance of medium chain triglyceride (MCT) and betaquick in the ketogenic diet').

4.0 History of use of MCT in the KD

Figure 3

1920's and 30's

The CKD based on LCT is devised. Its application is efficacious in many children and adults with drug resistant epilepsy[1 - 3].

Late 1930's

The development and availability of anti-epileptic drugs, e.g. phenytoin, leads to declining use of the KD[46].

1960's

The ability of MCT and individual MCFA C8 and C10 to generate ketones and establish ketonaemia more rapidly and efficiently than LCFA, even in the presence of dietary carbohydrate is recognised[6, 7].

This characteristic is due to the unique physiological properties, functions, and biological features of MCT and its constituent fatty acids. A faster assimilation enhances bioavailability for beta-oxidation to acetyl Co-A, providing a more efficient method of ketone production.

1970's

The MCTKD is devised as a modification of the CKD to take advantage of the greater ketogenic capacity of MCT. A proportion of LCT (60%) is replaced with MCT oil as an alternative source of fatty acids[8, 9].

This change achieves equitable efficacy with the CKD despite the reduction in total fat content, whilst the inclusion of more carbohydrate and protein improves dietary palatability and acceptability.

1980's and onwards

Continued efficacious use of MCTKD is reported, mainly in children[11, 12, 47-51].

Practical experience and use of the MCTKD shows 45 – 50% of energy intake from MCT achieves a good balance between adequate ketosis, dietary efficacy, and gastrointestinal tolerance[52, 53], although successful use up to 70% is reported[54].

The development of emulsions of MCT as an alternative to MCT oil aids acceptability and tolerance as part of a KD[11].

The inclusion of approximately 100g of MCT oil daily in a normal diet is beneficial in the dietary management of adult epilepsy[55].

1990's

Use of the KD for the dietary management of drug resistant epilepsy is re-established[5].

The KD becomes the standard treatment for Glut-1DS, first diagnosed in 1991[56].

Today, and into the future...

Results from clinical and scientific research is emerging, indicating specific functions and potential advantages of MCT and the individual ketogenic MCFA (C8 and C10) for the management of epilepsy and other neurological conditions[13-15].

Due to its unique and specific attributes, the inclusion of MCT in combination with LCT offers potential benefits in all versions of the KD.

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6.1. Assimilation of fatty acids

The process of assimilation by the body is shown in Figure 4. The length of the carbon chain of the fatty acid molecule determines their digestion, absorption and transportation. The route to ketone production is more rapid for MCT compared to LCT. Figure 5 shows the metabolic pathway of ketogenesis, the production of energy from ketones, produced in preference to glucose when on the high fat KD.

Figure 4 - Comparison of the assimilation of MCT, MCFA, LCT and LCFA by the body.

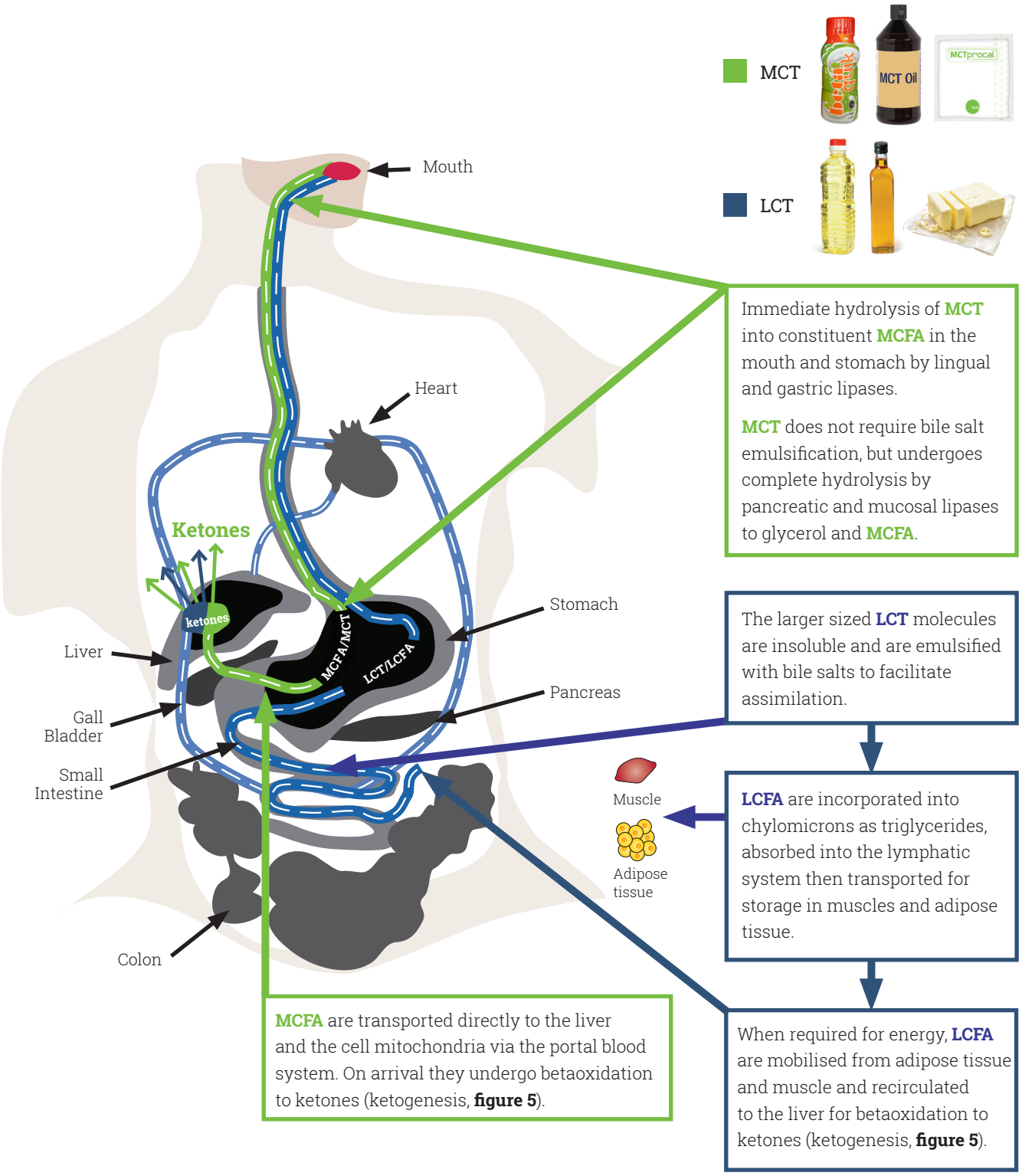
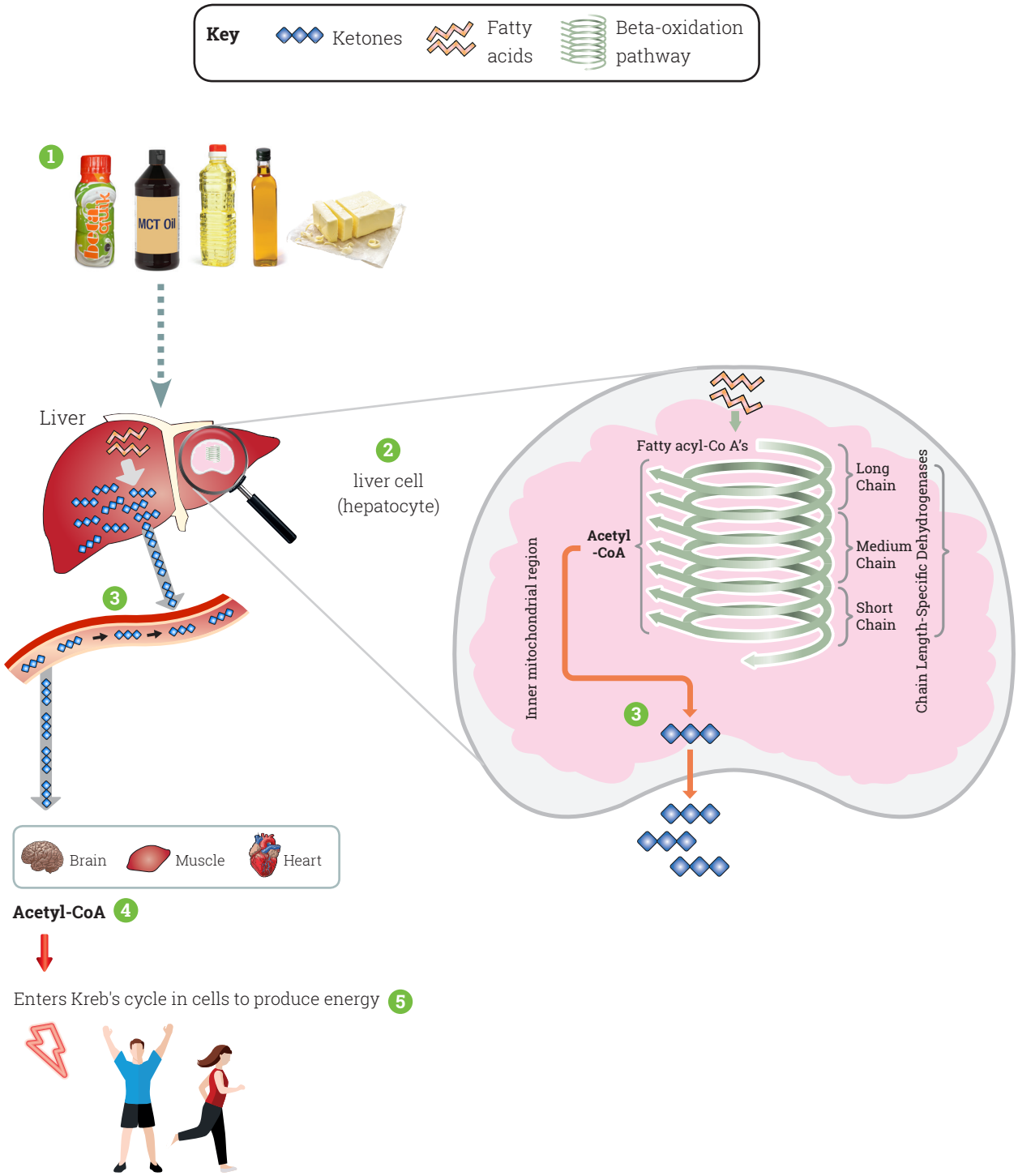


Figure 5 - Ketogenesis - the conversion of ketones by the body into energy whilst on a KD.

1. The very high fat, low carbohydrate intake on the KD provides an abundant mixture of fatty acids.
2. On arrival in the liver hepatocytes after assimilation (Figure 4), fatty acids undergo beta-oxidation. This results in an excess of acetyl-CoA, which is converted, via ketogenesis, into ketones.
3. The ketones are transported in the blood to tissues and organs e.g. the brain, heart and muscles.
4. Here they are absorbed into the cells and converted back into acetyl-CoA.
5. The acetyl-CoA enters the cell mitochondria and is oxidised via the Kreb's cycle to produce energy.



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Vitaflo International Ltd,
Suite1.11, South Harrington Building,
182 Sefton Street, Brunswick Business Park,
Liverpool L3 4BQ, UK

+44 (0)151 709 9020
www.vitaflo-VIA.com

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