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Running head: MCT and satiety: a systematic review

Abbreviations list: Medium-chain triglycerides (MCT), cholecystokinin (CCK), long-chain triglycerides (LCT), body mass index (BMI), pancreatic polypeptide (PP), gastric inhibitory polypeptide (GIP), peptide YY (PYY), glucagon-like peptide-1 (GLP-1).

Data described in the manuscript, code book, and analytic code will be made available upon request.

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Abstract

Research has indicated that consuming medium-chain triglycerides (MCT) may be more satiating than consuming long-chain triglycerides (LCT) potentially causing a reduction in energy intake. However not all studies have demonstrated this acute reduction in energy intake and it has yet to be systematically reviewed. Our main objective was to examine how ingestion of MCT influences energy intake, subjective appetite ratings and appetite-related hormones compared to LCT. Web of Science, MEDLINE, CINHAL and Embase were searched for publications comparing the effect of MCT on appetite (commonly hunger, fullness, desire to eat, and prospective food consumption), appetite-related hormones (pancreatic polypeptide (PP), gastric inhibitory polypeptide (GIP), peptide YY (PYY), glucagon-like peptide-1 (GLP-1), neurotensin, leptin, total ghrelin and active ghrelin) and energy intake to LCT. A random-effects meta-analysis was conducted on studies which examined energy intake.

Seventeen studies (291 participants) were included in the systematic review, of which 11 were included in the energy intake meta-analysis. Synthesis of combined data showed evidence of a statistically significant moderate decrease in *ad libitum* energy intake after both acute and chronic ingestion of MCT compared to LCT when assessed under laboratory conditions (mean effect size: -0.444, 95% CI -0.808, -0.080, $p < 0.017$), despite little evidence of any effect of MCT on subjective appetite ratings or circulating hormones.

The current evidence supports the notion that MCT decreases subsequent energy intake, but does not appear to affect appetite. Further research is warranted to elucidate the mechanisms by which MCT reduce energy intake.

Key words: Medium-chain triglycerides, satiety, appetite, energy intake, systematic review, meta-analysis

Introduction

Overweight and obesity are defined as the accumulation of excess body fat which may lead to impaired health (World Health Organisation 2018). Despite the well-reported risks of increased body fat, including type 2 diabetes, coronary heart disease, some cancers, and stroke (National Health Service 2016), overweight and obesity are still increasingly prevalent. In 2016, more than 1.9 billion adults were overweight globally and 650 million of these were obese; figures which have nearly tripled since 1975 (World Health Organisation 2018). These conditions are caused by a chronic energy surplus from either excessive energy intake or inadequate energy expenditure (Hill, Wyatt, and Peters 2012). It is known that adherence to dietary interventions aiming to reduce bodyweight is low due to feelings of hunger (Franklin et al. 1948), meaning that the target weight loss is not always achieved.

As a result of this, foods with enhanced satiety have gained much attention, both commercially and in research (Hetherington et al. 2013; Chambers, McCrickerd, and Yeomans 2015). Medium-chain triglycerides (MCT) are triglycerides with shorter chain lengths (6-12 carbon atoms long) than 'traditional' long-chain triglycerides (LCT; 12+ carbon atoms long). Due to the shorter chain length of MCT, its consumption results in attenuated release of cholecystokinin (CCK) compared to LCT (Feltrin et al. 2007, 2006; Feinle et al. 2001; Matzinger et al. 2000; French et al. 2000). CCK is involved in lipid-related satiety (McLaughlin et al. 1999), and thus LCT promote satiety via this mechanism. However, MCT are absorbed much quicker than LCT (Marten, Pfeuffer, and Schrezenmeir 2006) which leads to large amounts of β-oxidation (Bach and Babayan 1982) and the production of β-hyroxybutyrate (Page et al. 2009); a process which is thought to be anorexigenic (Laeger, Metges, and Kuhla 2010; Scharrer 1999). Studies have shown decreased appetite and subsequent energy intake

after a preload (Rolls et al. 1988), breakfast (Coleman, Quinn, and Clegg 2016; Kinsella, Maher, and Clegg 2017; Van Wymelbeke et al. 1998) or lunch (Van Wymelbeke, Louis-Sylvestre, and Fantino 2001) containing MCT. This is not a universal finding however, as some studies have reported no difference in energy intake after meals containing MCT or a control oil (St-Onge et al. 2014; Poppitt et al. 2010), and have even shown increased feelings of hunger after MCT-based meals (Valente et al. 2018).

Clearly, the findings surrounding MCT and satiety are mixed. It is therefore important to systematically determine whether MCT ingestion results in greater satiety and decreased energy intake. Thus, this review aims to assess if there is sufficient evidence to support the hypothesis that MCT can increase satiety in comparison with LCT. Specifically, the objectives are to examine if the consumption of MCT decreases energy intake in subsequent eating episodes, if MCT ingestion favourably alters subjective sensations of appetite (i.e. increased fullness and decreased hunger/desire to eat), and to compile the data on the effects of MCT on circulating hormones involved in appetite regulation.

Methods

This review is reported according to the PRISMA guidelines (Moher et al. 2009), and is registered in the PROSPERO database (registration number: CRD42018092550).

Search Strategy

The research question of this systematic review was formulated using PICOS (Population, Intervention, Comparison, Outcome, Setting). The population was defined as adults of healthy status excluding overweight or obesity. The intervention was considered to be any investigation examining medium-chain triglycerides or medium-chain fatty acids on appetite and satiety measures. Outcomes incorporated any measure of appetite (i.e. visual analogue scales), physiological markers of appetite regulation (e.g. PYY, ghrelin) and energy intake measures

(*ad libitum* meals, diet diaries). There was no restriction to the settings in which studies were conducted.

The databases Web of Science, MEDLINE, CINHAL and Embase were searched for studies in the English language between 1970 and 2018 comprising of all human participants using the strategy ("medium chain triglycerides" AND "satiety" AND "human"). The last search was run on 14 May 2018. Previous systematic reviews were screened to identify relevant subject headings and key words to include within each subject category. Reference lists from the resulting articles were also screened to identify any additional articles. **Table 1** shows a full list of the specific key words.

Exclusion criteria

Studies were excluded if they did not examine MCT or medium chain fatty acids (or a product containing either) and subjective measurement of appetite sensations or energy or food intake. Studies were also excluded if they were conducted in animals, or if they contained individuals outside the age range of 18-70 years, or if they did not include an LCT arm that was matched in calories and composition to an MCT arm.

Data Screening

Records were screened for duplicates, which were removed. Potential studies were identified by examining all titles and removing those which did not contain reference to MCT and appetite or energy intake by one reviewer. The abstracts of the remaining titles were read, and full text copies were obtained if they still met the initial criteria. Information on the remaining studies after abstract screening was tabulated by one researcher (TM), and both investigators (TM and MC) discussed the inclusion of the studies until a mutual consensus was met. The following information was extracted from the included into a spreadsheet: authors, date of publication, sample size, participant characteristics (age, sex, body mass index [BMI]), study setting, source and amount of MCT, appetite outcome measures and results.

Quality Checks

Risk of bias was assessed within the individual studies using the Cochrane Collaboration's Tool (Higgins et al. 2011). Selection bias, reporting bias, performance bias, detection bias, attrition bias and other sources of bias (such as funding etc.) were assessed. Eligible studies were included regardless of risk of bias. **Table 2** details risk of all sources of bias for each study.

Meta-analysis procedures

Due to inconsistent reporting of visual analogue scale data (i.e. presented in a variety of ways, graphical format, as raw data or calculated AUC), and the small number of studies examining appetite hormones (four), only acute *ad libitum* energy intake data was included in the meta-analysis (either at a single meal or over the course of a whole day). The remaining 11 studies were broken down into 20 subgroups, accounting for studies investigating multiple doses of MCT (Rolls et al. 1988, Stubbs and Harbron 1996) or coconut oil (Rizzo et al. 2016), and for studies with multiple investigations (St-Onge et al. 2014). Energy intake (kJ) was measured at both *ad libitum* meals and habitual daily intake. Where needed, reported values were converted to kJ before computation to standardise the units. Meta-analysis software (Comprehensive Meta-Analysis, Version 3, Biostat, Englewood, NJ, USA) was used to conduct a meta-analysis on extracted data. Data inputted included sample sizes, mean energy intake for LCT and MCT trials, their respective SDs, and a correlation coefficient to account for the fact that the included studies were crossover trials (r = 0.940, calculated from energy intake data from the studies included in the review). The software computed effect sizes for each study, as well as an overall effect size using a random-effects model (DerSimonian-Laird inverse variance approach). Effect size was calculated as the standardised difference in means, which we interpreted to be trivial at <0.2, small at 0.2-0.3, moderate at 0.4-0.8, and large at >0.8, as per Cohen (Cohen 1992). Negative effect sizes indicate decreased consumption in MCT trials/conditions, whereas

positive effect sizes indicated LCT led to decreased energy intake. Publication bias was assessed utilising funnel plots and by quantifying Egger's regression intercept. A significant regression indicates the presence of a small study effect (Sterne, Egger, and Moher 2011).

Results

Descriptive

The database search yielded 4,547 results, which was reduced to 3,517 after the removal of duplicates. After the screening of titles and abstracts, 3,302 were removed. Of the remaining 216 texts, 17 satisfied the inclusion criteria (**Figure 1**.).

Seven studies were conducted in the UK (Clegg, Golsorkhi, and Henry 2013; Clegg et al. 2012; Coleman, Quinn, and Clegg 2016; Kinsella, Maher, and Clegg 2017; Stubbs and Harbron 1996; Rizzo et al. 2016), two in Australia (Feltrin et al. 2004, 2008), two in France (Van Wymelbeke et al. 1998; Van Wymelbeke, Louis-Sylvestre, and Fantino 2001), two in the US (St-Onge et al. 2014; Rolls et al. 1988), and one each in Italy (Barbera et al. 2000), Sweden (Krotkiewski 2001), Brazil (Valente et al. 2018), and New Zealand (Poppitt et al. 2010). Participants were 28.57 ± 6.20 years of age with a BMI of 23.49 ± 3.42 kg/m^2, and there was an average of 15 ± 8 participants per study (means ± SD). Participants in one study were classified as 'overweight' according to BMI (M. St-Onge et al. 2014), and were classified as 'obese' in one other (Krotkiewski 2001); all others were in the 'normal' BMI category. There was a total of 291 participants, of which 107 were male and 184 were female. There were 11 acute feeding studies (Rolls et al. 1988; Clegg, Golsorkhi, and Henry 2013; Coleman, Quinn, and Clegg 2016; Kinsella, Maher, and Clegg 2017; Rizzo et al. 2016; Miriam E. Clegg et al. 2012; M. St-Onge et al. 2014; Valente et al. 2018; Van Wymelbeke et al. 1998; Van Wymelbeke, Louis-Sylvestre, and Fantino 2001; Poppitt et al. 2010), three acute infusion studies (Barbera et al. 2000; Feltrin et al. 2008, 2004), and two chronic dietary intervention studies, of which one examined

participants three times across all arms of the intervention and quantified habitual daily energy intake (Stubbs and Harbron 1996) and the other was a comparison of independent matched groups (Krotkiewski 2001). One dietary intervention provided all foods consumed by participants in 14-day long manipulations, where the amount of energy from MCT was altered (Stubbs and Harbron 1996), and the other was a very low calorie diet, with either MCT or LCT was incorporated into the low-calorie formula incorporated into the diet (Krotkiewski 2001).

Measures

Fourteen out of fifteen studies used 100mm visual analogue scales to measure subjective sensations of appetite (St-Onge et al. 2014). Ten studies examined energy intake during at least one subsequent *ad libitum* eating episode after consumption of a meal/preload containing LCT/MCT (Rizzo et al. 2016; Coleman, Quinn, and Clegg 2016; Feltrin et al. 2004; Kinsella, Maher, and Clegg 2017; Poppitt et al. 2010; Feltrin et al. 2008; Rolls et al. 1988; St-Onge et al. 2014; Van Wymelbeke, Louis-Sylvestre, and Fantino 2001; Van Wymelbeke et al. 1998), and one examined daily habitual energy intake after MCT was covertly incorporated into the diet (Stubbs and Harbron 1996). In that study, participants were required to consume all meals in the laboratory, but were allowed to leave and were not required to 'live' in the laboratory; and thus ad libitum daily energy intake was quantified. Three of those also included diet diaries for subsequent energy intake (Coleman, Quinn, and Clegg 2016; Kinsella, Maher, and Clegg 2017; Van Wymelbeke et al. 1998). Four studies examined appetite hormones, including pancreatic polypeptide (PP) (Barbera et al. 2000), CCK (Barbera et al. 2000; Feltrin et al. 2004, 2008), gastric inhibitory polypeptide (GIP) (Barbera et al. 2000; Feltrin et al. 2004), peptide YY (PYY) (Feltrin et al. 2008; St-Onge et al. 2014), leptin (St-Onge et al. 2014), glucagon-like peptide-1 (GLP-1) (Feltrin et al. 2004) and both active and total ghrelin (St-Onge et al. 2014).

Test lipids

The main results of included studies are shown in **Table 3**. Six studies directly compared MCT to LCT, which acted as a control (Barbera et al. 2000; Clegg, Golsorkhi, and Henry 2013; Feltrin et al. 2004; Rolls et al. 1988; St-Onge et al. 2014; Stubbs and Harbron 1996). Two studies compared MCT and LCT, and also included a low-fat/no-fat control (Feltrin et al. 2008; Krotkiewski 2001; Van Wymelbeke, Louis-Sylvestre, and Fantino 2001). Three studies had multiple fats, including several LCT conditions such as sunflower oil, olive oil and butter (Clegg et al. 2012); olive oil and lard (Van Wymelbeke et al. 1998); and two with another test oil, which was conjugated linoleic acid (Coleman, Quinn, and Clegg 2016) and short-chain triglycerides (Poppitt et al. 2010). Two studies used coconut oil as the source of MCT in the study (Rizzo et al. 2016; Valente et al. 2018), and another study used coconut oil as well as MCT (Kinsella, Maher, and Clegg 2017). For the LCT trials and controls, three studies used sunflower oil (Clegg, Golsorkhi, and Henry 2013; Clegg et al. 2012; Rizzo et al. 2016), two used rapeseed oil (Coleman, Quinn, and Clegg 2016; Kinsella, Maher, and Clegg 2017), two used corn oil (Rolls et al. 1988; St-Onge et al. 2014), one used beef tallow (Poppitt et al. 2010), one used extra virgin olive oil (Valente et al. 2018), one used margarine (Van Wymelbeke, Louis-Sylvestre, and Fantino 2001), one study used an unspecified vegetable oil (Stubbs and Harbron 1996), and three studies (which administered the lipids via infusion and not feeding) used emulsions of oleic and linoleic acid (Barbera et al. 2000), oleic acid (Feltrin et al. 2008), and lauric acid (Feltrin et al. 2004). One study did not specify the LCT used in their study (Krotkiewski 2001). In terms of saturation of LCT, six studies utilised LCT with a mixture of polyunsaturated and monounsaturated acids (Barbera et al. 2000; Rolls et al. 1988; Clegg, Golsorkhi, and Henry 2013; St-Onge et al. 2014; Rizzo et al. 2016; Valente et al. 2018), four used purely monounsaturated fatty acids (Kinsella, Maher, and Clegg 2017; Coleman, Quinn, and Clegg 2016; Stubbs and Harbron 1996; Feltrin et al. 2008), two used mixtures of monounsaturated and saturated fatty acids (Van Wymelbeke, Louis-Sylvestre, and Fantino

2001; Poppitt et al. 2010), and two studies used multiple sources of LCT; polyunsaturated and monounsaturated (sunflower oil), monounsaturated (olive oil) and saturated (butter) fatty acids (Clegg et al. 2012), and saturated (lard) or monounsaturated (olive oil) (Van Wymelbeke et al. 1998). When accounting for studies that provided multiple doses, the dosage of MCT ranged from 10 g (Poppitt et al. 2010) to 42.4 g (Van Wymelbeke et al. 1998), with an average dose of 23.8 g. Three studies provided 10-15 g (Poppitt et al. 2010; Rolls et al. 2004; Rizzo et al. 2016), four provided 20-25 g (Coleman, Quinn, and Clegg 2016; Kinsella, Maher, and Clegg 2017; St-Onge and Jones 2002; Rolls et al. 2004), three provided 30-35 g (St-Onge et al. 2014; Van Wymelbeke, Louis-Sylvestre, and Fantino 2001; Rolls et al. 1988) and one provided 40-45 g (Van Wymelbeke et al. 1998).

Outcomes

One out of 11 studies (Feltrin et al. 2004) reported decreased energy intake at an *ad libitum* meal after MCT compared to LCT, although this was only significant in seven studies (Coleman, Quinn, and Clegg 2016; Feltrin et al. 2008; Rolls et al. 1988; St-Onge et al. 2014; Stubbs and Harbron 1996; Van Wymelbeke, Louis-Sylvestre, and Fantino 2001; Van Wymelbeke et al. 1998). The one study that reported decreased intake after LCT compared to MCT reported a significantly lower energy intake after LCT compared to MCT (Feltrin et al. 2004). The average energy intake at the *ad libitum* meal in that study after LCT and MCT trials, respectively, was 1,747 ± 633 kJ and 4,109 ± 589 kJ. Five studies out of 14 reported significant differences in appetite ratings, which were decreased hunger and increased satiety after MCT (Krotkiewski 2001), increased fullness after MCT (Kinsella, Maher, and Clegg 2017), increased satiety after LCT (Barbera et al. 2000), decreased hunger but also decreased desire to eat after infusion of MCT (Feltrin et al. 2004), and increased hunger and decreased fullness after MCT (coconut oil) (Valente et al. 2018). Three studies (Rolls et al. 1988; Feltrin et al. 2004; Barbera et al. 2000) reported significant adverse effects, which manifested as gastric

aching after the MCT drinks (Rolls et al. 1988), and increased nausea after infusions LCT compared to MCT (Barbera et al. 2000; Feltrin et al. 2004).

Only four studies examined blood parameters in response to the oils which showed LCT led to increased postprandial concentrations GIP, neurotensin, PP (Barbera et al. 2000), CCK (Barbera et al. 2000; Feltrin et al. 2008, 2004), PYY (Feltrin et al. 2008) and GLP-1 (Feltrin et al. 2004). Conversely, one study showed that relative to MCT, LCT led to increased postprandial leptin and PYY, and no effect on GLP-1 or total ghrelin, but active ghrelin concentrations were reduced to a lesser extent after MCT (St-Onge et al. 2014).

Meta-analysis

Due to high levels of heterogeneity (I^2 = 97.0%, Q = 333.9, T^2= 0.355, d_f = 10), a random effects model was chosen (Ades, Lu, and Higgins 2005). Effect size for acute *ad libitum* energy intake ranged from -2.235 to 3.789. Statistics for each individual study are reported in Supplementary table 1. There was a statistically significant moderate decrease in *ad libitum* energy intake after MCT ingestion compared to LCT ingestion (mean effect size: -0.444, 95% confidence intervals -0.808 to -0.0.80, N = 11, p = 0.017; Figure 2). Sensitivity analysis showed that the removal of each study had only minor effects on overall effect size, and no effect on significance. In order to further examine and specify the effect of consuming MCT on satiety, a sensitivity analysis was conducted by removing infusion studies. This did not alter the direction of significance, but it did increase the level of significance (mean effect size: -0.681, 95% confidence intervals -0.950 to -0.412, N = 8, p < 0.001). More sensitivity analyses were conducted in order to specify the effect of MCT without the influence of coconut oil. Similarly to the removal of infusion studies, removal of the comparison of LCT to coconut oil increased the size of the effect of MCT on energy intake (mean effect size: -0.529, 95% confidence intervals -0.598 to -0.460, N = 10, p < 0.001). The funnel plot (**Figure 3**.) along with Egger's

regression intercept showed that there were no small study effects (intercept = -1.094, 95% confidence intervals: -11.481 to 9.293, $p = 0.817$).

Discussion

Main results

Prior to this review, MCT had been identified as potentially having more satiating properties than LCT, but studies investigating this are sparse and have found equivocal findings. Understanding how MCT may affect appetite may have implications for weight management, as feelings of hunger are known to the linked to the low rates of adherence commonly seen in dietary strategies (Heymsfield et al. 2007; Franklin et al. 1948). Whereas it is well known that protein is the most satiating of the macronutrients and fat the least, a significant portion of energy in the western diet comes from fat, and therefore methods to increase the satiety response to fat has implications for weight management strategies. The purpose of this review was to examine the appetite responses and energy intake after meals containing either MCT or LCT. It was hypothesised that MCT would increase satiety compared to LCT. The analyses show that MCT suppress energy intake compared to LCT, and this appears to be independent of changes in subjective sensations of appetite and alterations in gut peptide hormones.

Energy intake

The present meta-analysis showed that nine out of 10 studies reported decreased energy intake at an acute *ad libitum* meal after ingestion or infusion of MCT, and the only study examining habitual energy intake when MCT was incorporated into the diet also led to decreased energy intake compared to LCT. Whereas the decreased energy intake after MCT consumption wasn't significant in all individual studies, the meta-analysis demonstrated a moderate effect of MCT on energy intake compared to LCT. However, it must be noted that these findings are predominantly limited to the first meal after ingestion of MCT and cannot be extrapolated to

300 further meals. More research is needed to elucidate whether compensation occurs in later
301 meals, or if an energy deficit is achieved. One study did incorporate MCT as part of the habitual
302 diet in different MCT:LCT ratios and found that habitual daily intake was lower after the high
303 MCT:LCT ratio period (Stubbs and Harbron 1996). Where this does corroborate the hypothesis
304 that chronic consumption of MCT decreases overall intake; whether this is due to repeat
305 exposure of MCT or a persistent effect is still not known. Furthermore, as only one study to
306 date has investigated chronic MCT consumption and habitual energy intake, these results
307 require validation.

308 *Appetite*

309 Despite reported alterations in energy intake, this appears to have occurred without any
310 reporting of an effect on subjective appetite responses, indicating that MCT suppresses *ad*
311 *libitum* energy intake without a concomitant change of feelings of hunger. As aforementioned,
312 this requires further investigation as there is a lack of studies investigating energy intake
313 beyond a single *ad libitum* meal or a single day. Extraction of subjective sensation data was
314 challenging due to the inconsistent reporting of raw values (i.e. only represented in graphical
315 format), and so these were not included in the meta-analysis. Inspection of the results (Table
316 3) shows that the majority of studies do not report significant differences in any subjective
317 sensation parameter, and when a difference is reported it is not consistent in all parameters in
318 the study (Barbera et al. 2000; Clegg et al. 2012; Kinsella, Maher and Clegg 2017; Stubbs and
319 Harbron 1996; Valente et al. 2017). The only study to show consistent changes in subjective
320 sensations of appetite incorporated MCT into the diet as part of a very low-calorie diet for 4
321 weeks (Krotkieski 2001). It is possible that acute feedings of MCT do not alter perceptions of
322 appetite, but repeated exposure may do so.

323 *Mechanisms*

Only four studies examined appetite-related hormones, and so drawing conclusions from these studies is mere speculation; however, secretion of CCK, GIP, PP or GLP-1 appears to be more potent after LCT than MCT. Additionally, another study showed that active ghrelin may be suppressed to a lesser extent than after LCT. MCT have been shown to increase stomach concentrations of acylated ghrelin, as MCT and MCFA are directly used for the acylation of ghrelin (Nishi et al. 2005), which may explain the suppression by LCT. Ghrelin is the only appetite hormone known to stimulate hunger (Wren et al. 2000), whereas CCK, GIP, PP and GLP-1 are involved in promoting satiety and satiation (Gibbs, Young, and Smith 1973; Kissileff et al. 1981; Batterham et al. 2002; Flint et al. 2001; Perry and Wang 2012). Taken together, this implies that MCT exert its anorectic affect through non-hormone mediated mechanisms, however the paucity of data makes this speculation. MCT have been shown to delay gastric emptying (Clegg et al. 2012), despite MCFA being absorbed at a much quicker rate than LCFA (Bach and Babayan 1982). MCT consumption also leads to the production of the ketone body of *β*-hyroxybutyrate, which may also be anorexigenic (Laeger, Metges, and Kuhla 2010). Future studies should include these measures in their protocols in order to shed further light on these mechanisms.

The one study that found greater *ad libitum* energy intake after MCT compared to LCT (Feltrin *et al.* 2004) compared lauric acid (C12) to decanoic (C10) acid via intraduodenal infusion and observed significant differences in *ad libitum* energy intake. This was accompanied by greater stimulation of CCK and GLP-1 after infusion of C12. This suggests that the longer chain length is more efficacious at decreasing appetite. It has previously been reported incretin responses to infusions of glucose and lipids are not as pronounced as the response to oral ingestion of glucose (Elrick et al. 1964) or lipids (Lindgren et al. 2011). As such, this makes drawing conclusions from infusion studies difficult. It must also be noted that infusion of C12 induced nausea, which may also explain the decreased *ad libitum* energy intake. This increased nausea

was also found after the infusion of LCT but not MCT (Barbera et al. 2000), which also may explain increased satiation scores in that study. Only one other study which examined energy intake reported adverse effects, which were in the form of 'gastric aching' (Rolls et al. 1988), which also may partly explain the decreased *ad libitum* energy intake after MCT ingestion in that study. In the first study to examine MCT and satiety (Rolls et al. 1988), there was a significant interaction between fatty acid chain length and dosage for gastric aching, suggesting that increased dosage of MCT was linked to stronger adverse effects. However, higher doses have been examined with no adverse effects (Van Wymelbeke, Louis-Sylvestre, and Fantino 2001; Van Wymelbeke et al. 1998), and the authors describe that, despite statistically significant differences, absolute differences were small (3.5 mm on a 100 mm scale). Only five of the studies included a rating of nausea (Barbera et al. 2000; Feltrin et al. 2008, 2004; Poppitt et al. 2010; Clegg, Golsorkhi, and Henry 2013), which may also confound the effect observed in our meta-analysis, as (although only two studies reported adverse effects) MCT have been shown to cause GI distress (Jeukendrup et al. 1998; Goedecke et al. 2005) and are generally unpalatable (Clegg 2010; Maher and Clegg 2018).

Methodology

The dosages of MCT provided in the studies included in this review had a large variation (10 g (Poppitt et al. 2010) to 42.4 g (Van Wymelbeke et al. 1998) with an average dose of 23.8 g). There did not appear to be a relationship between dose and whether there was an effect on energy intake, as despite the study providing the lowest dose reported no effect (Poppitt et al. 2010), another study found significant effects with all three doses administered in their study; the lowest providing 12.04 g of MCT (Rolls et al. 1988). Furthermore, the greatest decrease observed after MCT ingestion occurred after 30 g of MCT was provided in a breakfast and preload study (St-Onge et al. 2014). The optimal dose required to beneficially affect appetite remains elusive. One point that must be taken into consideration is the energy contributed from

the MCT compared to the decrease in subsequent energy intake it begets. MCT was administered in a variety of ways in the studies in this review, including duodenal infusions (Barbera et al. 2000; Feltrin et al. 2004, 2008), being added to beverages (Coleman, Quinn, and Clegg 2016; Kinsella, Maher, and Clegg 2017; Rolls et al. 1988; St-Onge et al. 2014), a low calorie formula (Krotkiewski 2001), being added to solid meals (Van Wymelbeke et al. 1998; Van Wymelbeke, Louis-Sylvestre, and Fantino 2001; Valente et al. 2018), being cooked into other foods (Clegg et al. 2012; Poppitt et al. 2010; St-Onge et al. 2014), ice cream (Rizzo et al. 2016), and being added into the whole diet (Stubbs and Harbron 1996). One practical limitation that must be considered is the fact that the majority of these studies added the test oils to other foods. however the foods were always kept constant and only fats changed ensuring they were controlled.

Limitations

There are several limitations to this review and meta-analysis. The main limitation to acknowledge is the fact that one reviewer reviewed all papers, instead of multiple reviewers screening all titles and a consensus being met. Furthermore, studies were initially excluded based on titles alone, instead of a title and abstract screening process. These two limitations mean that incomplete retrieval of records cannot be ruled out. Only 16 studies were included based on our criteria, of which 11 were included in the meta-analysis of energy intake (consisting of 20 subgroups). This highlights the limited data examining the role of MCT in satiety rather than a limitation of this review, however there are methodological differences in the studies included which do need to be acknowledged. Three studies used coconut oil as the means of administering MCT (Rizzo et al. 2016; Poppitt et al. 2010; Valente et al. 2018). One study included in this review examined the effect of MCT to coconut oil as well as a control LCT oil, and reported that MCT resulted in lower energy intake compared to both LCT and

coconut oil (Kinsella, Maher, and Clegg 2017). This could be due to the higher concentration of lauric acid (~50%) (Denke and Grundy 1992) in coconut oil than in MCT oil (1-3%) (Bach and Babayan 1982; Clegg 2017). It has been shown that only 20-30% of lauric acid acts as an MCT, whereas the remainder is packed in chylomicrons as with LCT (Denke and Grundy 1992). This implies that coconut oil may not be a suitable method of examining MCT, and this may have affected the results of the meta-analysis. A sensitivity analysis was conducted by removing the one study investigating coconut oil (Rizzo et al. 2016) and the one subgroup that compared coconut oil and LCT (Kinsella, Maher and Clegg 2017), which led to the effect size to increase; which supports the notion that coconut oil is not as effective as MCT at inducing satiety. Two studies, including the only study that reported increased intake after MCT, administered the oils via infusion and not incorporated into a meal (Feltrin et al. 2008, 2004). We did not specify in our criteria that studies included required to have the MCT in a meal, and thus we decided to include these studies, however, the validity of these studies among other feeding studies could be questioned. Furthermore, the one study that reported an increase intake after LCT (Feltrin et al. 2004) compared lauric acid (C12) to decanoic (C10) acid, which is arguably not MCT compared to LCT due to the absorption of lauric acid, as aforementioned. Removal of these studies did not affect the results of the meta-analysis, and thus they have been kept in in order to better represent the available data. However, similar to studies investigating coconut oil, a sensitivity analysis was conducted by removing the two studies which infused MCT (Feltrin et al. 2004, 2008), and this increased the effect size; meaning the inclusion of infusion studies weakened the effect of MCT on energy intake. From a practical standpoint, this further highlights that consumption of MCT leads to suppressed energy intake compared to LCT.

These limitations should be taken into consideration for future research examining this topic, and also shows the small number of appropriate studies examining the effect of MCT on appetite and energy intake.

Conclusion

The present meta-analysis indicates a moderate reduction in energy intake after consumption of MCT, predominantly at single *ad libitum* meals, but also total daily energy intake after daily incorporation of MCT into the diet. Whether this reduction persists past the first meal after consumption of MCT remains to be elucidated. The systematic review indicates that there is no effect of MCT on subjective sensations of appetite. Further work is required to confirm the role of appetite hormones in the satiety response to MCT, but there is currently no evidence to suggest a hormonal role of MCT satiety. Due to the small total number of studies, coupled with the fact not all included a feeding component and only four examined hormonal responses to MCT, this paper calls for more studies examining MCT and satiety incorporating these measures, as well as appropriate sources of MCT.

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T.M. and M.E.C. designed the manuscript, developed the search terms and inclusion and exclusion criteria. T.M. did the searches and both authors screening the final papers. TM did the analysis and wrote the paper. MC had responsibility for the final content.

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