Cellular and Physiological Effects of Medium-Chain Triglycerides

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Abstract: From a nutritional standpoint, saturated triglycerides with a medium (6 to 12) carbon chain length (MCT) have traditionally been regarded as biologically inert substances, merely serving as a source of fuel calories that is relatively easily accessible for metabolic breakdown compared with long chain triglycerides (LCT). This quality of MCT has been shown to offer both benefits and risks depending on the clinical situation, with potential positive effects on protein metabolism in some studies on one side, and an increased risk for ketogenesis and metabolic acidosis on the other. At another level, studies regarding lipid effects of MCT on the immune system, as with LCT, so far have yielded equivocal results, although there is a recent experimental evidence to suggest that MCT posses immune modulating properties and should in fact be regarded as bioactive mediators. Most of this information comes from studies where effects of MCT have been compared with those of LCT in lipid emulsions, as part of parenteral (intravenous) nutrition formulations. Unfortunately, the relevance of these observations for clinical practice remains largely unclear because adequately powered trials that clearly point out the position of MCT in relation to structurally different lipids have not been performed. In the present paper we review the experimental and clinical evidence for cellular and physiological effects of nutritional MCT. In addition, studies describing possible mechanisms behind the observed effects of MCT will be discussed.

INTRODUCTION: LIPID STRUCTURE

The recognition that nutritional compounds regulate such important biological functions as immune and inflammatory responses has resulted in new areas of research as well as commercial interest in recent years. This notion especially applies to lipids, the macronutrient category that is the major source of fuel calories and building blocks for cellular components. Nearly all of the 100-200g of fat that inhabitants of Western countries consume per day are triglycerides (TG), consisting of three fatty acids (FA) attached to a glycerol backbone. FA can be characterised based on carbon chain length and the number and place of single (saturated) and double (unsaturated) bonds. FA carbon chain length in biological substances may vary from 4 up to 30 C atoms, and thus FA and corresponding TG can be classified as short chain (up to 4-C), medium chain (6 to 12-C) Fig. (**1**); long chain (14-22C) or very long chain (24-C and longer) [1].

Depending on the place of the first double bond from the terminal methyl end of the carbon chain, long chain poly-unsaturated FA (PUFA) belong to the ω-3, ω-6, ω-7 or ω-9 families Fig. (**2**). Importantly, the ω-3 and ω-6 classes, which are found in fish oil and soybean- or safflower oils, respectively, establish essential FA in man [2]. The non-essential monounsaturated oleic acid (C18:1), present in olive oil, is a representative of the ω9 class. Recently, synthetic structured lipids (SL) have been developed and introduced in clinical practice. SL are made by the random transesterification of medium-, long- or very long chain FA in the 1-, 2- or 3 position of the triglyceride to the glycerol backbone [3-5]. The metabolic and immunologic effects of MCFA-containing SL have been reviewed recently [6, 7].

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MEDIUM CHAIN TRIGLYCERIDES: METABOLIC EFFECTS

For nutritional use, MCT are synthesised from fractionated coconut or palm kernel oils by steam hydrolysis, subsequent distillation of the free saturated 6 to12-C FA, and reesterification of the FA to glycerol [8]. The nomenclature of MCFA and MCT is shown in Table 1.

MCT have since long been advocated as a superior nutritional substrate compared to LCT based on their special physicochemical properties, resulting in simpler and more rapid metabolic pathways [9]. Indeed, MCT are approximately 100 times more water-soluble than LCT, a result of the shorter hydrocarbon chain length, with a lesser interfacial tension against the aqueous phase [10]. Also, MCT are hydrolysed faster than LCT, and while LCFA have to bind to albumin to cross capillaries, MCFA do not depend on protein binding for passage into the cell. MCFA, similar to LCFA, are metabolised by mitochondrial β-oxidation to acetyl- CoA, which then enters the citrate cycle. However, in contrast with the latter, MCFA do not require carnitine for transport into mitochondria, with the possible exception of a small percentage of caprylic acid (C8:0) [11]. MCT appear to be a superior energy source in clinical situations of depletion, as in critically ill patients, where carnitine is in the subnormal range. Finally, MCFA, and especially C8:0 and C10:0, unlike LCFA are also oxidised in the peroxisomal system [12].

Data on metabolic effects of MCT in enteral nutrition come from studies in patients with impaired fat digestion, diminished absorptive capacity or lymphatic transport. The application of MCT in these clinical situations results from the notion that MCT are more rapidly hydrolyzed in the intestinal lumen than LCT and do not require bile or pancreatic lipase for absorption [10, 13, 14]. Also, in contrast with LCFA, MCFA are directly transported into the

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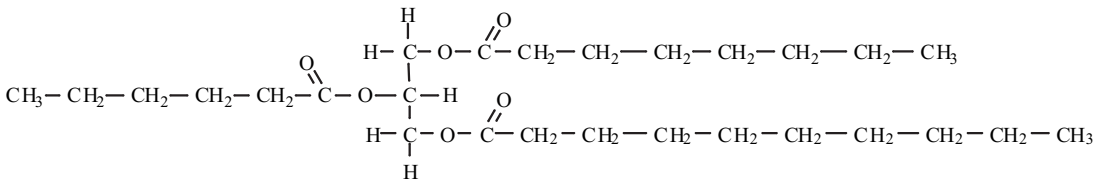

Fig. (1). Medium chain Triglyceride.

portal venous blood, are not stored as body fat, but instead are taken up in peripheral tissues. In healthy overweight male human subjects, the consumption of a diet rich in MCT has recently been shown to result in a greater loss of adipose tissue when compared with LCT [15]. In another study, the authors of this group showed, at least for adipose female subjects, that this observation might be explained by the fast rate of oxidation of MCT, resulting in increased energy expenditure when compared with LCT [16]. Thus, in the view of the authors, MCT should be regarded as potential agents in the prevention of adipositas [17]. An increased plasma clearance of MCT is suggested by the observation that upon oral administration, MCT give rise to decreased triglyceride concentrations compared with LCT [18]. Accordingly, the half-life time of MCT in plasma estimates 17min., compared with 33min. for LCT [8, 19].

Most of the information that is available on MCT is based on studies where lipids have been used as an emulsion, i.e. an aqueous solution of microscopic droplets about 0.3μm in size, as part of total parenteral nutrition (TPN) [6, 20]. Designed to simulate naturally occurring chylomicrons, the droplets of such an emulsion consist of a lipid core surrounded by a surface layer of phospholipids. The latter establish the emulsifier, which is most often derived from egg yolk and renders the lipids soluble in the aqueous environment.

Since the introduction of TPN in the 1960s, a number of structurally different emulsions have been developed [21]. An overview of characteristics of clinically applied lipid emulsions is shown in Table 2. So far, soybean-derived LCT have remained the most widely used lipid source. These LCT are primarily composed of ω-6 PUFA, with large amounts of α-linoleic acid (C18:2ω6), the parent FA of the ω-6 family and a precursor of arachidonic acid (20:4ω- 6), and relatively small amounts of the ω-3 parent α-linolenic acid (C18:3ω-3). In the 1980s, MCT were introduced in Europe as part of physical lipid mixtures containing 50% long- and 50% medium chain triglycerides (LCT/MCT), based on metabolic concepts described above, as well as in order to decrease the high content of ω-6

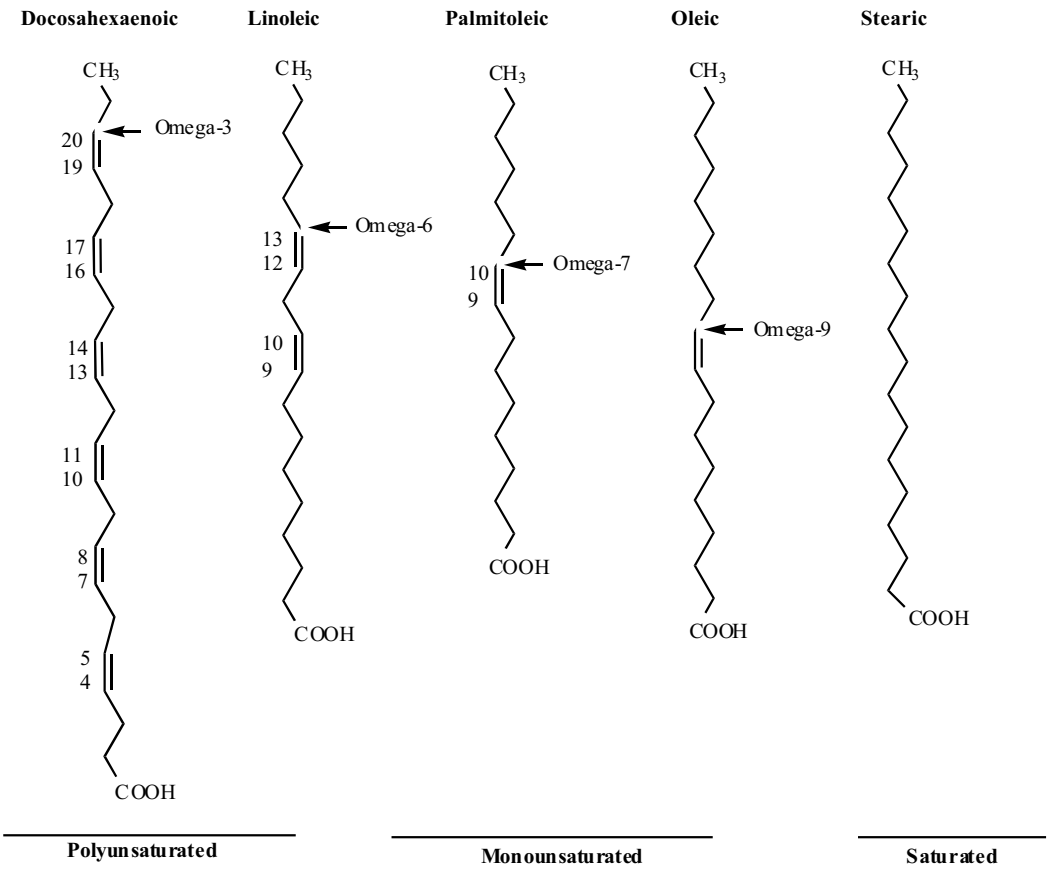

Fig. (2). Structure of fatty acids: Classified on the basis of saturation / unsaturation and position of first double bond from methyl terminal

PUFA that was considered to underlie supposed immune-suppressive effects of pure LCT [22]. On the other hand, it proved necessary to add LCT to MCT for practical use as pure MCT are not tolerated in humans. This is a direct result of their rapid metabolic breakdown with the generation of ketone bodies that leads to an increased risk for the development of metabolic acidosis, especially in clinical conditions where ketosis is a problem, such as diabetes. Also, essential FA by definition are all LCT and therefore not provided by pure MCT [20, 23, 24].

Table 1. Nomenclature of Medium-Chain Fatty Acids (MCFA) and Triglycerides (MCT)

MCFA		MCT	
Caproic acid	C6:0	Tricaproin	TG 6:0
Caprylic acid	C8:0	Tricaprylin	TG 8:0
Capric acid	C10:0	Tricaprin	TG 10:0
Lauric acid	C12:0	Trilaurin	TG 12:0

Apart from these considerations it has been shown recently that MCT, which are mainly located on the outside of the lipid droplets of a physical LCT/MCT mixture, increase the physicochemical stability of the emulsion [25]. As can be expected from emulsions containing saturated MCFA, LCT/MCT when compared with pure LCT is less susceptible to lipid peroxidation, a process that can result in significant tissue damage and haemolysis, resulting in inflammatory responses and multiple organ dysfunctions [26].

Dietary TG are transported through the lymphatic system into the bloodstream as chylomicrons that subsequently become covered by phospholipids and apoproteins. Similarly, upon intravenous administration the fat droplets of a lipid emulsion become covered by lipoprotein-derived apoproteins and are metabolised similarly to natural chylomicrons, with lipoprotein-lipase-mediated TG hydrolysis [27, 28]. While LCT infusion has been shown to increase plasma cholesterol, due to the exogenously administered cholesterol as well as cholesterol uptake from high-density lipoproteins, this effect is slowed down when MCT are included [29]. As mentioned before, MCT have been shown to displace LCT at the lipid droplet surfaces. This phenomenon selectively enhances their interaction with water-soluble proteins, such as lipases [25, 30].

So far, MCT emulsions have not become commercially available in the US, despite the fact that safety of and tolerance to LCT/MCT have been demonstrated in severely ill, malnourished patients, and patients with diverse clinical conditions [8, 13, 31-36]. Also, in accordance with the concepts described above, LCT/MCT have been shown to be clear and deliver energy more rapidly, to induce less

Table 2. Composition and Characteristics of Frequently Used Lipid Emulsions, According to Manufacturer

	LCT	**LCT/MCT**	**SL**
	Intralipid	Lipofundin	Structolipid
fractionated soy bean oil (g/l)	200	100	0
medium-chain triacylglycerols (g/l)	0	100	0
fatty acid (% w/w of total)			
caproic acid (C6:0)	-	0.5	0.1
caprylic acid (C8:0)	-	28.5	23.4
capric acid (C10:0)	-	20	10.4
lauric acid (C12:0)	-	1	0.2
palmitic acid (C16:0)	9	6.5	7.5
stearic acid (C18:0)	5	2	3.2
oleic acid (C18:1)	25	11	16.2
linoleic acid (C18:2)	55	26	33.3
α-linolenic acid (C18:3)	8	4	4.2
arachidonic acid (C20:4)	1	0.5	-
structured triacylglycerols (g/l)	0	0	200
mean molecular triglyceride weight	865	634	683
fractionated egg phospholipids (g/l)	12	12	12
glycerol (g/l)	22.5	25	22.5
pH	8.0	6.5-8.5	6.5 - 8.5

hyperlipaemia, and to interfere less with linoleic acid metabolism compared with pure LCT [8, 37-40]. The latter concern was raised by studies showing that administration of LCT resulted in accumulation of α-linoleic acid and reduced ω-3 FA content of cellular membranes, with negative effects on immune cell function [41-43]. In human patients, the intravenous administration of LCT/MCT during several weeks has been shown to result in a fatty acid profile in plasma phospholipids that resembles the natural situation more closely than is the case with LCT, with regard to ω-6 FA concentrations. Inhibition of Delta-5-desaturase by LCT but not MCT was suggested to underlie these observed effects of LCT [44].

Clinical advantages of LCT/MCT over LCT have been reported in surgical patients, with improved anabolic protein metabolism (nitrogen balance), reduced weight loss and less fatty infiltration of the liver [34, 45-48]. Also, LCT/MCT seem not to impair pulmonary function [49], while LCT have been associated with the development of acute respiratory events, possibly due to fat overload [50, 51]. However, other studies have not consistently demonstrated advantages of LCT/MCT over LCT in this respect, with the quantity and rate of lipid administration possibly being the critical factor [52-54]. While administration of LCT has been shown to potentiate endotoxin-induced coagulation activation, suggesting a potential thrombotic complication risk in patients with infections, other studies comparing LCT/MCT and LCT in critically ill patients have not reported any coagulation disorders [55, 56]. In contrast, disadvantages of LCT/MCT over LCT, as indicated by higher insulin and plasma free FA concentrations, have also been reported [32, 36, 57, 59].

For a recent overview of metabolic aspects of MCFA-containing SL for intravenous administration we refer to a recent paper, showing beneficial effects of SL on protein metabolism and rapid lipid clearance in both human and animal studies [7]. Infusion of MCFA-containing SL in humans has been shown to be well tolerated and more rapidly oxidised and cleared from the plasma, without hyperlipidaemia or metabolic acidosis due to ketosis, compared with LCT and LCT/MCT [3, 60]. Surprisingly, a study on the biodistribution of radioactively labelled emulsions showed that emulsions with MCFA in the 1, 3 position were removed slower from the circulation than those with LCFA in the 1, 3 position, indicating that the type of core material influences the circulation time of lipids [5]. A beneficial effect of SL was seen in a study regarding liver morphology where livers of SL and LCT fed rats showed less fatty change than those of lipid-free and MCT groups [61]. SL made from MCFA and ω-3 FA have demonstrated inhibited tumour growth and improved maintenance of body weight and nitrogen balance when compared with pure LCT in rat cancer and burn models, indicating that dietary fats may influence tumour protein kinetics [62-64].

MEDIUM CHAIN TRIGLYCERIDES AND INFECTIOUS COMPLICATIONS*:* CLINICAL STUDIES

Initial concerns with respect to the effect of lipids on immune functions were raised after studies with intravenous LCT suggested impaired leukocyte functions [65]. Indeed, intravenous LCT administration has been shown to lower the incidence of graft-versus-host-disease in patients following bone-marrow transplantation, indicating immune suppression [66]. The incidence of infections related to phagocytic leukocyte dysfunction, such as pneumonia and wound abscesses, appears to be increased by lipids as suggested by findings in the Veterans Affairs Study [67]. The question of whether the emulsion type affects the infectious complication rate has been addressed in a study comparing LCT with LCT/MCT in critically ill patients in need of TPN. Neither toxic nor infectious or metabolic complications were encountered in either group, nor there was an evidence for any advantageous effects of LCT/MCT over LCT [68]. When the effect of perioperative LCT/MCT-based TPN in addition to an oral diet in cancer patients was compared to an oral diet alone, a decreased morbidity and infectious complication rate was observed [69]. In surgical cancer patients, FO/MCT-derived structured lipids have been shown to reduce the number of infectious complications, possibly due to effects on leukocyte eicosanoid metabolism [70]. The effects of MCT in enteral nutrition on survival in critical illness remains limited to an animal study, where in rats the administration of enteral MCT was found to result in increased survival following endotoxin(LPS)-challenge [71].

Overall, the contradicting results of the limited number of studies with clinical endpoints indicate that the question of whether the use of lipids, and more specifically the lipid type (including MCT), significantly affects the incidence of infectious complications that is associated with the use of TPN can not be answered. There is a strong need for clinical trials with adequate power and follow up periods.

MEDIUM CHAIN TRIGLYCERIDES: EFFECTS ON IMMUNE FUNCTION

The defence of the human body against invasion by pathogens is established by a complex interplay of components and mediators of the non-specific (innate) and the specific (adaptive) immune system [72]. The non-specific branch comprises humoral and cellular components, such as the complement system and various phagocytes (granulocytes, macrophages) and natural killer lymphocytes. The specific immune response is established by mononuclear cells (B- and T-lymphocytes, monocytes) and involves the production of humoral signalling and effector substances such as cytokines and immunoglobulins (by T- and B-lymphocytes, respectively), as well as microbial phagocytosis, killing and antigen presentation (by monocytes, macrophages and dendritic cells). Monocytes and macrophages constitute the reticulo-endothelial system (RES), or mononuclear phagocyte system (MPS).

Lipid Effects on Neutrophil Functions

Neutrophilic granulocytes, or neutrophils, establish our first line of defence against invading microorganisms. The neutrophil response to activation is a multistep process that includes adhesion to vascular endothelial surfaces and subsequent extravascular migration (chemotaxis) into inflamed tissue, and finally, microbial ingestion

Table 3. Effects of Lipids on Leukocyte Migration (Cells other than Neutrophils are Indicated) p: Patients; v: Volunteers; ↑: Increase; = no Effect; ↓: Decrease

Author, year	Subjects	Design	Lipid, dose, time)	Outcome
Waitzberg, 1997	Human cancer p	*in vivo*	LCT; LCT/MCT 10% 0.08 g/kg/h; 48h	monocyte = neutrophil: =
Bellinati-Pires, 1992	Human v	*in vitro*	LCT; LCT/MCT, MCT; 20 mg/ml; 0.5h	LCT: = (LCT)/MCT: ↓
Waitzberg, 1996	Rat	*in vivo in vitro*	LCT; LCT/MCT 10% 1-1.5 ml/h; 44 h 20 mg/ml; 0.5h	*in vivo*: all: = *in vitro*: LCT/MCT: ↓ LCT =
Monico, 1988	Human v	*in vivo*	LCT/MCT 10% 120 ml/h; 5-7 h	=
Waitzberg, 1992	Rat E.coli peritonitis	*in vivo*	LCT; LCT/MCT 10% 5 ml/kg/h; 44 h	=
Wanten, 2000	Human v	*in vitro*	LCT;LCT/MCT;MCTSL (2.5 mmol/l; 1 h)	LCT, SL = LCT/MCT, MCT ↓

(phagocytosis) and killing by means of reactive intermediates, such as oxygen radicals.

Neutrophil Adhesion

So far, one *in vitro* study has included MCT when evaluating the effects of structurally different lipids on neutrophil adhesion [73]. MCT, in contrast with LCT and SL, increased the expression of β_2 integrin adhesion (comprising CD11a to d/CD18) and degranulation markers (CD63, CD66b) on the cellular membrane. Also, increased neutrophil adhesion to intercellular adhesion molecule-1 (ICAM-1)-coated latex beads and increased shedding of L-selectin (CD62L) was observed after neutrophil exposure to MCT, but not with LCT and SL. All of these phenomena are compatible with neutrophil activation and were observed within 15min of exposure to MCT, in a lipid concentration range (0.6 - 5 mmol/L) that is clinically relevant in patients on TPN. Interestingly, whereas the expression of CD11b/CD18, a receptor for the opsonic fragment of the third component of the complement system (iC3b), was increased by MCT but not LCT or SL, the expression of the receptor for the Fc region of IgG (FcγRIII, CD16) was not influenced by either lipid.

Neutrophil Migration (Table 3)

LCT/MCT and MCT, contrary to LCT, have been shown to decrease neutrophil migration *in vitro* [74]. These findings have been corroborated recently in a study where LCT/MCT and MCT decreased random neutrophil migration and stimulus-induced chemotaxis in a concentration-dependent manner, whereas LCT and SL exerted no effects [75]. Others have observed no effects of LCT and LCT/MCT in the *in vivo* setting [76, 77]. Decreased migration *in vitro*, and unaffected mobility *in vivo* has also been reported for LCT/MCT in animal studies [78, 79].

Neutrophil Phagocytosis and Reticulo-Endothelial System (RES) Function (Tables 4 and 6)

When LCT/MCT were compared with LCT *in vivo* in cancer patients, phagocytosis remained unaffected with either emulsion [77], whereas *in vitro* MCT displayed a detrimental effect [80]. In contrast, these investigators have found rat leukocyte phagocytosis with LCT to be decreased *in vivo*, when compared with LCT/MCT [81].

In a recent study comparing neutrophil ingestion of the fungal pathogen *Candida albicans* under influence of various 5mM lipid emulsions, no differences in yeast-neutrophil association after incubation in LCT, LCT/MCT,

Table 4. Effects of Lipids on Phagocytosis and Reticulo-Endothelial System (RES) Function (Cells other than Neutrophils are Indicated) p: Patients; v: Volunteers; ↑: Increase; = no Effect; ↓: Decrease

Author	Subjects	Design	Lipid (time)	Outcome
Waitzberg, 1997	Human cancer p	*in vivo*	LCT; LCT/MCT 10% 0.08 g/kg/h; 48 h	monocyte = neutrophil =
Bellinati-Pires, 1993	Human v	*in vitro*	LCT;LCT/MCT;MCT 10%; 20 mg/ml;0.5h	LCT: = (LCT/)MCT ↓
Waitzberg, 1996	Rat	*in vivo in vitro*	LCT; LCT/MCT 10% 1-1.5 ml/h; 30h 20 mg/ml; 0.5h	*in vivo*: all: = *in vitro*: LCT/MCT: ↓ LCT =
Waitzberg, 1992	Rats E.coli peritonitis	*in vivo*	LCT; LCT/MCT 10% 5 ml/kg/h; 44h	=
Monico, 1988	Human v	*in vivo*	LCT/MCT 10% 120 ml/h; 5-7 h	=
Wanten, 2001	Human v	*in vitro*	LCT;LCT/MCT;MCT; SL 2.5 mmol/l; 1h	All =
Kuse, 2002	Human, p liver Tx	*in vivo*	LCT; LCT/MCT	RES function recovery with LCT/MCT > LCT
Pscheidl, 1995	Rat	*in vivo*	LCT/MCT; SL	RES function with SL > LCT/MCT

Table 5. Effects of Lipids on Microbial Killing and Oxygen Radical Production (ORP) by Leukocytes (Cells other than Neutrophils are Indicated) p: Patients; v: Volunteers; ↑: Increase; = no Effect; ↓: Decrease

Author	Subjects	Design	Lipid	Outcome
Waitzberg, 1997	Human cancer p	*in vivo*	LCT; LCT/MCT 10% 0.08 g/kg/h; 48 h	monocyte: ORP, killing = neutrophil: ORP, killing =
Waitzberg, 1992	Rats	*in vivo*	LCT;LCT/MCT;MCT 10%; 5 ml/kg/h; 44h	All: killing =
Bellinati-Pires, 1993	Human v	*in vitro*	LCT;LCT/MCT;MCT 10% 20 mg/ml; 0.5h	LCT: ORP , killing = LCT/MCT: ORP, killing ↓
Wu, 1998	Human v	*in vitro*	LCT; LCT/MCT; SL	all: ORP ↓
Wanten, 1999	Human v	*in vitro*	LCT; LCT/MCTMCT; SL 2.5 mmol/L; 60 min	LCT; SL: do not induce ORP LCT/MCT; MCT: induce ORP
Heine, 1999	Human v	*in vivo*	LCT 60-600 mg/ml LCT/MCT < 0.5 h	LCT: ORP ↓ LCT/MCT: ORP ↑
Kruimel, 2000	Human v	*in vitro*	LCT; LCT.MCT; SL 1-100 mM/l; 0.5h	LCT, SL = LCT/MCT ↑
Wanten, 2001	Human v	*in vitro*	LCT; LCT/MCT MCT; SL (60 min)	LCT; SL killing = LCT/MCT; MCT killing ↓
Waitzberg, 1996	Rat	*in vitro*	LCT; LCT/MCT 10% 20 mg/ml; 0.5h	LCT/MCT: killing ↓ LCT =

MCT or SL were found [82]. However, the capacity of the neutrophils to kill Candida was significantly influenced by the lipid type (see below).

Neutrophil Microbial Killing Capacity and Oxygen Radical Production (Table 5)

In vitro studies indicate that saturated MCFA and MCT stimulate neutrophil oxidative metabolism, depending on carbon chain length. Especially the C-6 tricaproin has been shown to display cell-activating properties [83, 84]. It has been found that MCT, when compared with LCT, increase neutrophil oxygen radical production, while after lipid removal decreased responses and decreased microbial killing were observed [80]. Similarly, it was found that MCT, in contrast with LCT and SL, induce immediate oxygen radical production in unstimulated neutrophils [85, 86]. However, after stimulation of neutrophils with opsonised zymosan particles, overall radical production under influence of MCT decreased, suggesting that continuous cell stimulation by MCT eventually impaired cell responses [85]. The latter was corroborated in a study in which MCT exposure decreased killing of *Candida albicans*, whereas LCT and SL left neutrophil function unaffected [82]. Other investigators found that both fish oil and LCT suppressed radical production, while LCT/MCT increased the respiratory burst. Here, the influence of lipids was more pronounced with increasing carbon chain length and increasing numbers of double bonds [87, 88]. In contrast, others found that neutrophil oxygen radical production was dose-dependently, and equally decreased by LCT, LCT/MCT and SL *in vitro* [89]. Conflicting results between studies *in vitro* (impaired neutrophil function) and *in vivo* (no effect) have been reported for MCT [77, 78].

Effects on Mononuclear Cells and Reticulo-Endothelial System Function (Table 6)

Lymphocyte Functions

Lipid effects on lymphocyte proliferation and cytokine production have been shown to depend on triglyceride concentration, degree of unsaturation and carbon chain-length [90]. Lymphocyte functions can be investigated by measuring the production of humoral immune mediators (immunoglobulins for B-lymphocytes and cytokines for T-lymphocytes, respectively), as well as by evaluating cell proliferation in response to stimuli (mitogens), which mostly are plant-lectins, such as pokeweed, Concanavalin A (Con-A) or phytohaemagglutinin (PHA).

A decreased ratio of helper to suppressor T-lymphocytes in response to LCT-, but not LCT/MCT administration has been observed in volunteers and patients [91]. In AIDS patients, LCT, but not LCT/MCT, induced abnormalities in lymphocyte function [92]. In another study, LCT, LCT/MCT and MCT emulsions all inhibited human lymphocyte proliferation in a dose-dependent manner. Here, LCT, but not LCT/MCT, inhibited the generation of a cytotoxic mononuclear cell type, the lymphokine-activated killer (LAK) cells [42]. On the other hand, other investigators found that MCT inhibited LAK cell function more strongly than LCT [93]. With respect to cytotoxic effects against tumour cells, in a human study MCT showed more effects than LCT, whereas in animals MCT, but not LCT, increased metastatic disease [94].

Several investigators have not observed inhibitory effects of lipids on PBMC function. For instance, LCT displayed similar effects on T-lymphocyte subsets as lipid-free TPN or LCT/MCT in surgical cancer patients [95]. Also in cancer patients, LCT and LCT/MCT did not evoke alterations in immunoglobulins, lymphocyte proliferation or cytokine (IL-1, IL-6, TNF-α) levels compared to placebo [69, 96].

Monocyte and Reticulo-Endothelial System Functions

In a recent study, LCT and LCT/MCT have been infused in healthy volunteers for 4 hours at such a rate that triglyceride concentrations were maintained at a clinically relevant concentration of 3-5mmol/l. It was found that LCT/MCT decreased Interferon-γ and increased IL-10 production by PBMC following stimulation with the fungal pathogen *Candida albicans*, whereas LCT or placebo did

Table 6. Effects of Lipids on Mononuclear Cells (Monocytes and Lymphocytes) p: Patients; v: Volunteers; ↑: Increase; = no Effect; ↓: Decrease

Author	Subjects	Design	Lipid	Outcome
Sedman, 1991	Human p	*in vivo*	LCT LCT/MCT	NK =, LAK ↓, IL-2 (T-lymph) ↑ NK and LAK ↑
Sedman, 1990	Human v	*in vitro*	LCT ; LCT/MCT	LCT>LCT/MCT: LP↓, LAK ↓ IL-2-dependent cell growth ↓
Gelas, 1998	Human p	*in vivo*	LCT; LCT/MCT	LCT: LP↓; LCT/MCT LP =
Gogos, 1994	Human p	*in vivo*	LCT; LCT/MCT	TNF-α: LCT ↑, LCT/MCT =
Gogos, 1992	Human p+v	*in vivo*	LCT; LCT/MCT	Th/Ts ↓ with LCT; with LCT/MCT= Total T, NK =
Kimoto, 1998	Human v	*in vitro*	LCT; LCT/MCT	(LCT)/MCT: LAK ↓, anti-tumor effect
Rodriguez, 1994	human p	*in vivo*	LCT; LCT/MCT	T-lymphocyte subsets =
Wanten, 2002	Human v	*ex vivo*	LCT; LCT/MCT	IFN-γ : LCT: = ; LCT/MCT ↓ IL-10 : LCT: = ; LCT/MCT ↑ TNF-α: LCT: = ; LCT/MCT ↑ IL-1β : LCT: = ; LCT/MCT ↑
Tufano, 1995	Mice	both	LCT; LCT/MCT	LCT: TNF-α ↑; LCT/MCT IL6 ↑

not influence cytokine production [97]. This suggests that MCT administration may alter the balance of pro- and anti-inflammatory cytokines (Th1/Th2 imbalance), a situation in which patients are considered to have an increased susceptibility to fungal infections. In addition, the growth of Candida in serum from subjects was increased after LCT/MCT infusion, but not with LCT or placebo [97]. Although possibly of importance, the relevance of these findings needs confirmation in the clinical setting.

In contrast, in malnourished patients receiving TPN, LCT has been shown to increase monocyte TNF-α synthesis, while no effect in the LCT/MCT group was observed. The latter is considered beneficial in seriously ill patients [98]. That LCT/MCT may better support RES function compared to LCT has been suggested in a study where LCT increased the level of bacteraemia and decreased sequestration of exogenous bacteria to the liver while increasing levels in the lung [43]. In contrast with MCT, LCT seem to impair RES function due to decreased clearance and accumulation of LCT in the liver, while feeding MCT stimulated the lung uptake of Technetium Sulphur Colloid [99]. Accordingly, in liver transplant patients, LCT/MCT have been suggested to be the lipid emulsions of choice due to an improved recovery of allograft RES function when compared with LCT [100]. When the effects of SL and LCT/MCT were compared in rats, SL improved RES function [101]. Intravenous treatment of human monocytes with LCT has been shown to result in increased TNF-α production compared with LCT/MCT, while LCT/MCT induced higher IL-6 release compared with LCT [102]. In a study in surgical patients comparing LCT/MCT and SL, it appeared that both MCFA-containing emulsions did not suppress RES-function as measured by Technetium-colloid clearance [103]. A study on the effects of structured lipids and LCT/MCT in rats revealed that SL increased sequestration of bacteria in liver and spleen compared to LCT/MCT, indicating better RES function [101].

MECHANISMS BEHIND THE EFFECTS OF MEDIUM-CHAIN TRIGLYCERIDES

Several mechanisms by which FA and TG may influence cellular functions have been proposed, all resulting from FA incorporation into the membrane phospholipid pool and affecting i) membrane fluidity, with effects on receptor and enzyme functions, ii) bioactive eicosanoid and cytokine mediator production as well as iii) effects on signal transduction pathways [104]. In addition, LCFA and PUFA have been shown to regulate various cell responses by acting as ligands for nuclear receptors [105]. Whether one or more of these mechanisms also account for the effects of MCT remains largely unclear at this time.

Effects on Cellular Membrane Function

FA are the main components of cell membranes and responsible for membrane structural integrity. Indeed, biological lipid effects in the past have been linked to FA incorporation and modification of cellular membrane composition, resulting in altered membrane characteristics and deformability of the cell [106, 107]. Although it has not been proven that MCT actually become incorporated into the cell membrane, recent experimental work has shown that MCT, and to a lesser degree MCFA-containing SL, but not LCT, influence membrane characteristics in that they increase membrane fluidity [108]. The latter refers to a complex feature of biological membranes involving mobility and order of membrane components as well as membrane permeability properties, which are important for enzyme and receptor functions. Importantly, these data reveal altered cellular membrane fluidity as a possible mechanism for the previously observed activation of neutrophils by MCT [73, 75, 84, 86]. Apart from fluidity, the induction of signalling pathways by the plasma membrane in immune cells is also coordinated by compartmentalisation into lipid rafts, i.e. micro-domains characterised by a unique lipid environment. Many receptors are constitutively or inducibly localised in

such lipid rafts and it could be speculated that the effects of MCT described above may include effects on lipid raft characteristics.

Effects on Intracellular Signal Transduction

Changes in membrane composition due to nutritional interventions may alter properties of phospholipids and their derived second messenger compounds that are involved in cellular signalling pathways [109, 110]. MCT have recently been shown to modulate intracellular calcium-mediated signalling in a manner that significantly differs from LCT, SL, fish oil- and olive oil derived lipids [111, 112]. When the effects of lipids on neutrophil activation were studied, opsonised zymosan particles (STZ) evoked a biphasic increase of cytosolic Ca^{2+} ($[Ca^{2+}]_i$) (Wanten, 2001). The protein kinase C (PKC) activating phorbol ester PMA markedly increased the initial rate of $[Ca^{2+}]_i$ rise, an effect that was mimicked by MCT, but not by LCT or SL. Importantly, these effects were observed at a clinically relevant lipid concentration of 2.5mmol/L. Because all lipids similarly activated purified PKC in a PMA-like manner *in vitro*, it is suggested that only MCT activate PKC in the context of the intact cell. Both PMA and MCT evoked a leftward shift of the dose-response curve for the effect of STZ on $[Ca^{2+}]_i$ rise, reflecting PKC-dependent sensitisation of neutrophils for stimulation by STZ.

Another recent study has shown that nutritional lipids can evoke a prompt and significant attenuation of the neutrophil stimulation induced by fMLP, a bacterial tripeptide. Emulsions based on fish oil (VLCT) and a mixture of coconut oil and soya oil (LCT/MCT) proved to be the most potent ones in this respect [112]. When the effects of various lipids on neutrophil activation were studied, all lipids reduced the fMLP-induced increase in $[Ca^{2+}]_i$ with the same efficacy but with different potency. Half-maximal inhibition was reached at emulsion concentrations of 0.24mmol/L (fish oil), 0.32mmol/L (LCT/MCT), 0.52mmol/L (LCT) and 0.82mmol/L (olive oil). The PKC inhibitor staurosporine did not interfere with the inhibitory lipid effect, indicating that the lipids act primarily in a PKC-independent manner. The mechanism(s) underlying the prompt inhibitory action of these lipid species might involve (i) binding of fMLP, thereby decreasing the effective concentration of the hormone; (ii) activation of intracellular mechanism(s) resulting in receptor desensitisation; or (iii) changes in membrane properties leading to impaired signal transduction. As neutrophil calcium signalling has been previously been shown to be modulated by platelet-activating factor (PAF), lipid effects might also be the result of changes in the production and/or sensitivity of the PAF receptor to this bioactive lipid substance.

Effects on Gene-Transcription

Lipids have been shown to modulate gene expression through effects on transcription factors belonging to the peroxisome proliferator-activated receptor family (PPAR), a group of nuclear receptors that are involved in the regulation of lipid homeostasis. FA have been shown to bind directly to PPARs, that subsequently regulate the expression of target genes by binding to DNA sequence elements [110]. In this manner, FA can regulate expression of adhesion molecules, such as integrins and selectins, and alter cell adhesion properties. The information on whether MCT influence gene transcription by this route is limited. Caprylic acid and MCT have been shown to suppress the secretion of the cytokine IL-8 by Caco-2 cells at the transcriptional level [113]. It was found that caprylic acid inhibited the activation of the IL-8 promotor but did not modulate the activation of NF-κB and other transcription factors.

Effects on Production of Lipid Mediators

In addition to the mechanisms mentioned above, FA interfere with other immune modulating mechanisms such as nitric oxide production and apoptotic pathways [110]. In addition, dietary lipids may modulate the production and function of immune-regulatory lipid mediators, such as eicosanoids and platelet-activating factor (PAF). FA are substrates for lipoxygenases and cyclooxygenases, enzymes that generate different families of eicosanoids, 20-C lipid compounds comprising prostaglandins, thromboxanes and leukotrienes, that regulate inflammatory and immune responses [2, 114]. In general, ω-3 PUFA give rise to biologically less active compounds [115], while ω-6 PUFA yield pro-inflammatory mediators and regulators of cytokine production [2, 114, 117]. In accordance with this notion, administration of ω-3 FA has been shown to beneficially influence clinical outcome in various immune-mediated diseases [104]. Interestingly, both ω-3 and ω-9 FA modulate cell apoptosis and differentiation, with possible repercussions for the formation of neoplastic processes [117]. However, so far there is no evidence that MCT do influence eicosanoid synthesis or availability.

OVERALL CONCLUSIONS AND SUGGESTIONS FOR FUTURE RESEARCH

So where do we stand with our knowledge regarding cellular effects of MCT? MCT as part of TPN appear to have a metabolic profile that offers potential advantages in compromised patients, but may pose a threat to others. On the other hand, experimental and clinical studies focussing on immune and inflammatory responses under influence of MCT (and LCT) so far have yielded conflicting results. Most probably these controversies result from differences in experimental approach and, as far as clinical studies are concerned, limited observation periods of small patient numbers with various clinical conditions. This lack of power may well obscure any lipid effects, e.g. due to genotypic variations in immune responses in the population [105, 118].

Illness severity is another point of consideration. As has been argued for other immune-enhancing compounds, clinical effects of lipids may only become clear with an early intervention and in the case of moderate illness, whereas severe disease states, such as sepsis, may be beyond the reach of any nutritional therapy [119]. However, despite the fact that their effects remain to be characterised, recent experimental evidence suggests that MCT are bioactive mediators, while MCFA-containing structured lipids appear to be more immune-neutral [73, 75, 82, 85, 108, 111].

It has been argued that MCT should be regarded as a superior lipid source over LCT in critically ill or immune compromised patients [49, 120]. In our opinion the evidence for this view from an immunologic standpoint is lacking, simply because adequate clinical studies that take into account the points mentioned above have not been performed. In contrast, recent studies suggest that "inappropriate" cell activation by MCT might result in impaired immune functions and increase the susceptibility to fungal infections [85, 97]. Importantly, these findings remain to be proven in the clinical setting as well.

CONCLUSION

We therefore conclude that, besides the increased rate of metabolic breakdown and its clinical sequelae, MCT, as part of physical lipid mixtures, display distinct effects on immune functions when compared with LCT. The relevance of and the repercussions for clinical practice of these findings remain to be established in future studies that are needed to define the adequate dietary lipid composition in different clinical situations.

ABBREVIATIONS

FA	=	Fatty acid
fMLP	=	N-formyl methionyl-leucyl-phenylalanine
LAK cells	=	Lymphokine-activated killer cells
LCT	=	Long-chain triglycerides
LCFA	=	Long-chain fatty acid
LP	=	Lymphocyte proliferation
MCT	=	medium-chain triglycerides
MCFA	=	medium-chain fatty acid
MP	=	macrophage
MPS	=	mononuclear phagocyte system
NK cells	=	Natural killer cells
PBMC	=	Peripheral blood mononuclear cell
PKC	=	Protein kinase C
PMA	=	Phorbol 12-myristate 13-acetate
PUFA	=	Polyunsaturated fatty acid
RES	=	Reticulo-endothelial system
SL	=	Structured lipids
STZ	=	Serum-treated zymosan
Th	=	T helper cell
Ts	=	T suppressor cell
TPN	=	Total parenteral nutrition

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