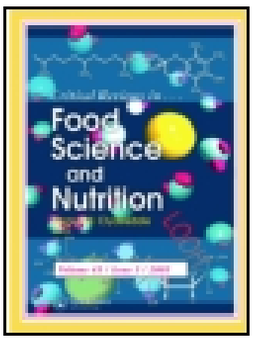

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REVIEW

A review on differential effects of dietary fatty acids on weight, appetite and energy expenditure

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ABSTRACT

The association between weight and chronic diseases is well defined. The quality and quantity of dietary fatty acids is an important external factor and appetite and energy expenditure, are important internal factors in determining body weight. On the other hand, dietary fatty acids composition can modulate appetite and energy metabolism, but not all fats are equal in producing metabolic responses.

Given the accumulating evidence for differential effects of various dietary fatty acids, one important area of investigation is to scrutinize their roles in weight, appetite and energy expenditure modulation. There is substantial evidence to suggest that saturated fatty acids have a greater effect on appetite control, although in the long run may result in more weight gain than unsaturated fatty acids due to a weaker stimulation of energy expenditure. In contrast, mono-unsaturated fats do not have much effects on appetite control, but they can be beneficial in weight control over the long term due to stimulatory effects on energy expenditure. Interestingly, in case of poly unsaturated fats, including n-3 and n-6, their effect on increasing energy expenditure is aligned, but they act differently in controlling weight and appetite.

KEYWORDS

Fatty acids; weight; appetite; energy expenditure; diet induced thermogenesis

Introduction

The high and growing prevalence of overweight and obesity continues as an undeniable public health concern (Ogden et al. 2014). To some extent, this epidemic can be attributed to the consumption of energy-dense foods, i.e. high in fat, as one of the environmental factors (French, Story, and Jeffery 2001). Although low-fat diets are still recommended as a dominant weight-loss approach today (Ludwig 2016), the evidence has not been able to prove the long-term benefits of these regimens in terms of health and meaningful weight loss when compared with usual diets (Howard et al. 2006; Group 2013). For this reason, investigators have considered the quality or type of fatty acids important. In fact, it seems that fat-derived calorie has only weak effects on body weight (Field et al. 2007) and the type of fatty acids (FA) seems to be more important. Although research on the potential effects of different fatty acids on the body is not yet comprehensive, it has been suggested that the effects of fatty acids on the balance of energy, weight and appetite vary depending on the length of the chain, the degree of saturation and the position of double bonds (French et al. 2000; Lawton et al. 2000; Strik et al. 2010).

According to previous researches in literature, not only the quantity of dietary fats, but also the type of dietary fatty acids is related to different weight gain rates (de Wit et al. 2012; Bjermo et al. 2012) with important health consequences and possibly energy expenditure alterations (Jones et al. 1992; Jones and Schoeller 1988; van Marken Lichtenbelt, Mensink, and Westerterp 1997). But since the results of the studies are contradictory, it cannot be conclusively concluded. For instance, diverging effects of different FA on long-term weight variations are cited in three large prospective cohorts. According to this report, total dietary monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA) intake were related with less weight gain, whereas dietary trans fatty acids and saturated fatty acids (SFA) were related with greater weight gain (Liu et al. 2018). Comparing the intake of energy and various fatty acids across body mass index (BMI) categories revealed that SFA and MUFA were positively correlated with BMI, while this association was not observed in PUFA (Raatz et al. 2017). Studies have not yet reached the definitive conclusion about body metabolic responses to the quality of dietary fats and research is ongoing. Accordingly, the content of this review provides a summary on the current body of knowledge on the differential effects of dietary fatty acids on weight, appetite and energy expenditure. It also refers to the putative mechanisms underlying this association and reflects the controversies on this topic.

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Weight

One of the reasons that researchers have been prompted to focus on the contributory role of dietary fatty acids, relates to increasing prevalence of overweight and obesity and relates to health and economic burden (Lawton et al. 1993; Willett 1998; Bray and Popkin 1998). Although, there is no doubt that a high-fat diet can induce weight gain, but not all dietary fatty acids will produce the same effects on body weight and metabolism regulation (Pellizzon et al. 2002). This in turn affects the signals of hunger and satiety. However, the effect of fatty acids on body composition changes should not be overlooked, Emamat et al., in a review study, have addressed these effects (Hadi et al. 2018).

Metabolic and physiologic effects of dietary fatty acids are fairly heterogenous. These differences are partially attributed to the degree of saturation of fatty acids consumed, as in most studies, adiposity is more attributed to SFA rather than unsaturated FA, in particular PUFA (Piers et al. 2003; Doucet et al. 1998; Baxheinrich et al. 2012). Results about MUFA are thought to be more contradictory (Piers et al. 2003; Piers et al. 2002). It seems that another probable mechanism accountable for the different impacts of fatty acids on body weight is related to the difference in diet induced thermogenesis (DIT) and energy expenditure (EE). According to the results of previous studies, high-fat diets rich in MUFA and PUFA would induce higher EE and DIT compared to high-fat SFA-rich diets (Kien et al., 2005; Casas-Agustench et al. 2009). In other words, compared to unsaturated FA, ingestion of SFA leads to a smaller increase in the oxidation of fatty acids and total EE (Piers et al. 2002; Soares et al. 2004; Delgado-Lista et al. 2008). Hence, it can be supposed that SFA plays a more prominent role in obesity than MUFA and PUFA. The positive effect of PUFA on EE leads to higher resting metabolic rate (RMR) and DIT after consumption of these fatty acids, which in the long run can be effective in weight maintenance and reducing the metabolic and chronic diseases risks (Jones, Jew, and AbuMweis 2008; Clevenger et al. 2014). However, in older studies and animal experiments, it has been pointed out that dietary fats induce a slight oxidative response, which in turn facilitates its storage (Scharrer and Langhans 1986; Surina-Baumgartner et al. 1996).

Energy expenditure

Maximizing DIT and following higher EE can assist in the regulating energy balance and achieving right weight (Westerterp et al. 2008). Although dietary fats have effects on DIT and EE, it is important to note that not all fatty acids produce same effects on metabolism. It turns out that among different dietary fatty acids, PUFA is oxidized faster than SFA and therefore SFA is more favorable for storage, since fat oxidation is inversely associated with its storage (Jones et al. 1992; Jones and Schoeller 1988). A large body of literature documents that DIT after consuming unsaturated fatty acids, is higher when compared with saturated fats (Piers et al. 2002; Casas-Agustench et al. 2009; Soares et al. 2004; Clevenger et al. 2014). But in the other three studies, contradictory results in comparison MUFA vs. PUFA have been achieved (Casas-Agustench et al. 2009; Jones, Jew, and AbuMweis 2008; Clevenger et al. 2014). In a study using the labeled isotopes indicated that MUFA $\geq$ PUFA $>$ SFA is the preferred arrangement for oxidation in the body (Krishnan and Cooper 2014).

Appetite

Another important and influential factor in weight control is appetite. Multiple physiological mechanisms play roles in controlling appetite. A number of hormones, neurotransmitters, and peptides are identified as stimulators of orexigenic or anorexigenic responses (Halford et al. 2003) which include leptin, ghrelin, peptide YY (PYY), cholecystokinin (CCK) and glucagon-like peptide 1 (GLP-1) (Feinle-Bisset et al. 2005). These hunger and satiety endocrine hormones are involved in suppressing energy intake through controlling appetite (Little and Feinle-Bisset 2011) and accelerate energy expenditure (Yannakoulia et al. 2003). The secretory activity of these factors is influenced by dietary factors such as various nutrients and composition of dietary fat and on the other hand, different fatty acids have different effects on these hormones' responses (Murata et al. 2000; Feltrin et al. 2004; Hand et al. 2010).

These events at least partly explicate the inhibitory effect of fats on appetite and energy intake (Chaudhri et al. 2008; Sturm et al. 2004), although other line of evidence reported that fat weakly stimulate satiety and palatability and high energy density of high-fat foods contribute to passive overconsumption (Blundell and MacDiarmid 1997; Blundell et al. 1993). Furthermore, the mechanisms behind these changes have not yet been completely discovered (de Wit et al. 2012; Bjermo et al. 2012), though it has been proposed that dietary fatty acid composition may have a modulatory role (Lawton et al. 2000). For instance, in the study by Lawton et al (Lawton et al. 2000) it has been shown that unsaturated fatty acids, in contrast to saturated fatty acids, induced a greater food intake reduction, while Flint et al (Flint et al., 2003) and Alfenas and Mattes (Alfenas and Mattes 2003) failed to find such difference between fatty acids in terms of satiety and controlling energy balance. In one study, fatty acids hierarchy with respect to satiety properties was considered to be PUFA $>$ MUFA $>$ SFA, although support of this hypothesis requires further research (Alfenas and Mattes 2003). Therefore, in addition to total amount of fats intake, dietary fatty acids profile is also effective in regulating weight, metabolism and appetite.

Saturated fatty acids

Weight

In most studies, it has been stated that SFA produce more weight gain than other type of fatty acids. Based on the analysis of 3 prospective cohorts, a 5% increase in energy intake from SFA was related to an increase of 0.61 kg per 4-y interval in men and women (Liu et al. 2018). It has even been

suggested that consumption of SFA may contribute to age-related weight gain (Liu et al. 2018). However, some studies have failed to demonstrate such an effect (Casas-Agustench et al. 2009).

A 6-month interventional study showed that SFA intake with person's body weight at following 18 months was positively correlated. These observations, in other words, indicate that the amount of SFA intake can be a predictor of future weight so that the lower the consumption of SFA is, the better the weight maintenance will be (Lin et al. 2012). SFA-rich diets possess a downward effect on fat oxidation, energy expenditure and DIT, which results in fat accumulation in the body and weight gain (Piers et al. 2003; Kien et al., 2005).

Appetite

It appears that a high-fat diet, even without taking too much calories, can lead to obesity, which indicates high-fat diet may induce an elevated feeding efficiency (Jen, Greenwood, and Brasel 1981). In comparison the appetite properties of SFA-rich butter with a MUFA-rich canola and peanut oil, results did not support a differential satiety effect of fat sources rich in MUFA relative to one rich in SFA (Alfenas and Mattes 2003). However, it was also revealed in the study by Robertson et al. (Robertson et al. 2002) that SFA prompt a greater boost in CCK secretion compared with either MUFA or PUFA. This result is also confirmed in another study that the peak PYY level following SFA-rich meal is much higher than that of PUFA-rich meal (Kozimor, Chang, and Cooper 2013). Intraduodenal administration of two isoenergetic doses of two fatty acids of Capric acid (C10) and Lauric acid (C12) showed that C12 suppresses appetite and energy intake through increasing GLP-1 level, while C12 causes greater increase in CCK concentration (Feltrin et al. 2004). These contradictions have been shown in various studies, and investigations will continue until a definite result is achieved.

Energy expenditure

Undeniably, dietary fatty acids differentially influence on DIT and overall energy expenditure. It is hypothesized that 24-h energy expenditure in a SFA-rich diet is lower than energy expenditure in a MUFA-rich diet (Kien et al., 2005). This difference can be partially attributed to the differences in the absorption and metabolism of fatty acids. The absorption of saturated fatty acids is slightly (about 2% in comparing SFA and MUFA) less than unsaturated fatty acids (Baer et al. 2003).

As with the question of whether the degree of unsaturation of fatty acids can affect the rate of energy expenditure, it is also worth noting that the length of the fatty acid chain can contribute to energy expenditure. This question has been addressed in a study of DeLaney et al. (DeLany et al. 2000). The results of this study indicate that the shorter the length of the fatty acid chain, the higher the oxidation rate would be. It was also shown that this preference for faster oxidation of shorter chain length fatty acids is applies to SFA more than other fatty acids such as unsaturated FA. The comparison of medium-chain triglycerides (MCT) and long-chain triglycerides (LCT) in intervention trial studies confirmed these findings by showing that the postprandial energy expenditure following MCT was higher than LCT (Matsuo et al. 2001; St-Onge et al. 2003). Since the medium-chain fatty acids are superior over long-chain fatty acids respecting EE, DIT and oxidation, it seems that consuming fatty acids with shorter chain length may assist weight maintenance and even weight reduction (St-Onge et al. 2003; Rego Costa, Rosado, and Soares-Mota 2012).

Assessment of RMR, 24-h EE and DIT by indirect calorimetry for 5 consecutive days failed to show the difference between the rich SFA diet and the MUFA-rich diet (Cooper et al. 2009), which is contradictory with what has been reported previously in the literature. These inconsistencies can be contributed to the difference in the type of dietary fatty acid consumed, duration of intervention, EE evaluation method and various other factors. However, it can be said that the energy expenditure after receiving saturated fatty acids is more than the unsaturated fatty acids due to a shorter chain length.

Mono unsaturated fatty acids

In various studies, it has been argued that a MUFA-rich diet can improve metabolic and anthropometric parameters, which is perhaps why MUFA consumption is recommended in most of the guidelines for up to 20% of the total energy intake. Also, increased DIT and postprandial oxidation rate following MUFA intake can influenced on weight loss and adiposity reduction (Piers et al. 2002; DeLany et al. 2000; Lovejoy et al. 2002). Differences in MUFA with other dietary fatty acids have been described in several studies in terms of effects on lipid oxidation, energy expenditure, DIT and weight alteration, although contradictions in the results of these studies are evident.

Weight

A four-year follow-up study showed that an 5% increase in percentage of energy intake from MUFA was associated with a slight increase (0.05 kg) in weight gain (Liu et al. 2018). In fact, it was exposed in this study that MUFA and body weigh relationship is relatively neutral, that means not the same as the relation between PUFA and weight, is negative and not the same as the relation between SFA and weight, is positive (Liu et al. 2018). In another study, olive oil consuming as a rich source of MUFA did not affect the weight and risk of obesity after adjustment for total energy intake (Benítez-Arciniega et al. 2012). In most studies, no clinically or statistically significant association have been found between the MUFA and weight or reverse relationship has been reported.

The results of the Nurses' Health Study and the "Seguimiento Universidadde Navarra" (SUN) project indicated an inverse relationship between MUFA intake and

weight gain (Field et al. 2007; Bes-Rastrollo et al. 2006). In a prospective study, it was shown that the use of olive oil in the context of the Mediterranean diet was not associated with the risk of obesity and overweight (Bes-Rastrollo et al. 2006). This study found that high fat intake (about 41% of total calorie) has not led to weight gain, as MUFA-rich olive oil was the source of dietary fat, and also SFA-derived calories were lower and intake of vegetables was higher in these individuals (Bes-Rastrollo et al. 2006). Therefore, as the results of these studies suggest, the risk of obesity will not increase with increasing olive oil consumption. Contrary to these results, it was stated in two other studies that olive oil consumption, even in the Mediterranean context, without considering energy compensation can cause obesity. This is one of the reasons for the increasing prevalence of overweight and obesity in European societies (Schröder et al. 2007; Berghöfer et al. 2008).

The underlying mechanism through which MUFA negatively affects the weight includes increasing fat oxidation and energy expenditure following MUFA intake, which can potentially facilitate weight loss (Jones, Jew, and AbuMweis 2008; Kien and Bunn 2008). It is also supposed that this weight-losing effect of MUFA is mainly due to the acceleration of oxidation of MUFA fats, not SFA (Piers et al. 2002; DeLany et al. 2000; Lovejoy et al. 2002).

Appetite

Appetite, satiety and hunger can be examined through subjective (visual analog scale: VAS) and objective (measuring the serum level of appetite-related hormones) responses. The results of studies in this regard on different fatty acids are very contradictory. Concerning the acute effects of fatty acids on appetite, Maljaars et al. (Maljaars et al. 2009) concluded that there was no difference in serum levels of PYY after infusions of MUFA, PUFA and SFA. Whereas the superiority of PUFA and SFA in stimulating greater PYY response compared to MUFA was revealed in the study conducted by Robertson et al. (Robertson et al. 2002). Similarly, Cooper et al. (Cooper et al. 2011) reported that the serum level of PYY over 24-h period following SFA intake was increased more than that of MUFA, but no significant difference was found in VAS scores. According to a study conducted in normal weight women, there is no significant difference between SFA, MUFA and PUFA in terms of altering PYY serum concentrations, but based on the subjective evaluation, SFA-rich meals induce a greater sense of satiety in individuals. Also, all three fatty acids were similar regarding the feelings of hunger (Kozimor, Chang, and Cooper 2013). Kozimor and colleagues (Kozimor, Chang, and Cooper 2013) ranked dietary FA in respect of stimulating PYY acute response as PUFA > SFA > MUFA. Although these data suggest that MUFA-rich meals have a weaker satiety response, there are also studies with contradictory results that find MUFA to be more satiating than PUFA (Burton-Freeman 2005; Kamphuis, Westerterp-Plantenga, and Saris 2001). In one of these studies, it was shown that participants after consuming MUFA-rich oil reached higher satiety score compared with a PUFA-rich oil (Burton-Freeman 2005). In comparing MUFA and SFA, MUFA also resulted in a longer satiety and less hunger (Maljaars et al. 2009). The difference between various fatty acids with varying degrees of saturation in terms of induction of satiety has not been reported (Flint et al., 2003; Alfenas and Mattes 2003).

Differential effects of FA on satiety may also depend on the type of measured hormone, as one other study has shown that MUFA has a greater effect on GLP-1 stimulation vs PUFA and SFA, which is in contrast to the results of the PYY serum concentration experiments (Thomsen et al. 1999). Therefore, it can be supposed that PUFA affects more on PYY, while GLP-1 is more influenced by MUFA. Regarding other hormones (CCK, ghrelin, leptin) no other specific studies have been performed on, or their level remained unaffected during intervention (Lithander et al. 2008).

It is apparent that a clear effect of various FA on satiety has yet to be established. The type of satiety hormone being measured, the method of assessing satiety feeling (subjective vs objective analysis), duration of intervention and the type of oil used as a source of specific fatty acids are some of the reasons that can be cited in justifying these mixed results. It can also be concluded that the effect of dietary FA composition on different appetite-related hormones varies. Appetite hormones are also regulators of energy homeostasis, so different FA can differentially affect energy status.

Energy expenditure

As previously mentioned, different FA possess varied physiological effects. One of these differences is the energy expenditure fluctuations following consuming different fatty acids and that part of the 24-h energy expenditure that is most affected by dietary fatty acids is DIT.

The important factors contributing to the differences in metabolic responses of fatty acids are their chain length and degree of unsaturation. For instance, the shorter the length of the FA chain are (<12 carbons), the faster the oxidation rate will be, and therefore the energy expenditure will increase, contrary to FA with long chain (>14 carbons) that are preferred for storage. Another important factor is the difference in intestinal absorption of various fatty acids, which is why FA with different saturation degree and chain lengths elicit different metabolic responses (St-Onge and Jones 2002; Bendixen et al. 2002).

Piers and colleagues (Piers et al. 2002) for the first time in a study conducted on normal weight or mildly obese men, via indirect calorimetry, have shown that postprandial oxidation of lipids following a MUFA-rich (virgin olive oil) high fat meal is higher than the SFA-rich meal SFA-rich (cream) isocaloric meal. The MUFA-rich meal also increased DIT potentially to 50 kcal/d in participants with total energy intake of 2400 Kcal/d. In a study conducted by Kien et al. (Kien et al., 2005) in healthy nonobese individuals, it was found that a MUFA-rich diet (31.4% oleic acid, 1.7% palmitic acid) after 28 days resulted in a higher level of postprandial lipid oxidation and energy expenditure compared

to the SFA-rich diet (16.8% palmitic acid, 16.4% oleic acid). Another study with 4 weeks follow-up exposed replacement of high-MUFA isocaloric diets (22% MUFA, 11% SFA) instead of high-SFA diets (24% SFA, 13% MUFA) resulted in a significant weight loss in a same fat-derive calorie (40%) (Piers et al. 2003). The increasing effect of MUFA on DIT, although is greater than SFA, does not appear to have a significant difference with PUFA (Casas-Agustench et al. 2009). In another study, a high MUFA (oleic acid, 75% of total fat energy) diet was compared to a high SFA (palmitic acid, 40% of total fat energy) diet in a 3-week intervention with a 1-week washout period in thirty-two obese and non-obese men and women. The results of this study indicated that RMR, fasting and postprandial EE, measured in a metabolic chamber, after the MUFA-rich diet were higher than the SFA-rich diet (Kien et al. 2013).

Promoting effect of MUFA on DIT and fat oxidation compared to SFA has been shown in both obese and normal-weight subjects, although the increase in fat oxidation was not necessarily allied with an increase in DIT (Piers et al. 2002; Casas-Agustench et al. 2009; Soares et al. 2004; Krishnan and Cooper 2014). However, these results were challenged in two other studies which found no difference in DIT following the MUFA-rich diet compared to SFA (Clevenger et al. 2014; Clevenger, Stevenson, and Cooper 2015). Beforehand, the effects of the moderate fat diet containing MUFA (oleic acid), SFA (palmitic acid), and trans (eladic acid) FA were also compared in 25 healthy subjects over a 4-week crossover study, which its results failed to show any differences in DIT and resting EE between the three diets (Lovejoy et al. 2002).

Furthermore, Jones et al. (Jones, Jew, and AbuMweis 2008) showed greater DIT following MUFA versus PUFA-rich high fat meals in normal-weight men. In contrary, the comparison of SFA, MUFA, and PUFA in another study revealed that MUFA and PUFA have greater DIT than SFA, but there was no difference between MUFA and PUFA (Casas-Agustench et al. 2009). Current evidence in support of the effect of the MUFA-rich diet compared with the SFA on weight maintenance is stronger than the evidence available to support the PUFA-rich diet effect compared with the SFA (Krishnan and Cooper 2014). One of the reasons for the effect of MUFA on maintaining body weight is to increase fat oxidation and hence increase in total energy expenditure (Kien et al., 2005).

These evidences support the opinion that high MUFA diets is likely to be more metabolically beneficial to health than the high SFA diet. In general, it can be concluded that unsaturated fatty acids, in comparison with saturated ones, produce greater DIT, but the difference in DIT response to MUFA and PUFA intake remains to be discussed. Differential changes in peroxisome proliferator-activated receptors (PPARs) expression and activity depending on dietary fat quality may partially explain these findings. PPARs play a role in modulating lipid oxidation, utilization and thermogenesis. In the postprandial state, the expression of PPAR-α is increased rapidly which subsequently suppress genes involved in fat synthesis and induce genes involved in fat oxidation and thermogenesis (Clarke et al. 2002). On the other hand, the expression and activity of PPAR-α following MUFA and PUFA intake is greater than the time when SFA is consumed. Hence, high-MUFA and high-PUFA oils generate greater EE and DIT than SFA-containing oils (Clarke et al. 2002). Another possible mechanism might be the increase of sympathetic nervous system activity due to MUFA-rich meals which results in greater DIT (Takeuchi et al. 1995; Matsuo et al. 1995). Also, in an animal experiments, upregulation of uncoupling protein (UCP) expression has been reported following the MUFA-containing oil administration, which in turn could contribute to the DIT increase (Rodríguez et al. 2002).

Poly unsaturated fatty acids

Although, there is some disagreement concerning the effectiveness of PUFA consumption on body weight control (Nimptsch, Berg-Beckhoff, and Linseisen 2010; Munro and Garg 2012), several experimental evidences have shown the consumption of PUFA is related to reversing body fat gain, adiposity and fat accumulation in visceral area (Doucet et al. 1998; Rokling-Andersen et al. 2009; Kalupahana et al. 2010), increasing fatty acid oxidation and improving insulin signaling in skeletal muscle cells (Kim et al. 2000). The effects of different types of PUFA, including n-3 and n-6, on weight, energy expenditure and appetite are in some cases concurrent and in some cases different, which are described in detail here.

Weight

Omega-3 fatty acids have the ability to induce several beneficial effects for the treatment of obesity and other metabolic disturbance (Rokling-Andersen et al. 2009). In individuals with overweight or obesity, n-3 fatty acids, especially Eicosapentaenoic acid (EPA) and Docosahexaenoic acid (DHA), have an important role in weight management (Flock et al. 2013; Flachs et al. 2009; Lorente-Cebrián et al. 2013). Prospective studies have shown a potential inverse relationship between n-3 PUFA and adipose tissue. The health professional 12-year follow-up cohort found that high fish intake is associated with a lower risk of overweight; however this study did not provide any data on the relationship between n-3 PUFA and BMI changes (He et al. 2002). Similarly, the results of the Nursès Health Study suggest that higher fish intake is related to higher prevalence of obesity (Iso et al. 2001). In a single-blind trial, comparison of control diet with intervention diet (6 g/d of visible fat replaced with 6 g/d DHA-rich fish oil) in healthy adults showed that lipid oxidation and energy expenditure were higher and body fat mass was lower in the intervention group (Fontani et al. 2005). In contrast, Shanghai Womańs and Mens Health study reported no association between BMI and tertiles of fish consumption (Takata et al. 2013). Similarly, two published meta-analysis studies failed to show a correlation between fish oil intake and weight (Du et al. 2015; Zhang et al. 2017). These findings suggest that although fish oil

intake can be effective in reducing abdominal fat, but it cannot decrease body weight in overweight and obese individuals. In other words, these limited evidences suggest that n-3 PUFA supplementation alone may attenuate the body fat deposition without any change in body weight. Excessive consumption of omega-3 fatty acids increases the body's need for vitamin E and increases the risk of blood thinning and hypertriglyceridemia.

N-3 PUFA combined with calorie restriction can cause more weight loss compared to calorie restriction alone. Thorsdottir et al. (Thorsdottir et al. 2007) investigated the effects of n-3 fatty acids in conjunction with 30% energy restriction on body weight in overweight men. Subjects were randomized to one of four isocaloric energy-restricted diets for 8 weeks as follow: (Ogden et al. 2014) control (sunflower oil capsules; no seafood); (French, Story, and Jeffery 2001) lean fish (3×150 g portions of cod/week); (Ludwig 2016) fatty fish (3×150 g portions of salmon/week); (Howard et al. 2006) fish oil (DHA/EPA capsules, no seafood). The results of this trial showed that volunteers receiving lean fish (cod), fatty fish (salmon) and fish oil capsules lost one kilogram more than those on energy restriction alone.

The effects of fatty acids on weight in women appear to be different from those of men (Fontani et al. 2005; Thorsdottir et al. 2007; Krebs et al. 2006). These gender differences raise the possibility that the effects of n-3 PUFA in weight control may be more beneficial in men than women.

There are several proposed mechanisms by which n-3 PUFA can improve metabolic status and body weight. N-3 fatty acids can regulate adipocyte quantity through modulating cell proliferation, differentiation and apoptosis. Downregulation of master transcription factors involved in adipogenesis by n-3 fatty acids deter adipocyte proliferation and induce apoptosis in pre-adipocyte cell line (Hanada et al. 2011; Tanabe et al. 2008; Manickam, Sinclair, and Cameron-Smith 2010; Barber et al. 2013). Moreover, n-3 fatty acids control cell signaling pathways related to fat storage and fat mobilization, stimulate mitochondrial biogenesis and fatty acid oxidation, which subsequently decrease weight and enhance energy expenditure (Flachs et al. 2005).

On the other hand, n-3 PUFA is considered as an anti-inflammatory agent due to the ability of interaction with the major inflammatory signaling pathways, inhibition of cytokines production (Lorente-Cebrián et al. 2013; Wall et al. 2010; Ellulu et al. 2015; Yates, Calder, and Rainger 2014), suppression of NF-κB activity and inhibition eicosanoids production (Flock et al. 2013; Chapkin et al. 2009). Given that inflammation is strongly associated with preventable chronic conditions such as obesity, n-3 PUFA consumption can be effective in preventing and treating obesity (Simopoulos 2008; Campbell and Bello 2012). But because of the great differences in the methodology of the studies, it is difficult to generalize their findings. So, the net effect of n-3 fatty acids on weight management needs further investigations.

There is increasing concern that exposure to excess n-6 PUFA may exert adverse effects on metabolic health due to hyperplasia, hypertrophy and increased fat deposition in the early in life (Muhlhausler and Ailhaud 2013). A series of in-vitro and experimental animal studies have demonstrated high levels of linoleic acid and other n-6 derivatives, can promote the differentiation of pre-adipocytes to the adipocytes, increase lipogenic genes expression and activities, fat deposition and adipocyte quantity and size (Gaillard et al. 1989; Azain 2004; Javadi et al. 2004; Muhlhausler et al. 2010). These findings are in line with the fact in humans that perinatal exposure to a high n-6 PUFA diets (similar to western diet) is associated with higher adipose tissue in the offspring (Muhlhausler and Ailhaud 2013; Donahue et al. 2011; Ailhaud et al. 2006; Ailhaud et al. 2007). In this regard, evidence from a review on animal and human studies also suggests that higher n-6 PUFA consumption is associated with more weight gain (Ailhaud et al. 2006). Although, in the nurses' health study, researchers found no significant correlation between body mass index and tertiles of n-6 PUFA intake (Melanson, Astrup, and Donahoo 2009).

Experimental studies have suggested that n-6 PUFA may affect body weight through modulating adipogenesis (Amri, Ailhaud, and Grimaldi 1994), fat homeostasis (Clarke et al. 2002; Jump et al. 1994), adipose tissue-gut-brain axis (Schwinkendorf et al. 2011) and systemic inflammation (James, Gibson, and Cleland 2000). Metabolites of n-6 PUFA play important role in adipocyte hypertrophy by increasing cellular free fatty acid content (Hennig and Watkins 1989). Adipose tissue expansion can be also a result of adipocyte hyperplasia that occurs through the proliferation and differentiation of pre-adipocytes into mature adipocytes, which is facilitated by n-6 PUFA (Gaillard et al. 1989). Another aspect of high n-6 fatty acid intake, which can affect weight control, is to induce hyperactivity of endocannabinoid system. Excessive endocannabinoid signaling leads to increase in appetite, food intake, weight gain and metabolic disturbances associated with obesity (Simopoulos 2016). Arachidonic acid inhibits the production and expression of leptin, which leads to impairment of hypothalamic leptin signaling and energy homeostasis (Cheng et al. 2015; Nuernberg et al. 2011). Moreover, cumulative pool of arachidonic acid causes increased production of prostaglandin 2, thromboxane 2 and leukotriene 4 which are pro-thrombotic and pro-inflammatory elements leading to stimulation of white adipogenesis and inhibition of mitochondrial biogenesis (Simopoulos 2016). This will eventually lead to weight gain and reduced energy expenditure.

There is an important issue that must be addressed in this review. Western diets contain high levels of n-6 PUFA-rich sources such as vegetable oils) corn, soybean, sunflower and safflower oils) and very low level of n-3 PUFA. The n-6/n-3 ratio is critical for the health and prevention of obesity-related problems. A high n-6/n-3 PUFA ratio in the diet (20:1) may be detrimental in terms of adiposity and weight gain due to pro-inflammatory and pro-thrombotic effects, while high levels of n-3 PUFA reduces fat deposition and risk of weight gain (Simopoulos 2016).

Table 1. Summary of clinical trials on the differential effects of dietary fatty acids on weight, appetite and energy expenditure.

Author, year	Groups	Number Duration	Intervention Study design	Results
(Payahoo et al. 2018)	Obese individuals	N = 60 4-week period	Two capsules containing 1 g/day n-3 fatty acids [180 mg EPA, 120 mg DHA] A randomized double-blind placebo-controlled clinical trial	Supplementation with n-3 resulted in a significant increase in satiety, a nonsignificant increase in serum leptin levels and a significant reduction in weight
(Polley et al. 2018)	Normal-weight men	N = 15 5-day period	Multiple phasic trial: 3 d lead-in diet, pre-diet visit, 5-d diet (50% fat) high in PUFA (25% of energy) or MUFA (25% of energy), post-diet visit A single-blind, randomized cross-over trial	High MUFA diet decreased RMR and increased DIT acutely. But these metabolic responses were greater in the PUFA diet after 5-day diet.
(Nguo et al. 2018)	Healthy overweight men	N = 13 A single meal	Three iso-energetic (3780 kJ) high fat (45%) meal rich in short-/medium-chain SFA (SMCSFA, <12 carbons, 27% of fat), long-chain SFA (LCSFA, >14 carbons, 99% of fat), or MUFA (71% of fat) A single blinded, cross-over trial	Fatty acid saturation and chain length have no acute differential effect on DIT and fat oxidation.
(Stevenson et al. 2017)	Normal-weight adults	N = 26 7-day period	A 7-day PUFA-rich diet (21% of total energy) versus control diet (7 % PUFA) A randomized, single blinded, placebo-controlled, parallel trial	No significant changes were found in weight and RMR in either PUFA-rich diet or control diet
(Clevenger, Stevenson, and Cooper 2015)	Healthy obese women	N = 16 A single meal	Isocaloric high fat meals (70% of energy) rich in either SFA (40% of energy, butter, coconut, and palm), MUFA (42% of energy, canola and olive oil) or PUFA (42% of energy, sunflower and flaxseed oil) A single blinded, randomized cross-over trial	No differentially effects on DIT or postprandial substrate oxidation were detected
(Stevenson, Clevenger, and Cooper 2015)	Obese women	n = 16 A single meal	Three high fat meals (70% of energy) rich in MUFA (42.4% of energy), PUFA (42.3% of energy), or SFA (45% of energy) A single-blind crossover	Decrease in ghrelin following PUFA and MUFA vs. SFA intake was significantly greater while PYY increased in PUFA more than two other FA No differences were seen in GLP-1, appetite (VAS score) or total energy consumed
(Clevenger et al. 2014)	Normal-weight premenopausal women	N = 15 A single meal	Three isocaloric high fat meals (70% of energy from fat): SFA-rich (40% of total energy), MUFA-rich 42% of total energy) or PUFA-rich (42% of total energy) a single-blinded, randomized cross-over trial	DIT following the PUFA-rich meal was greater than that of the SFA- or MUFA-rich meals No significant differences were found for substrate utilization
(Harden et al. 2014)	Overweight and obese women	N = 40 12-week period	45% oil-in-water emulsions, containing predominantly DHA (140-g portion of oily fish) or oleic acid (OA: olive oil) A randomized, double-blinded, parallel trial	Weight significantly reduced after DHA compared with OA
(Kozimor, Chang, and Cooper 2013)	Normal weight women	N = 15 A single meal	High fat (70% of total energy) liquid meals rich in MUFA (42% of total energy), PUFA (42% of total energy), or SFA (45% of total energy) A single-blind randomized crossover trial	The postprandial PYY response was significantly weaker in the MUFA-rich meal compared to other two meals The SFA-rich meal provided more satiety feelings compared to other two meals, based on the VAS rating, and showed a significant correlation with PYY
(Kien et al. 2013)	Young adults	N = 32 3-wk period	high–palmitic acid diet (HPA) or low–palmitic acid and high–oleic acid diet (HOA)	HOA was associated with increased physical activity and REE

(*continued*)

Table 1. Continued.

Author, year	Groups	Number Duration	Intervention Study design	Results
			A randomized, double-blind, crossover trials	
(Baxheinrich et al. 2012)	Patients with the metabolic syndrome	N = 81 6-month period	A hypoenergetic diet with either rapeseed oil (high MUFA, 3·5 g/d ALA) or olive oil (high MUFA, low ALA) A randomized, parallel trial	Canola oil caused more weight loss than olive oil (7·8 v. 6·0 kg; $P < 0·05$)
(Strik et al. 2010)	Healthy, lean men	N = 18 A single meal	High-fat breakfasts containing 26 g lipid rich in SFA (65% of total fat), PUFA (76%) or MUFA (76%) A randomized cross-over	No differential effect on hunger or satiety feeling fullness was revealed
(Poppitt et al. 2010)	lean men	N = 18 A single meal	A breakfast containing 52 g fat (58% of total energy) enriched in either short chain (dairy), medium chain (coconut oil) or long chain (beef tallow) fatty acids A randomized, cross-over trial	There was no significant difference between fatty acids with different chain length respecting to energy intake, hunger and satiety feeling
(Casas-Agustench et al. 2009)	Young healthy men	N = 29 A single meal	Three isocaloric meals: high in PUFA from walnuts, high in MUFA from olive oil, and high in SFA from fat-rich dairy products. a randomized crossover trial	5-h postprandial thermogenesis was higher by 28% after the high-PUFA meal and by 23% higher after the high-MUFA meal compared with the high-SFA meal. Fat oxidation rates increased after meals high in unsaturated FA and decreased after the high-SFA meal, but both nonsignificant.
(Cooper et al. 2009)	Healthy men	N = 8 A single meal	4 treatments: high-fat diet (50% of energy) rich in MUFA (30% of energy) with or without exercise, or rich in SFA (22% of energy) with or without exercise A randomized crossover trial	No significant difference was found in average 24-h EE between MUFA- and SFA-rich diet
(Maljaars et al. 2009)	healthy subjects	N = 15 one-day period	Intra ileum administration one of the following four lipid emulsions: 6 g of 18:0 (shea oil) or 18:1 (canola oil), or 18:2 (safflower oil) oils, or control infusion A double-blind, randomized, crossover trial	Compared with the control, only 18:2 and 18:1 significantly increased satiety and reduced hunger
(Due et al. 2008)	Nondiabetic overweight or obese adults	N = 125 6-month period	3 ad libitum diets: High-MUFA diet (>20% of 35–45% total fat), Low-fat (20–30% of energy), Control diet (35% fat). A parallel, randomized trial	Body weight increased nonsignificantly in all groups and no difference was found respecting weight regain prevention
(Brunerova et al. 2007)	Obese non-diabetic (OB, n = 31) and type 2 diabetic patients (DM, n = 23)	N = 54 3-month period	hypocaloric, high-fat diet enriched with MUFA (M = 22.5% MUFA, 11.25% SFA, 11.25% PUFA) versus conventional diet (C = 10% MUFA, 10% PUFA, 10% SFA) (4 groups: DM/M, DM/C, OB/M and OB/C) A randomized, open-labeled trial	significant weight reduction in all four groups REE significantly decreased only in the obese non-diabetic subjects using the conventional diet
(Rasmussen et al. 2007)	Overweight nondiabetic subjects	N = 27 6-month period	A MUFA-rich diet (>20% of energy in a diet with 35–45% fat) or low-fat diet (20–30% of energy) following an 8-wk low-calorie diet (800–1000 kcal/d) and a 2-wk weight-stabilizing diet A parallel intervention trial	MUFA diet had no significant effect on 24-h EE DIT was significantly lower following MUFA compared with low-fat diet
(Kien et al. 2005)	Healthy young adults	N = 43 28-day period	high palmitic acid (PA) (40% fat, 16.8% PA, 16.4% as OA) or high oleic acid (OA) (40% fat, 1.7% PA, and 31.4% OA). after a 28-day baseline diet	No significant difference was seen in RMR, although EE was greater in OA diet than that in the high-PA group

(*continued*)

Table 1. Continued.

Author, year	Groups	Number Duration	Intervention Study design	Results
			(41% fat, 8.4% PA, and 13.1% OA) A randomized, double-masked, controlled trial	
(Feltrin et al. 2004)	Healthy males	N = 8 A single meal	Intraduodenal administration of lauric acid (C12) or decanoic acid (C10), administered at 0.375 kcal/min A double-blind, randomized trial	C12, but not C10, suppressed appetite perceptions and energy intake
(Piers et al. 2003)	Overweight or obese men	N = 8 4-week period	Two high-fat diets (40% energy) rich in SFA (24% of energy) or MUFA (22% of energy) A randomized cross-over trial	Although the MUFA-rich diet resulted in more weight loss, there was no difference in energy intake and energy expenditure.
(Soares et al. 2004)	Postmenopausal women	N = 12 A single meal	Two high-fat, isoenergetic meals rich in SFA (cream) or MUFA (olive oil) A single blind, randomized trial	MUFA significantly stimulated postprandial fat oxidation and DIT
(Flint et al. 2003)	Overweight young men	N = 19 A single meal	Different meals (60% energy from fat) with three fat sources including PUFA, MUFA, and trans, all in 18 carbons. A randomized, cross-over trial	No significant differences were seen among the 3 test meals regarding basal or postprandial appetite, based on VAS ratings, and EE
(Piers et al. 2002)	Adult male	N = 14 A single meal	high-fat (43% of total energy) meals, rich in either MUFA (olive oil) or SFA (cream) A randomized trial	MUFA induced significantly greater postprandial fat oxidation rate and DIT in subjects with a high waist circumference (>99 cm)
(Alfenas and Mattes 2003)	healthy adults	N = 20 A single meal	Three muffins with either 40 g MUFA (peanut oil and canola oil), or 40 g SFA (butter) or no fat besides 150 mL of water within 15 minutes A within-subject cross-over trial	MUFA-containing muffins in satiety boosting and two fat-containing muffins in hungry reducing were effective as compared to fat-free muffins. But no difference was found between two fat-containing muffins.

Appetite

There is promising evidence indicating that n-3 PUFA may suppress appetite and increase satiety sensation. Perez-Matute fed 6-week-old male rats a high-fat-diet (62% w/w) containing one gr/kg/d EPA for 5 weeks, and reported an increase in the plasma concentration of leptin, appetite-suppressing hormone, and consequent reduction in food intake (Perez-Matute et al. 2007). Increased sensation of fullness and satiety following n-3 PUFA intake, has been reported repeatedly in various studies (Takahashi and Ide 2000; Parra et al. 2008).

There is no doubt that the sense of satiety caused by n-3 PUFA-enriched meals can play an important role in weight control. Both in-vitro and in-vivo studies support the ability of n-3 PUFA in regulation of hormones involved in food intake (Gray et al. 2013). For instance, Stevenson et al. (Stevenson, Clevenger, and Cooper 2015) reported PUFA induce highest satiety hormone (PYY) response and greatest hunger hormone (ghrelin) suppression. Another study indicated that PUFA have strongest control over food intake and appetite among fatty acids (Lawton et al. 2000). It has been shown that EPA supplementation increases the production of leptin in obese subjects. By contrast, some studies have shown that n-3 PUFA decreases leptin gene expression (Reseland et al. 2001; Pieke et al., 2000; Izadi, Saraf-Bank, and Azadbakht 2014). Also, appetite suppression can result from binding of n-3 PUFA to free fatty acid receptor family (FFARs). FFAR4 elicits the secretion of cholecystokinin, which its role in suppressing appetite has been proven (Tanaka et al. 2008).

Energy expenditure

Elevation of n-3 fatty acids and reduction of n-6 fatty acids increased energy expenditure in an animal model of obesity (Li et al. 2014). Findings of molecular studies indicate that n-3 PUFA promote fat oxidation, up-regulate uncoupling proteins and increase resting energy expenditure (Couet et al., 1997). In this line, a single blind intervention exposed that 6 gr/d of DHA–rich fish oil can increase resting energy expenditure and resting fat oxidation (Couet et al., 1997). The increase in energy expenditure following PUFA in animal study was also confirmed (Janovska et al. 2013). In normal weight premenopausal women, a high fat diet enriched in PUFA increased DIT compared to high MUFA or SFA diet (Clevenger et al. 2014). The study by Casas-Agustench et al (Casas-Agustench et al. 2009) also confirms these findings. Furthermore, EPA can induce thermogenic genes

expression, such as peroxisome proliferator activated receptor-gamma coactivator (PGC)1-α and uncoupling proteins (Pahlavani et al. 2017), which intensify mitochondrial oxidative capacity in white adipose tissue and skeletal muscle (Bertrand et al. 2013). In general, high PUFA consumption can positively affect energy expenditure through increasing DIT, RMR and rates of FA oxidation, which all may potentially lead to weight loss (Jones, Jew, and AbuMweis 2008).

A list of clinical trials on the effects of fatty acids on weight, appetite and energy expenditure is summarized in Table 1.

Conclusion

Although high-fat diet is one of the identified factors associated with obesity, there are considerable evidences that the body's physiological response to various FA is different. This difference may lead to certain fats being considered as obesogenic, while others are not. For example, the high-fat diet rich in SFA is considered obesogenic, while the increase in unsaturated fatty acids in the diet does not appear to lead to obesity. On the other hand, SFA has a greater effect on the satiety sensation and appetite suppression than other fatty acids, while MUFA is probably the least satiating type of FA. As well, the effect of different fatty acids on the energy expenditure is very inconsistent. Generally, PUFA increase energy expenditure, but about weight and appetite, n-3 fatty acids lead to appetite and weight reduction, while the effects of n-6 are reversed. The overall composition of diet, health status of participants, quantity and quality of dietary fat source, and length of time studied are just a few of the factors that may produce contradictory results.

From the clinical point of view and prevention of chronic diseases, it is recommended to increase the MUFA and PUFA intake and to limit SFA intake. MUFA, although does not induce much satiety feeling, but is more heart friendly than other FA and DIT enhancer. In order to create a sense of satiety, instead of recommending an increase in the intake of SFA and its rich sources include high-fat meat and milk, it is better to increase the fruits, vegetables and whole grains. Also, regarding PUFA, the consumption of more n-3 fatty acids is recommended to target overall health benefits.

Information provided in this review study, can have significant clinical implications to human health, dietary and pharmacological therapies for the prevention and treatment of obesity and non-communicable diseases. Further studies are required, however, to determine the precise mechanisms involved in the differential effects of fatty acids on energy metabolism, weight and appetite.

Disclosure statement

The authors declare that they have no competing interest.

Abbreviation

FA	fatty acids
MUFA	monounsaturated fatty acids
PUFA	polyunsaturated fatty acids
SFA	saturated fatty acids
BMI	body mass index
DIT	diet induced thermogenesis
EE	energy expenditure
RMR	resting metabolic rate
PYY	peptide YY
CCK	cholecystokinin
GLP-1	glucagon-like peptide 1
MCT	medium-chain triglycerides
LCT	long-chain triglycerides
VAS	visual analog scale
PPARs	peroxisome proliferator-activated receptors
UCP	uncoupling protein
EPA	Eicosapentaenoic acid
DHA	Docosahexaenoic acid
FFARs	free fatty acid receptor family

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