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Effects of Monounsaturated Fatty Acids on Glycaemic Control in Patients with Abnormal Glucose Metabolism: A Systematic Review and Meta-Analysis

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Key Words

Monounsaturated fatty acids · Glycosylated haemoglobin · Low fat · Abnormal glucose metabolism

Abstract

Background/Aims: In 2008, the American Diabetes Association recommended low-carbohydrate or low-fat diets for weight management in patients with established type 2 diabetes (T2D), while the amount of monounsaturated fatty acids (MUFA) was not specified. This systematic review focused on the effects of diets high in MUFA versus diets low in MUFA on important risk factors of T2D (i.e. plasma glucose, insulin, homeostasis model assessment of insulin resistance and glycosylated haemoglobin, HbA1c). ***Methods:*** Nine randomized controlled intervention trials with a total of 1,547 participants and a running time of at least 6 months, comparing diets high versus low in MUFA among adults with abnormal glucose metabolism (T2D, impaired glucose tolerance and insulin resistant), being overweight or obese, have been included in the meta-analysis. We performed a random effects meta-analysis to determine the weighted mean differences with 95% confidence intervals using the software package Review Manager 5.0.25 of the Cochrane Collaboration. ***Results:*** Significant differences in HbA1c were found (weighted mean difference –0.21%, 95% CI –0.40 to –0.02; p = 0.03), favouring the high MUFA groups. In contrast, fasting plasma glucose, fasting plasma insulin as well as the homeostasis model assessment of insulin resistance were not affected by the amounts of MUFA in the dietary protocols. ***Conclusions:*** In summary, this systematic review found that high MUFA diets appear to be effective in reducing HbA1c, and therefore, should be recommended in the dietary regimes of T2D.

Introduction

The pandemic spreading of type 2 diabetes (T2D) with 380 million cases worldwide forecasted for the year 2025 leads to enormous challenges for national and international health care systems [1, 2]. Long-term inter-

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vention trials have demonstrated a significant correlation between substantial weight loss or increased physical activity and a reduced incidence of T2D [3, 4]. Dietary composition could play a significant role in improving insulin sensitivity and reducing the risk of T2D as well as its associated complications [5]. The Wisconsin Epidemiologic Study of Diabetic Retinopathy showed that endogenous insulin and glycosylated haemoglobin (HbA1c) were associated with an increased risk of all-cause and cardiovascular disease (CVD) mortality among individuals with late-onset diabetes [6]. The homeostasis model assessment of insulin resistance (HOMA-IR) is an independent predictor of CVD in T2D [7]. The improvement in IR might have beneficial effects, not only on glucose control, but also on CVD in patients with T2D [7]. In the Framingham Heart Study, impaired fasting glucose was associated with increased coronary heart disease risk in women [8]. A meta-analysis of observational studies showed that chronic hyperglycaemia is associated with an increased risk of CVD in persons with T2D [9]. The role of dietary fat in T2D has been of clinical interest for many decades. Kinsell et al. [10] reported that the type of fat consumed might influence insulin action in humans.

However, nutrition recommendations still differ with respect to the effectiveness of different diets in achieving weight loss and better glycaemic control. In 2008, the American Diabetes Association recommended low-carbohydrate or low-fat, calorie-restricted diets for weight loss and weight management in overweight and obese patients with T2D [11]. However, no consideration of a specific quota of monounsaturated fatty acids (MUFA) is given within the daily recommendations [11]. Previous meta-analyses, comparing diets with different amounts of fats in daily nutrition, reported an inconclusive impact of MUFA on biomarkers of CVD, which might be due to the fact that these meta-analyses included short-term intervention trials [12, 13]. To our knowledge, there is only one meta-analysis including only short-term trials dealing with the potential benefits of MUFA in patients with T2D. The outcome of this analysis shows that a high-MUFA diet had more favourable effects on glucose control in T2D than low-MUFA diets, while no effects on fasting insulin had been observed [12]. Therefore, the purpose of our study was to evaluate long-term effects of randomized controlled trials (RCTs) with a duration of at least 6 months comparing high-MUFA (>12% of total energy content, TEC) versus low-MUFA (≤12% of TEC) diets on glycaemic control in participants with abnormal glucose metabolism.

Methods

Literature Search

The methods recommended by the Cochrane Collaboration have been used to carry out an efficient selection process of adequate publications [14]. A wide research strategy was applied to identify as many relevant RCTs as possible, investigating the management of impaired glucose tolerance (IGT), T2D and IR and its associated risk factors. Queries were performed in three electronic databases, i.e. Medline (between 1966 and May 2011), Embase (between 1980 and May 2011) and the Cochrane Trial Register (until May 2011). The research strategy incorporated diabetes-related terms and text terms, adjusted to each database. Key words and Boolean operators were as follows: 'diet *and* type 2 diabetes', 'fasting glucose *and* diet', 'fasting insulin *and* diet', 'glycosylated hemoglobin *and* diet', 'HOMA *and* diet', 'monounsaturated fatty acids *and* type 2 diabetes', 'Mediterranean diet *and* type 2 diabetes', 'impaired glucose tolerance *and* diet'. In addition, reference lists of selected studies were reviewed. Only RCTs conducted in a population with abnormal glucose metabolism (IGT, T2D and IR), and an initial mean or median body mass index of >25 were taken into account. The minimum period of dietary intervention and follow-up was set to 6 months, and nutritional counselling had to be done by a dietician.

Study Selection

The following types of dietary interventions were evaluated: for primary analysis, we defined high-MUFA diets using the threshold set by the Dietary Guidelines for Americans (>12% of TEC) [15]. Accordingly, low-MUFA diets provided ≤12% of TEC in the form of MUFA. Low MUFA were differentiated to be: low-fat diets (LF; total fat content ≤30%, saturated fatty acids ≤7–10%); low glycaemic index diets (LGI); high glycaemic index diets (HGI); high-protein diets (HP); control diets (total fat content >30% and/or saturated fatty acids ≥10%).

Assessed Outcomes

The main outcome parameters of the RCTs included in this study have been T2D risk factors. The following biomarkers were used: fasting plasma glucose (mg/dl); fasting plasma insulin (μU/ml); HOMA-IR; HbA1c (%).

Quality Assessment of Studies

Full copies of the studies were assessed independently by two researchers using the Jadad score to achieve methodological quality [16]. This 5-point quality scale includes points for randomization (described as randomized, 1 point; table of random numbers or computer-generated randomization, additional 1 point), double blinding (described as double blind, 1 point; use, such as identical placebo, additional 1 point), and follow-up (the numbers and reasons for withdrawal in each group are stated, 1 point) within the report of an RCT. An additional point was accepted if the analysis was done by intention-to-treat. Final scores between 0 and 2 were considered as low quality, whilst final scores of ≥3 were regarded to represent studies of high quality, since double-blinded study protocols are hard to achieve in these types of interventions.

Data Extraction and Statistical Analysis

A standardized data extraction form for this systematic review has been created according to Avenell et al. [14]. For each outcome measure of interest, a meta-analysis was performed in order to determine the pooled effect of the intervention in terms of weighted mean differences (WMDs) between the post-intervention values of the intervention and control groups. All data were analysed using the Review Manager 5.0.25 software, provided by the Cochrane Collaboration (http://ims.cochrane.org/revman). Heterogeneity between trial results was tested with a standard χ^2 test. The I^2 parameter was used to quantify any inconsistency: $I^2 = [(Q - d.f.)] \times 100\%$, where Q is the χ^2 statistic and d.f. is its degrees of freedom. A value for $I^2 > 50\%$ was considered to represent substantial heterogeneity [17]. To consider heterogeneity, the random-effects model was used to estimate WMDs with 95% confidence intervals (CIs). Forest plots were generated to illustrate the study-specific effect sizes along with a 95% CI. Funnel plots were used to assess potential publication bias (i.e. the tendency for studies that yield statistically significant results to be more likely to be submitted and accepted for publication). To determine the presence of publication bias, we assessed the symmetry of the funnel plots in which mean differences were plotted against their corresponding standard errors. A primary analysis of all studies was performed, oriented towards the definition of high- and low-MUFA diets, followed by a sub-analysis of the specific kind of dietary intervention, as described in the selected studies.

Handling of Missing Data

Data processing for this review required the input of the mean and standard deviation (SD) of post-intervention values. Where SD was not available, the authors of the original publication have been asked for the missing data. With regard to one trial [18], the baseline SD had to be imputed. We assumed that this is a valid procedure, since the baseline and post-intervention SD were found to be similar within the other trials included in the meta-analysis. In addition, this strategy had been used before in a meta-analysis by Boulé et al. [19].

Results

Characteristics of Studies and Participants

A total of 9 studies, recruiting 1,547 participants met the inclusion criteria [18, 20–27]. Two RCTs were performed for a period of 6 months [23, 26], 4 trials were performed for 12 months [20, 21, 24, 27], 2 trials for a period of 24 months [22, 25], and 1 study lasted 4 years [18]. All studies compared a high- versus a low-MUFA regimen (LF, LGI, HGI, high-protein and control diets, respectively). Attrition rates did not differ significantly between the intervention groups. One trial [23] showed different approaches of intervention with regard to the high-MUFA diet: one included the high-MUFA setting in an HGI protocol, whilst the other combined high-MUFA with an LGI regime. Both types of high-MUFA diets had been included in the meta-analysis via a separate comparison of high-MUFA/LGI versus LF/LGI, high-MUFA/HGI versus LF/HGI and high-MUFA/HGI versus high saturated fatty acids/HGI (defined as control group). This was done to minimize a potential bias of HGI and LGI, especially when comparing high- with low-MUFA diets. The characteristics of all RCTs included in the present meta-analysis are summarized in table 1, and an overview of the results is given in table 2.

Outcome Measures

Fasting Glucose

The pooled estimates of effects of high- versus low-MUFA diets on fasting plasma glucose were –3.02 mg/dl, which was statistically not significant (95% CI –6.66 to 0.63; p = 0.11).

Fasting Insulin

Fasting insulin was assessed in a total of 1,547 subjects. WMD for the effects of high- versus low-MUFA regimens was –0.05 mg/dl (95% CI –1.60 to 1.49; p = 0.94), which was not statistically significant.

HOMA Insulin Resistance

Decreases in HOMA-IR did not differ significantly between high- and low-MUFA dietary protocols (WMD –0.26, 95% CI –0.75 to 0.24; p = 0.31).

Haemoglobin A1c

High-MUFA diets were associated with significantly decreased values of HbA1c compared to low-MUFA settings (WMD –0.21%, 95% CI –0.40 to –0.02; p = 0.03). The post-hoc analyses showed that the HbA1c reduction was significant following a high-MUFA as compared to LF diets (WMD –0.28%, 95% CI –0.52 to –0.03; p = 0.03) (fig. 1).

Publication Bias

The funnel plot with respect to effect size changes for HbA1c response to high-MUFA diets indicates little asymmetry, suggesting that there might be a small potential publication bias (fig. 2).

Heterogeneity

In relation to outcomes, the review demonstrated relatively homogeneous values between studies with regard to HbA1c ($I^2 = 15\%$). However, we found heterogeneity across trials concerning fasting plasma glucose, fasting plasma insulin and HOMA-IR ($I^2 > 80\%$).

Table 1. General characteristics of the randomized controlled dietary intervention trials included in the meta-analysis

Reference	Sample size	T2D pharmacology therapy	Dietary interventions	Study length months	Energy re-stricted	Primary outcomes	Study quality[1]
Brehm et al. [20] 2009	124 T2D	only oral agents (no insulin)	MUFA vs. LF	12	yes	FPG, FPI, HOMA-IR, HbA1c	2
Elhayany et al. [21] 2010	259 T2D	only oral agents (no insulin)	MUFA vs. LGI vs. LF	12	yes	FPG, FPI, HOMA-IR, HbA1c	2
Esposito et al. [18] 2009	215 T2D	only if HbA1c >7% started on medication[2]	MUFA vs. LF	48	yes	FPG, FPI, HOMA-IR, HbA1c	4
Esposito et al. [22] 2004	180 IGT	no medication	MUFA vs. control	24	yes	FPG, FPI, HOMA-IR	3
Jebb et al. [23] 2010	720 IGT	no medication	MUFA/LGI vs. LF/LGI MUFA/HGI vs. LF/HGI HS/HGI (control)	6	no	FPG, FPI, HOMA-IR	4
Keogh et al. [24] 2007	38 HI	no medication	MUFA vs. HP	12	yes	FPG, FPI	2
Shai et al. [25] 2008	24 T2D	5 subjects started on medication[3]	MUFA vs. LF	24	yes	FPG, FPI, HOMA-IR, HbA1c	4
Wien et al. [26] 2003	65 IGT	n.d.	MUFA vs. LF	6	yes	FPG, FPI, HOMA-IR	2
Wolever et al. [27] 2008	110 T2D	no medication	MUFA vs. LGI	12	no	FPG, FPI, HbA1c	3

FPG = Fasting plasma glucose; FPI = fasting plasma insulin; IGT = impaired glucose tolerance; HS = high saturated fatty acids; HI = hyperinsulinaemia; n.d. = not defined.

[1] Assessment of study quality was done using the 5-point quality scale Jaded score [16].

[2] Started on medications only if HbA1c levels were >7% and a 3-month intensive dietary and physical intervention failed.

[3] 13 subjects used oral hypoglycaemic drugs; in the LF group, 2 subjects with insulin treatment.

Table 2. Pooled estimates of effect size expressed as WMD for the effect of high versus low MUFA on plasma glucose, plasma insulin, HbA1c and insulin sensitivity (HOMA) in changes from baseline

Outcome	Studies, n	Sample size	WMD	95% CI	p value	I^2, %
Plasma glucose						
High vs. low MUFA	9	1,545	–3.02	–6.66 to 0.63	0.11	81
Plasma insulin						
High vs. low MUFA	9	1,547	–0.05	–1.60 to 1.49	0.94	84
HbA1c						
High vs. low MUFA	5	667	–0.21	–0.40 to –0.02	0.03	15
HOMA-IR						
High vs. low MUFA	6	1,355	–0.26	–0.75 to 0.24	0.31	86

Discussion

Optimal control of glycaemic parameters in T2D subjects is essential to reduce the risk of long-term health damages. The United Kingdom Prevention study showed that hyperglycaemia is a greater risk factor for coronary artery disease than raised insulin concentrations in T2D patients [28]. Recently, the Emerging Risk Factors Collaboration Study revealed that fasting glucose levels exceeding 100 mg/dl (but not levels between 70 and 100 mg/dl) were associated with an increased risk of cause-specific death [29]. In addition, the Framingham Offspring study detected a strong association between fasting glucose levels >100 mg/dl and a higher risk of developing T2D in middle-aged men [30]. In the present meta-analysis, reduction in fasting plasma glucose, fasting plasma insulin and HOMA-IR did not differ when comparing high- with low-MUFA diets. These results are in discrepancy with the results of a meta-analysis including short-term intervention trials [12]. However, the high-MUFA dietary protocol resulted in a 0.21% decrease in HbA1c as compared to the low-MUFA regimens, which was not observed in the meta-analysis by Garg [12].

Study or sub-group	High MUFA mean	High MUFA SD	High MUFA total	Low MUFA mean	Low MUFA SD	Low MUFA total	Weight %	Mean difference IV, random (95% CI)
1.7.1 High MUFA vs. LF								
Brehm et al., 2009	7.5	1.95	43	7.2	1.44	52	6.6	0.30 (–0.40 to 1.00)
Elhayany et al., 2010	6.3	1.4	61	6.7	0.9	55	16.4	–0.40 (–0.82 to 0.02)
Esposito et al., 2009	6.85	0.9	108	7.21	0.9	107	38.4	–0.36 (–0.60 to –0.12)
Shai et al., 2008	7.31	1.03	8	7.28	1.19	9	3.0	0.03 (–1.03 to 1.09)
Subtotal			220			223	64.4	–0.28 (–0.52 to –0.03)
Heterogeneity: $\tau^2 = 0.01$, $\chi^2 = 3.63$, d.f. = 3 (p = 0.30), $I^2 = 17\%$								
Test for overall effect: Z = 2.19 (p = 0.03)								
1.7.2 High MUFA vs. LGI								
Elhayany et al., 2010	6.3	1.4	61	6.5	0.8	63	17.8	–0.20 (–0.60 to 0.20)
Wolever et al., 2008	6.62	0.938	50	6.58	1.117	50	17.7	0.04 (–0.36 to 0.44)
Subtotal			111			113	35.6	–0.08 (–0.37 to 0.21)
Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 0.68$, d.f. = 1 (p = 0.41), $I^2 = 0\%$								
Test for overall effect: Z = 0.55 (p = 0.58)								
Total (95% CI)			331			336	100.0	–0.21 (–0.40 to –0.02)
Heterogeneity: $\tau^2 = 0.01$, $\chi^2 = 5.89$, d.f. = 5 (p = 0.32), $I^2 = 15\%$								
Test for overall effect: Z = 2.22 (p = 0.03)								
Test for subgroup differences: $\chi^2 = 1.03$, d.f. = 1 (p = 0.31), $I^2 = 2.9\%$								

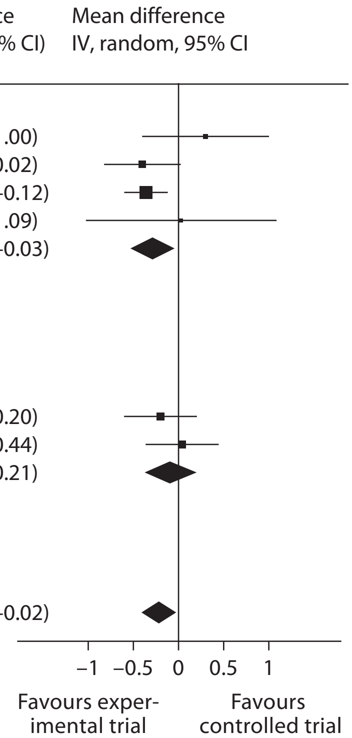

Fig. 1. Forest plot showing pooled WMDs with 95% CIs (in parentheses) for HbA1c (%) for 5 randomized controlled high-MUFA diets. The different types of low-MUFA diets were separated in sub-groups. For each high-MUFA study, the black square represents the point estimate of the intervention effect. The horizontal line joins the lower and upper limits of the 95% CI of these effects. The area of the black square reflects the relative weight of the study within the respective meta-analysis. The diamond at the bottom of the graph represents the pooled WMD with the 95% CI for the 6 study groups.

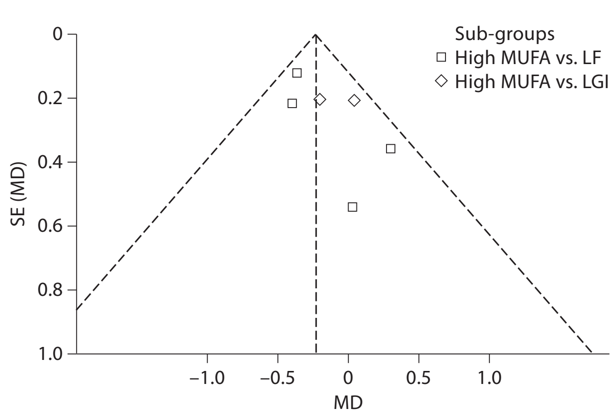

Fig. 2. Funnel plot showing study precision against the WMD effect estimate with 95% CIs for HbA1c. SE = Standard error.

In a retrospective study by Currie et al. [31], investigating 47,970 patients with diabetes, HbA1c values >6.5% were correlated with an increased mortality rate. In the EPIC-Norfolk study, an increase in HbA1c of 1 percentage point was associated with a 20–30% increase in mortality or in risk of cardiovascular events [32]. Likewise, an HbA1c increase of 1 percentage point was associated with a relative risk for death from any cause of 1.24 in men and 1.28 in women [32]. IR is a precursor to glucose intolerance and T2D. Early pancreatic β-cell dysfunction causes IR and IGT [33, 34]. Lopez et al. [35] showed that meals rich in MUFA buffered β-cell hyperactivity and IR in subjects with high fasting triglyceride concentrations. These effects could not be observed by meals rich in saturated fat. These data suggest that MUFA-based dietary strategies might provide cardiovascular benefits to persons at risk, by limiting lipid and insulin excursions, and may thereby contribute to optimal glycaemic control after meal challenges.

Recent data from the 4-year PREDIMED-Reus nutrition intervention randomized trial showed that a Mediterranean diet reduces the incidence of T2D compared to the control low-fat group [36]. Regarding the potential mechanisms explaining the effects of MUFA on glycaemic control, membrane translocation of glucose transporter type 4 was decreased in the skeletal muscle of rats being on a diet rich in saturated fat [37]. These changes in the insulin signalling pathway could not have been observed in rats fed a high-MUFA diet. The authors concluded that the beneficial effect of dietary MUFA on insulin sensitivity is associated with a conserved IRS-1/PI3 kinase insulin signalling pathway, which was altered by saturated fatty acids [37]. In addition, high levels of adiponectin have been shown to be associated with a reduced risk of T2D [38]. Esposito et al. [18] reported significant improvements in adiponectin levels in the high-MUFA group, compared with an LF protocol after a 4-year intervention period with a simultaneous reduction in the need for antihyperglycaemic medication in the high-MUFA group.

In a recently published review, Gillingham et al. [39] concluded that more and more epidemiological and human clinical trial data demonstrate the cardioprotective activity of the MUFA content of dietary fat.

The present study focused on long-term dietary protocols using a high-MUFA approach. We found a significant decrease in HbA1c values following a high-MUFA diet, which was more pronounced than the respective changes following a low-MUFA diet. Specific recommendations for MUFA are given by the American Heart Association (≤15% of TEC) and by the American Dietetic Association (<20% of TEC) [40, 41], but not by the American Diabetes Association [11].

Limitations

This systematic review does not consider unpublished data, and it cannot be excluded that these results may have had at least a moderate impact on the effect size estimates. Another limitation lies in the diversity of the included publications. Heterogeneity with respect to study characteristics is a common problem in nutritional intervention trials. Therefore, it is not surprising that the literature chosen for the present analysis varies regarding type(s) of diets used, definitions of MUFA diets, study population, intervention time as well as long-term follow-up protocols. In addition, the drug regimen was not identical for all participants in the included studies. Subjects with IGT, IR as well as with T2D were included, and the effects of the intervention on glucose parameters might be especially strong in patients with T2D. The funnel plot to effect size changes for HbA1c response to high-MUFA diets shows a small asymmetry, which indicates a reduced risk of publication bias.

The present meta-analysis included long-term RCTs (≥6 months) comparing high- versus low-MUFA diets in patients with abnormal glucose metabolism. In summary, the results demonstrate beneficial effects of diets containing >12% of TEC in the form of MUFA on glycaemic control. Therefore, international dietary recommendations directed to treat T2D could bear in mind specific percentages of MUFA within the range of current guidelines.

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