

## Medium-chain fatty acids in nutritional therapy: A review

Nur Izzati Zulkanain<sup>a</sup>, Sharaniza Ab-Rahim<sup>b</sup>, Siti Nazrina Camalxaman<sup>c</sup>, Musalmah Mazlan<sup>b,\*</sup>

<sup>a</sup> Institute of Medical and Molecular Biotechnology, Universiti Teknologi MARA, Cawangan Selangor, 47000 Sg. Buloh, Malaysia

<sup>b</sup> Dept. of Biochemistry and Molecular Medicine, Faculty of Medicine, Universiti Teknologi MARA, Cawangan Selangor, 47000 Sg. Buloh, Malaysia

<sup>c</sup> Centre of Medical Laboratory Technology, Faculty of Health Sciences, Universiti Teknologi MARA, Cawangan Selangor, 42300 Bandar Puncak Alam, Kuala Selangor, Malaysia

\* Corresponding author: musalmah6393@uitm.edu.my

### Article history

Received 3 May 2019  
 Revised 10 September 2019  
 Accepted 2 January 2020  
 Published Online 15 June 2020

### Abstract

Medium-Chain Fatty Acids (MCFA) are saturated fats with aliphatic rings of 6-12 carbons. It is widely accepted that the metabolism of MCFA induces ketogenesis in the liver. Ketone bodies have been suggested to produce larger amounts of energy compared to glucose. Its benefit in providing an alternative source of energy has been as one of the strategies to prevent disease development especially those diseases that are associated with glucose metabolism or mitochondrial dysfunction. The current review highlights the nutritional impacts of MCFA and its utilization in disease therapy.

**Keywords:** Medium chain fatty acid (MCFA), medium chain triglycerides (MCT), nutritional therapy, diabetes mellitus type 2, cardiovascular disease

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## INTRODUCTION

Medium chain fatty acid (MCFA) is a saturated monocarboxylic acid that made up of fatty acids with glycerol backbone and aliphatic tails of 6-12 carbon atoms. In comparison, short chain fatty acids (SCFA) have six or fewer carbon atoms while long chain fatty acids (LCFA) have twelve or more carbon atoms [1]. MCFA binds to triacylglycerol forming medium chain triglycerides (MCT). The most common dietary sources of MCT are coconut milk, palm kernel oil and full cream milk products such as butter or goat cheese [2]. Other sources include the oils of rice bran, safflower seed and soya bean. MCFA is also produced by bacterial fermentation. For commercial use, its production involves an open-culture biotechnological process that converts ethanol and SCFA of food waste into MCFA [3].

MCFA has been widely used as nutritional therapy [4-6]. Primarily, MCT is used to reduce the malabsorption of fat and acted as a source of calories in order to optimize nutritional status [4]. Rapid digestion, obligatory oxidation and passive absorption are also the specific nutritional and metabolic effects of MCFA and MCT for the nutrition of young animals [7]. MCFA also possesses antibacterial, anticoccidial and antiviral effects in human and animals. The use of organic acids, essential oils or probiotics together with MCFA will allow these acids to act energetically [8].

## MEDIUM CHAIN FATTY ACIDS

### Metabolism

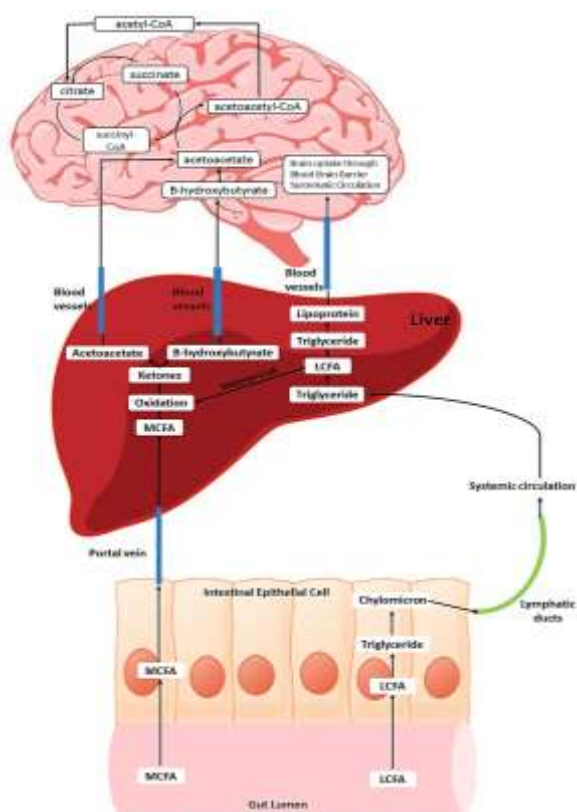
The absorption and transportation of MCT are different from long chain triglycerides (LCT) due to their structural differences [9]. Following digestion in the gastrointestinal tract by lipases, fatty acids of LCT are packaged into chylomicrons which are then transported to

the peripheral circulation through the lymphatic system. On the other hand, the shorter chains of MCFA allow it to be transported directly into the liver without forming chylomicrons [10].

MCFA is metabolized in the liver via  $\beta$ -oxidation. The metabolism of MCFA results in the production of ketone bodies; mainly  $\beta$ -hydroxybutyrate, acetoacetate and acetone (Figure 1). These ketone bodies are converted into acetyl-CoA, the main substrate for the production of ATP in the citric acid cycle [11]. Ketone bodies are able to produce a higher amount of energy compared to glucose because of the differences in their mitochondrial metabolism [12-14].

MCFA is oxidized into ketone bodies in the liver while LCFA metabolism is dependent on the metabolic state of an organism. LCFA needs to be transported by carnitine palmitoyltransferase I (CPT1) into the mitochondria and proceeds with the oxidation process if energy is required. On the other hand, MCFA does not require CPT1 for transportation into mitochondria as it can enter mitochondria directly. Thus, the metabolism of MCFA into the liver can occur rapidly and quickly. Ketone bodies that produced from the oxidation of MCFA are then transported to the brain through the blood-brain barrier (BBB) [11] and other tissues including muscles.

MCFA is also able to cross the mitochondrial membrane of muscles without the mediation of carnitine shuttle system. This makes MCFA a readily available energy source [15]. Nagasaka *et al.* (2018) suggested MCT as an important source of energy for muscle and heart in young children with CD36 deficiency, a disease which usually causes hypoglycemia and myalgia in young children [16]. This is because the lower levels of total ketone bodies and blood glucose can be increased through the supplementation of MCT which will decrease the possibility for hypoglycemia to occur. MCT can also reduce the probability of myalgia by restoring the endurance and tolerance of exercise [16].



**Fig. 1** The metabolism of MCFA versus LCFA. The absorption of MCFA is directly into the portal vein meanwhile LCFA needs to be transformed into Chylomicron before being absorbed into the lymphatic system [11].

## ROLE

Most studies on MCT are focused on the role of MCT in weight loss diet and nutritional management of metabolic disorders. The role of MCT in weight loss is demonstrated by St-Onge and Bosarge (2008) [17]. The authors observed that subjects who consumed MCT were able to reduce their weight by an average of 1.7 kg more than those subjects consumed olive oil. They suggested that MCT has a higher potential to burn more calories in human compared to LCT and meals containing MCT have fewer calories compared to LCT. This is because, the oxidation of shorter MCT is greater compared to LCT, thus, reducing the chances of fatty acids to be deposited in adipose tissues [17]. The characteristics of MCFA versus LCT supplementations have been widely studied *in vivo*. Animal study revealed that rats fed with MCT have smaller adipose tissue mass compared to rats fed with LCT [18, 19]. Studies in human also showed that MCT increased oxidation of fat and thermogenesis more than LCT in both short and long-term periods of supplementation [20, 21]. Moreover, consumption of both LCT and MCT not only have the potential to induce the reduction of body weight but they do so without changing lipid profiles [22]. However, the consumption of MCT may result in greater satiety due to the difference in its digestion and absorption as well as in the consequent effects on  $\beta$ -oxidation [23-25]. MCT is absorbed directly into the portal vein and then it is oxidised at a higher oxidation rate which results in muted lipaemia [24].

MCFA is also recommended to be used in "Ketogenic diet" (KD). Ketogenic diet has been used since the 1920's in the treatment of epilepsy [26, 27]. It is a high fat, low carbohydrate diet used to increase the levels of circulating ketones in the body. The purpose of this controlled diet is to increase the dependence on fat compared to glucose for energy. Classic ketogenic diet is derived from LCT but since the 1970s, this diet has been started to use MCT as an alternative fat source [28]. Compared to LCT, MCT is able to produce more ketones per kilocalories of energy. The increased ketogenic potential allows the preservation of circulating ketones in the body. Thus, less

total fat is needed which enables more carbohydrates and proteins to be included in the diet.

## NUTRITIONAL THERAPY

Nutritional therapy is an evidence-based therapeutic approach that aimed to promote optimum health and to alleviate chronic disorders by improving the physiological functions of the body. Its main concept is to prevent and reverse diseases such as diabetes, obesity and heart disease by using food as therapy. The therapeutic ability of the food can be measured by measuring the nutrients and anti-nutrients contents in the consumed foods [29].

Nutritional therapy is gaining importance due to scientific and technological advancements. Although most of the therapies are focused on patients with metabolic syndrome including diabetes mellitus, therapy has still been introduced to more disorders including cardiovascular disease, Alzheimers disease, Parkinsons disease, cancer and traumatic brain injury.

## Type 2 Diabetes

Diabetes mellitus type 2 (T2D) is a long-term metabolic disorder associated with high blood sugar and insulin resistance. A person with insulin resistance will convert most of carbohydrates into fats in the liver instead of oxidising them into energy [30]. Most of the fats converted from the dietary carbohydrates enter the circulation as saturated fats. When dietary carbohydrate is limited to a level in which the carbohydrate is not necessarily converted into fat, the insulin resistance signs and symptoms are improved or disappeared totally [31].

A study of 40 overweight T2D subjects in which half of them consumed MCT while the other half consumed LCT for 90 days was carried out by Han *et al.* (2007) [32]. Significant improvements were noted by these authors in the subjects given MCT compared to LCT specifically in body weight reduction and waist circumference, reduction in insulin resistance, increased concentration of serum C-peptide and a decreased serum cholesterol level. These results were in accordance with the study by Deng *et al.* (2009) on the effects of MCT on insulin resistance in T2D subjects with LCT as control [33]. However, Hoeks *et al.* (2012) observed no significant effect on triglyceride-rich lipoprotein metabolism profile in insulin resistance subjects supplemented with MCT for six hours [34]. A longer duration of MCFA supplementation may be needed since another study that supplemented the subjects for 14 days showed significant improvement towards the systolic function and lipidomic profile in diabetes mellitus type 2 patients [35].

The role of MCT in weight and waist circumference reduction may be due to the efficiency of its absorption directly into the portal blood before being metabolised by the liver. The efficient uptake and metabolism in the liver make less fatty acids from MCT that available in the blood and hence, less fats are stored [4].

## Alzheimers disease

Alzheimers disease (AD) is a neurodegenerative disorder that causes progressive loss of memory and decrease in cognitive function, disorientation and behavioral changes. AD was first described in 1907 by Alois Alzheimer who noted the presence of cognitive impairment with senile plaques formation and neurofibrillary tangles [36-38]. The main component of senile plaque is beta amyloid protein which is neurotoxic. Neurofibrillary tangles are clumps of unbound *Tau* proteins which are believed to initiate cellular dysfunction and death [39]. The function of *Tau* proteins is to stabilize the microtubules in nerve axons [40]. When *Tau* proteins are failed to function, the microtubules become unstable and start to disintegrate [39]. Other factor that has been suggested to cause AD is abnormality in glucose metabolism.

The impairment of glucose brain metabolism has been suggested as a contributing factor for the progression of AD [41, 42]. Impairment of glucose metabolism is observed to be highly correlated with clinical disabilities in dementia [41, 42]. Normally, metabolic changes at the molecular level are closely linked with glucose consumption and oxidative phosphorylation. Brain metabolism dysregulation can result in the excess production of reactive oxygen

species (ROS). Although the production of ROS is a normal process of the electron transport chain in the mitochondria, the excess production of ROS in mitochondrial dysfunction may lead to excitotoxicity and oxidative stress in the brain [43].

AD and T2D are closely associated whereby, people with T2D have a higher chance to develop AD [44]. The brains of these patients are thought to lose the ability to use glucose as the energy source. In T2D, cells are not able to use glucose because of resistance to insulin action. Therefore, ketone bodies play an important role as the alternative energy source for the brain. A pilot trial study by Nathan and Panjwani (2017) showed that supplementation of MCT was able to reduce insulin resistance in AD and stabilize the cognitive function [45]. They also observed the improved cognitive function in mild cognitive impairment (MCI) patients. These authors suggested that the ketone bodies also could act as peroxisome proliferator-activated receptor (PPAR) agonist which would reduce amyloid beta burden [45].

Axona, a prescription medical food consisting of MCT (Accera Inc., Boulder USA), has been suggested to improve the energy content needed by the brains of mild to moderate AD patients. Ohnuma et al. (2016) administered Axona to AD patients with mild to the moderate cognitive impairment for three months and examined the changes in cognitive functions using the Mini-Mental State Examination (MMSE) and AD assessment-scale scores [46]. The authors observed that Axona did not improve cognitive function in these patients except in ApoE4-negative patients with baseline MMSE score of more than or equal to 14. They therefore concluded that Axona might be beneficial for patients with MMSE score of  $\geq 14$  together with a lack ApoE4 allele [46]. Another study involving 20 Japanese patients with mild-to-moderate AD who consumed 20 g of MCT-based ketogenic formula for 8 weeks showed significant improvement in their immediate and delayed logical memory tests compared to their initial baseline scores. Up to 12 weeks of supplementation, the patients showed significant improvements on verbal memory and processing speed [47].

### Cardiovascular disease

Cardiovascular disease (CVD) is a class of diseases that involves heart or blood vessels. CVD includes heart attack, chest pain or stroke and other heart diseases [48]. It is still doubtful whether foods with low carbohydrates and high-fats are able to benefit the cardiovascular. Some studies demonstrated that reduction of carbohydrate consumption to the levels that induced ketogenesis, improved blood lipid profiles [49-51]. MCT consumption has also been observed to reduce the total cholesterol and increase high-density lipoprotein levels [52, 53], as well as to result in increased thermogenesis and decreased deposition of fat [54]. Since the total cholesterol level is reduced, the potency for cardiovascular disease such as atherosclerosis to occur can be minimised. In an animal study, rats supplemented with fish oil, MCT and monounsaturated fatty acid (MUFA) showed that MCT or MUFA was effective in reducing risk factors for cardiovascular disease [55].

### Parkinsons disease

Parkinsons disease (PD) is a neurodegenerative disease caused primarily by decrease levels of dopamine as a result of degeneration of dopaminergic neurons in substantia nigra region of the brain [56]. Dopamine is a neurotransmitter involved in the controls of coordination and movement. Although the cause and pathogenesis of the death of dopaminergic neurons remain unknown, it is suggested that environmental and genetic factors may be involved. According to a study carried out by Eriksen et al. (2005), the impairments in mitochondrial and ubiquitin-proteasome system (UPS) might be one of the factors contributing to the progression of PD [56].

Most studies on PD use animal models and the neurotoxin MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine). Exposure to MPTP causes degeneration of dopamine neurons which mirrors the clinical features of human PD [57]. A number of studies showed that ketogenic diet was able to improve PD induced by MPTP. Mice fed ketogenic diet were shown to have reduced motor dysfunction when exposed to MPTP, probably by the inhibiting MPTP-induced

microglial activation in the substantia nigra [58]. The use of ketogenic diet together with the administration of pramipexole was observed to enhance motor function in parkinsonian rats [59]. As reviewed by Gasior et al. (2006), calorie restriction has been found to be resistance to the toxicity of MPTP in dopaminergic neurons of the substantia nigra and improved motor dysfunction [60]. In addition, according to a study carried out by de Lau et al. (2005), it was suggested that the risk for developing PD might be lowered with the intake of foods containing higher amounts of essential fatty acids [61].

Coconut oil which contains high concentrations of MCT is believed to improve brain function and the nervous system. In a study carried out by Mischley et al. (2017), coconut oil is one of the dietary foods that resulted in lower rates of PD progression [62]. This may due to the properties of coconut oil that can improve lipid profile and increase antioxidant defenses [63, 64].

Despite the positive findings on the use of MCT in PD, it still exhibits concerns on its use since it causes bloating and abdominal discomfort [65]. Schwartz et al., (1989) reported that consumption of natural KD in combination with MCT produced similar result to when natural KD was consumed alone, indicating that MCT might not be the cause for the abdominal discomfort [66]. Until now, there is still lack of data on the use of MCT/MCFA in the treatment of PD. Currently, majority of the nutritional therapies involving PD are based on the use of natural ketogenic diet or dietary restriction that promotes the production of ketones naturally from endogenous fatty acids.

### Cancer

Cancer is a multifactorial disease which often resulted from genetic interactions with agents such as physical, chemical, and biological carcinogens [67-69]. Previous studies have shown that the main source of energy for cells to make new cells is glucose [70-72]. Cancer cells are shown to use a higher amount of glucose compared to normal cells and these cells are reported to have increased rates of glutaminolysis and synthesis of fatty acids. Cancer glycolysis is also responsible for the production of ATP and biosynthesis [73]. This explains the Warburg Effect in which glucose undergoes fermentation to form lactate even in the state of completely functioning mitochondria [74]. In addition, studies have discovered that mitochondria in cancer cells can use lactate as fuel for biochemical reactions and for the production of compounds involved in cell growth [75-77].

Many studies have suggested that MCFA is anticarcinogenic. An *in vitro* study on the effect of supplementing goat milk fatty acids (which contain the MCFAs capric, caprylic and caproic acids) on human colorectal, skin and breast cancer cells showed the decreased cancer cell viability by 70% to 90% compared to untreated cells. This has been attributed to the ability of MCFA to downregulate the regulatory genes involved in cell cycle and to upregulate genes involved in apoptosis [78]. A similar observation was noted by Eur et al. (2014) on malignant prostate cancer cells [79]. These authors also showed that the cancer cells were not able to metabolise MCT in the absence of glucose [79]. When the antineoplastic properties of butyrate (SCFA) and lauric acid (MCFA) on colon cancer cells were compared, lauric acid was shown to induce apoptosis in Caco-2 colon cancer cell and IEC-6 normal cell instead of butyrate [80].

Medium chain fatty acids (MCFAs) and ketone bodies produce acetyl-CoA which is then further metabolised to produce energy. Kadochi et al (2017) compared the effect of treating mouse CT26 colon cancer cells with 3-hydroxybutyric acid and lauric acid (MCFA) [81]. The study observed that addition of 3-hydroxybutyric acid or lauric acid was able to inhibit the growth of colon cancer cells by converting energy metabolism from glycolysis-lactate fermentation to oxidative phosphorylation [81]. Oxidative phosphorylation is a major source of intracellular oxidative stress that may induce cell and tissue apoptosis [82]. Hence, tumor cells lack the ability to use and metabolise fatty acids or ketones for energy and the conversion to oxidative phosphorylation may be harmful to the cells [83]. There is still lack of randomized controlled trials on the effect of MCFA on patients with cancer. However, MCFA and ketogenic diet through glucose restriction are shown to have positive effects in certain cancers especially in patients with advance metastatic tumours [84].

## Traumatic brain injury (TBI)

Traumatic Brain Injury (TBI) is defined as brain damage due to external impact or force which leads to the impairment of brain function and physical damage, which can be temporary or permanent [85]. The severity of TBI can be classified into three categories which are mild, moderate and severe. Mild TBI can be classified through the loss of consciousness (LOC) for less than 30 min while for moderate TBI, the LOC is between 30 min to 24 h. Loss of consciousness for more than 24 h of LOC is classified as severe TBI [86]. TBI occurs in two different stages before a patient died from TBI. The first stage is primary brain injury where damages occur right after the trauma in which the tissues and blood vessels are damaged, compressed or stretched [87]. These events will lead to secondary injury which then includes blood-brain barrier damage, excitotoxicity caused by free radicals and glutamate, the increase in ions (calcium and sodium) into neurons and mitochondrial dysfunction [88, 89]. Besides that, hypoxia (decreasing of oxygen in the brain), hypercapnia (increasing of cerebral blood flow), hypotension (loss of cerebrospinal fluid) and intracranial hypertension (raising of pressure within the skull) are also other factors contributing to the secondary injury of TBI [90-92].

A study on calorie restriction diet has noted that ketone bodies improved mitochondrial function leading to decreased reactive oxygen species production and increased energy production [93].  $\beta$ -hydroxybutyrate has been shown to prolong the survival of rat models of hypoxia, anoxia and global ischemia [94]. The same study also showed that  $\beta$ -hydroxybutyrate was able to reduce the size of infarct induced by blocking the middle cerebral artery. Adult rodents with cortical impact injury starved for 24 hours were observed to exhibit cortical tissue preservation, improved cognitive outcome and improved mitochondrial function [95]. TBI is usually associated with impairment of cerebral energy production due to prolonged reduction in glucose metabolism. Therefore, ketone metabolism will function as a source of energy to improve the cerebral injury [94]. There is however, limited study involving the use of MCT/MCFA on TBI therapy. The treatment of TBI through MCT/MCFA is suggested by the positive effects possessed by ketone bodies [96].

## CONCLUSION

In summary, MCFA may be an easy, safe and cost-effective nutritional approach to treat diseases involving derangement of glucose metabolism or mitochondrial dysfunction. However, despite clinical and medical researches in this area, there are still gaps that need to be further investigated. Although there are few observations that showed MCFA and the ketone bodies that are produced, may be beneficial, there is still insufficient data to validate its use for therapy. Improvement in knowledge on the metabolism and effect of MCFA is necessary for the advancement of nutritional strategies using MCFA for the prevention and treatment of these diseases.

## ACKNOWLEDGEMENT

This research was funded by MITRA PERDANA GRANT, grant number 600-IRMI/PERDANA 5/3/MITRA (001/2018)-01. The authors would like to thank Sime Darby Research Sdn Bhd and Universiti Teknologi MARA for the support and grant provided to carry out this project.

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