Dietary fatty acids as nutritional modulators of sirtuins: a systematic review

Ana Paula S. Caldas, Daniela Mayumi U. P. Rocha, Josefina Bressan, and Helen Hermana M. Hermsdorff

Context: *The sirtuins (SIRT1 to SIRT7) constitute a family of highly conserved nicotinamide adenine dinucleotide–dependent proteins. When activated, sirtuins control essential cellular processes to maintain metabolic homeostasis, while lack of expression of sirtuins has been related to chronic disease.* ***Objective:*** *The aim of this systematic review is to analyze the role of fat consumption as a modulator of human sirtuins.* ***Data Sources:*** *This review was conducted according to PRISMA guidelines. Studies were identified by searches of the electronic databases PubMed/MEDLINE, Scopus, and Web of Science.* ***Study Selection:*** *Randomized clinical trials assessing the effect of fatty acid consumption on sirtuin mRNA expression, sirtuin protein expression, or sirtuin protein activity were eligible for inclusion.* ***Data Extraction:*** *Two authors screened and determined the quality of the studies; disagreements were resolved by the third author. All authors compared the compiled data.* ***Results:*** *Seven clinical studies with 3 different types of interventions involving healthy and nonhealthy participants were selected. Only SIRT1 and SIRT3 were evaluated. Overall, the evidence from clinical studies to date is insufficient to understand how lipid consumption modulates sirtuins in humans. The best-characterized mechanism highlights oleic acid as a natural activator of SIRT1.* ***Conclusion:*** *These results draw attention to a new field of interest in nutrition science. The possible activation of sirtuins by dietary fat manipulation may represent an important nutritional strategy for management of chronic and metabolic disease.* ***Systematic Review Registration:*** *PROSPERO registration number CRD42018114456.*

INTRODUCTION

Sirtuins are nicotinamide adenine dinucleotide $(NAD)^+$–dependent protein deacetylases and mono-adenosine diphosphate (mono-ADP) ribosyltransferase enzymes that regulate diverse biological processes, including energy metabolism, stress responses, DNA regulation, and longevity.[1–3] The sirtuin family comprises 7 members (SIRT1–SIRT7) that possess conserved NAD^+-binding and catalytic domains. The flanking N- and C-termini of the different sirtuins are distinct from one another, which contributes to differences between sirtuins in subcellular localization, enzymatic activity, and substrate specificity.[4] Besides exhibiting deacetylase activity, some sirtuins also exhibit weak adenosine diphosphate (ADP)-ribosyltransferase activity.[5] The process of ADP-ribosylation is a reversible post-translational modification of proteins catalyzed by ADP-ribosyltransferases and some sirtuins (SIRT4–SIRT7).[6] Proteins with ADP-ribosyltransferase activity catalyze the transfer of adenosine diphosphate ribose (ADP-ribose) from NAD^+ onto specific target proteins.[7]

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Key words: high-fat meal, homeostasis, lipids, overfeeding, SIRT1.

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Sirtuins are also classified as class III histone deacetylases, and, according to phylogenetic analysis, are grouped into 4 main classes (I–IV) of protein deacetylases, which include the human isotypes as well as at least 1 more class containing enzymes found in archaea and bacteria (class U).[8] In this classification, SIRT1–SIRT3 belong to class I, SIRT4 to class II, SIRT5 to class III, and SIRT6 and SIRT7 to class IV.[1] Different sirtuins also have different subcellular localizations: SIRT1, SIRT6, and SIRT7 have nuclear localization, SIRT2 has mainly cytosolic localization but can also shuttle to the nucleus during mitosis, while SIRT3, SIRT4, and SIRT5 have mitochondrial localization. In addition, some isoforms of SIRT1 and SIRT5 have been found in the cytoplasm.[1]

All sirtuins play fundamental roles in health maintenance. Sirtuins regulate several metabolic pathways and improve cellular and systemic adaptive responses to stress by modulating the activity of proteins.[9] Of the 7 human sirtuins, SIRT1 is studied most widely. This sirtuin deacetylates target proteins, such as transcription factors and histones,[8] mainly those involved in the regulation of energy metabolism, stress, and inflammatory responses.[10] For example, activated SIRT1 upregulates peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α) by deacetylation, leading to an increase in mitochondrial biogenesis and, consequently, the expression of PGC-1α target genes linked to fatty acid oxidation pathways.[11,12] Currently, the SIRT1/PGC-1α pathway is described as a major regulator of metabolic processes in various tissues, such as liver, skeletal muscle, and white adipose tissue.[13] The main activity of SIRT2 is related to cell cycle control.[14] This sirtuin deacetylates forkhead box protein O transcription factors in response to caloric restriction and oxidative stress. SIRT3 improves mitochondrial activity by deacetylating and activating acetyl coenzyme A synthetase and several components of the electron transport chain complexes I and II. It also increases respiration in mitochondria by stimulating cyclic adenosine monophosphate (cAMP)[15] and protects cells from reactive oxygen species.[16] The mitochondrial SIRT4 regulates the pyruvate dehydrogenase complex via enzymatic hydrolysis of the lipoamide cofactor, thus modulating acetyl coenzyme A production, Krebs cycle activity, and generation of reactive oxygen species.[17] SIRT6, which is widely distributed in biological tissues, modulates telomeric chromatin and plays a role in DNA repair, human aging, glucose homeostasis, and genomic stability.[18–20] This sirtuin was also recently reported to preferentially hydrolyze long-chain fatty acyl groups over acetyl groups.[21] Lastly, SIRT7 is an activator of RNA transcription and may regulate cellular growth, metabolism, and survival.[10] As for catalytic activities, SIRT1, SIRT2, and SIRT3 have potent deacetylase and long-chain deacylase activities. SIRT4 exhibits deacylase, ADP-ribosyltransferase, and substrate-specific deacetylase and lipoamidase activities. SIRT5 displays unique affinity for negatively charged acyl modifications to lysine and is involved in protein desuccinylation, demalonylation, and deglutarylation reactions.[22] SIRT6 exhibits deacetylase, ADP-ribosyltransferase, and long-chain deacylase activities, and SIRT7 mediates deacetylation, histone desuccinylation, and long-chain deacylation reactions and is involved in shutting down rDNA transcription.[20,22]

Since the discovery of the sirtuins and their functions, different modulators of sirtuin enzymatic activity have been investigated, and several studies have found a vast array of synthetic and natural compounds with the ability to modulate sirtuin function.[1,23,24] Recently, a wide spectrum of studies proposed an association between lipids and sirtuins, since weight loss and fat mass loss by caloric restriction interventions have been associated with an increase in *SIRT1*, *SIRT3*, and *SIRT6* mRNA concentrations in the subcutaneous tissue of severely obese individuals.[25] Feldman et al[21] demonstrated that low intrinsic activity of SIRT6 might be activated in vivo in response to elevated levels of fatty acids, such as oleic acid and linoleic acid. In addition, SIRT1 appears to promote greater rates of lipolysis and a reduction in inflammatory processes; hence, the reduction in *SIRT1* mRNA levels observed in the adipose tissue of obese individuals might be associated with excessive fat accumulation and development of obesity-related comorbidities.[26] In animal studies, a high-fat diet (≈ 42%–60% fat) was shown to reduce both the expression of *SIRT1* mRNA and SIRT1 protein levels in liver,[27,28] adipose,[29,30] and cardiac tissue.[31,32]

Despite the above findings, the mechanisms through which sirtuins modulate fatty acids remain unknown. Here, evidence from interventions investigating the effect of high-fat diets or supplementation with specific fatty acids on human sirtuins is reviewed.

METHODS

Protocol and registration

The present review was conducted according to the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) statement[33] and has been registered with PROSPERO (https://www.crd.york.ac.uk/prospero/), registration number CRD42018114456. The PRISMA checklist is provided as Appendix 1 in the Supporting Information online.

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Table 1 **PICOS criteria for inclusion of studies**

Parameter	Inclusion criteria
Participants	Adults
Intervention	Dietary intervention with high-fat diet or supplementation with specific fatty acids
Comparison	Placebo diet; supplementation with different types or the quantity of fatty acids; or before and after the intervention period, in studies with a single group
Outcomes	Change in mRNA expression or activity of sirtuin proteins after the intervention period (with fatty acid intake)
Study design	Clinical trials

Literature search

Studies were identified by searching the following electronic databases: MEDLINE/PubMed, Scopus, and Web of Science. Table 1 lists the PICOS (Participants, Intervention, Comparison, Outcomes, and Study design) criteria adopted for this review. The following search terms were used to search titles and abstracts in the databases: (sirtuin OR SIRT OR SIRT1) AND (fatty acid OR fatty acids OR polyunsaturated fatty acid OR polyunsaturated fatty acids OR PUFA OR omega 3 OR n3 OR n-3 OR w3 OR w-3 OR monosaturated fatty acid OR eicosapentaenoic acid OR EPA OR docosahexaenoic acid OR DHA OR monosaturated fatty acids OR MUFA OR saturated fatty acid OR saturated fatty acids OR SFA). The search was conducted from database inception to November 11, 2018.

Eligibility criteria

The following criteria were applied for inclusion of studies: (1) original, randomized controlled trials; (2) fatty acid consumption used as an intervention; (3) expression or activity of sirtuins or expression of sirtuin mRNA as the outcome of interest. If data were duplicated in more than 1 study, the most complete and detailed study was included. The following exclusion criteria were applied: (1) publications that did not report original studies, such as letters, comments, or reviews; (2) comparisons not based on fatty acid interventions; (3) interventions in which fatty acids were consumed together mineral/vitamin supplements, other nutrient supplements, or alcohol; and (4) interventions that included behavior modifications, such as physical activity.

Study selection and data collection process

Study selection was performed independently in an unblinded standardized manner by 2 authors. Disagreements were resolved by consensus or by consulting a third author. The following information was extracted from each study: authors; year of publication; characteristics of study participants; intervention design; study duration; and results. This information was summarized in a standard data extraction template.

Risk-of-bias assessment

Risk of bias in the included studies was assessed using the Cochrane risk of bias tool.[34] Independently, 2 authors (A.P.S.C. and D.M.U.P.R.) assessed the 7 included studies to determine whether there was low, high, or unclear risk of bias in the following domains: (1) selection bias, (2) performance bias, (3) detection bias, (4) attrition bias, and (5) reporting bias. Disagreements were resolved by an independent evaluation of a third author. The outcomes reported in published reports were compared with the outcomes described in the study protocol, when available. The evaluation of risk of bias was recorded in Review Manager (RevMan) software, Version 5.3.[35] Studies with a low risk of bias for at least 3 items were considered to be of good quality; studies with a low risk of bias for 2 items were considered to be of fair quality, and studies with a low risk of bias for only 1 item or no items were considered to be of poor quality.[34]

RESULTS

Study selection

A total of 1646 records were identified through searches of the MEDLINE/PubMed, Scopus, and Web of Science databases. Duplicate records were removed using Mendeley reference manager software, resulting in 1005 records. During screening of titles and abstracts, 979 records were removed because they did not meet the inclusion criteria: 125 were not original articles, 392 were not relevant to the topic, and 462 reported in vitro or animal studies. The remaining 26 records were retrieved and reviewed for further assessment. After reviewing the full-text articles for eligibility, 7 studies were included (Figure 1).

Study characteristics

Study design. Only SIRT1[36–41] and SIRT3[13] were evaluated in the 7 selected studies. Initially, all selected

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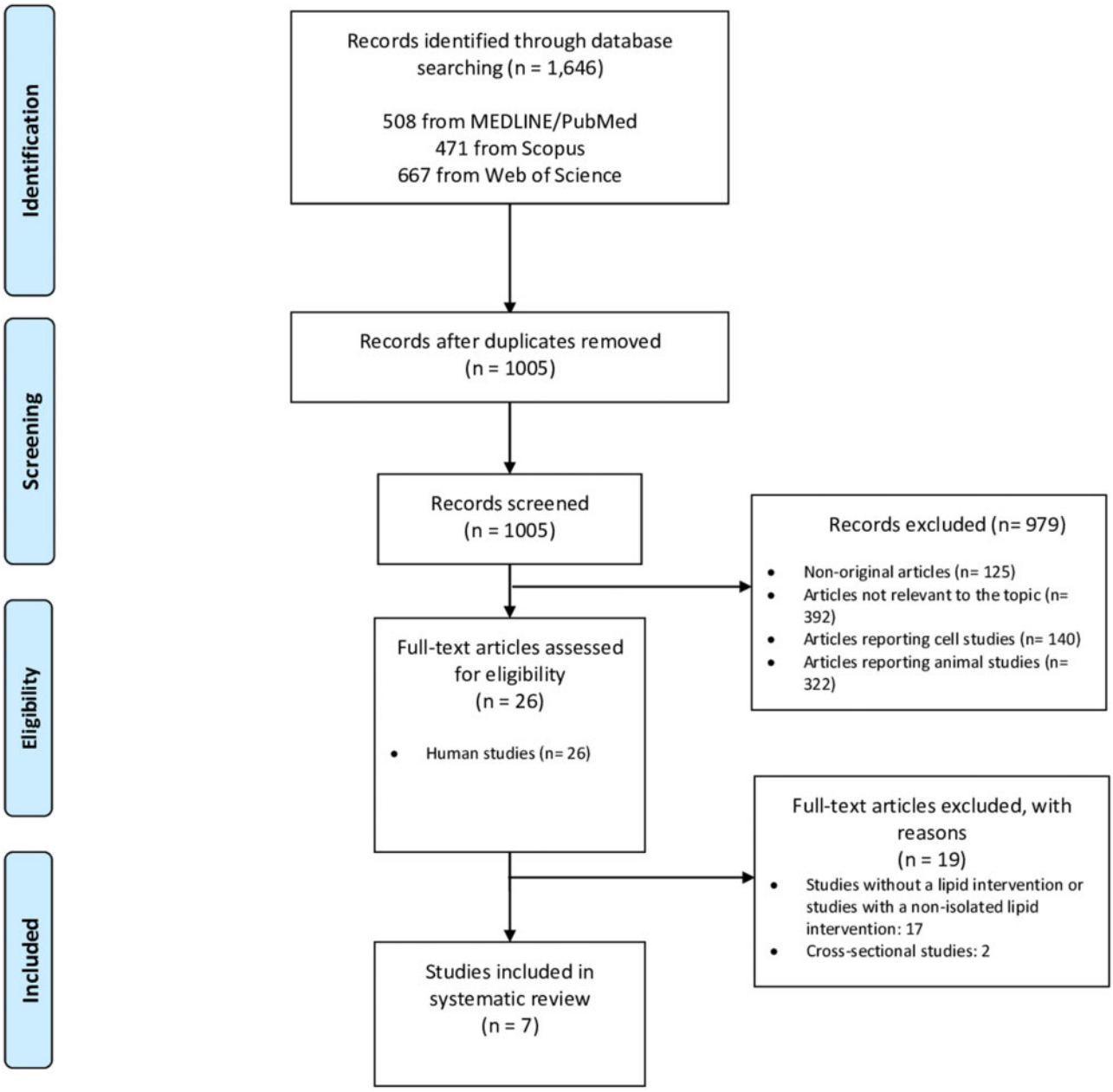

Figure 1 **Flow diagram of the literature search process.**

studies had to be randomized clinical trials, but non-randomized clinical trials also were considered, given their importance to ensuring the objective of the review was met. Four studies were conducted with subgroups of previous studies.[13,36,37,39] Two of the included studies had a single-arm design,[13,39] 2 had a crossover design,[36,38] and 3 had a parallel-arm design.[37,40,41] Two are short-term studies (2 days of intervention)[36,38] and 5 are intervention studies (8–12 weeks).[13,37,39–41] Two studies evaluated overfeeding,[13,39] 3 assessed dietary interventions,[36–38] and 2 examined the effects of supplementation with fatty acids on the expression or activity of sirtuins.[40,41]

Study participants. Eligible trials included healthy participants (n = 118),[13,36,38,39] patients with coronary artery disease (n = 60),[40,41] patients with type 2 diabetes mellitus (n = 85), and patients with metabolic syndrome (n = 75).[37] Three studies involved both men and women.[36,39,40] Three studies were conducted with men only,[13,38,41] and 1 study did not describe the sample.[37] The mean age of the participants ranged from 25 ± 5 to 56 ± 7 years. The mean body mass index at baseline ranged from 25.3 ± 3.1 to 35.1 ± 3.1 kg/m^2.

Type of intervention Three different types of interventions were used: hyperlipidic overfeeding,[13,39] dietary

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interventions,[36–38] and supplementation with fatty acids[40,41] (Table 2[13,36–41]). One hyperlipidic overfeeding intervention was based on the daily addition of 70 g of lipids (100 g of cheese, 20 g of butter, and 40 g of almonds, consisting of 46.3% saturated fatty acids [SFAs], 44.7% monounsaturated fatty acids [MUFAs], and 9% polyunsaturated fatty acids [PUFAs]), which represented 760 kcal/d.[13] The other hyperlipidic overfeeding intervention provided a diet containing 1.4 times the baseline energy requirements, composed of 41% carbohydrate, 15% protein, and 44% fat (40% of which comprised saturated fatty acids).[39] In both supplementation studies, omega-3 (n-3) fatty acids were used.[40,41] The dietary interventions used a high-fat diet with or without the addition of specific fatty acids.[36–38] The controls in the interventions varied: low-fat diets,[36,37] high-fat meals,[38] and placebo, which was either paraffin[40] or unspecified.[41] Two studies used the baseline values of interest variables.[13,39]

Outcomes evaluated All of the included studies assessed SIRT1.[13,36–41] *SIRT1* expression was verified in all 7 included studies, while the SIRT1 protein level was assessed only in 1 study.[36] Although SIRT1 activity was not evaluated directly in any study, Bergouignan et al[36] and Seyssel et al[13] measured AMP-activated kinase (AMPK), acetylation of PGC-1α, and NAD^+ concentrations as markers of SIRT1 activity. One study evaluated *SIRT3* expression.[13] No study evaluated SIRT2, SIRT4, SIRT5, SIRT6, or SIRT7.

Risk of bias within studies

Figure 2[13,37–41] and Figure 3 summarize the results of the risk of bias assessment. Most studies did not provide sufficient information to be graded as having a low risk of bias and were classified as having an unclear risk of bias for most of the domains evaluated. No study was classified as "high risk of bias" for any domain evaluated. Only the study by Mazaherioun et al[40] was classified as having a low risk of bias in 6 of the 7 domains evaluated. The study by Bergouignan et al[36] was classified as having an unclear risk of bias in all 7 domains.

Short-term response studies

The effect of fat on SIRT1 activity was evaluated in 2 short-term studies.[36,38] In a randomized crossover study (with a 2-week washout period) in healthy adults, postprandial expression of *SIRT1* in peripheral blood mononuclear cells (PBMCs) was unchanged after 2 days of a high-fat meal supplemented with 15 mL of sacha inchi oil, a vegetable oil containing high levels of alpha-linolenic acid and linoleic acid (65.0% energy from fat: 19.4 percent energy (E%) from SFAs, 20.0 E% from MUFAs, 14.9 E% from PUFAs) in comparison with *SIRT1* expression after a high-fat meal without sacha inchi oil (59% energy from fat: 18.8 E% from SFAs, 13.5 E% from MUFAs, 2.3 E% from PUFAs).[38] Similarly, a high-fat diet (50.0% energy from fat: 16.0 E% from SFAs, 20.0–30.0 E% from MUFAs, 8–12 E% from PUFAs) for 2 days compared with a low-fat control diet (20.0% energy from fat: 6.0 E% from SFAs, 8.0–12.0 E% from MUFAs, 3.0–5.0 E% from PUFAs) did not modify *SIRT1* mRNA expression or SIRT1 protein levels in skeletal muscle of healthy adults.[36] Acetylation of PGC-1α was significantly reduced but total PGC-1α protein was unchanged, suggesting that the deacetylating activity of SIRT1 was markedly enhanced after the high-fat diet.

Intervention studies

Overfeeding interventions Two studies evaluated *SIRT1* expression after chronic overfeeding (8–12 weeks).[13,39] Toledo et al[39] reported that *SIRT1* expression in the skeletal muscle of healthy volunteers increased in comparison with baseline values after 8 weeks of overfeeding (diet providing 1.4 times the baseline energy requirement, containing 44% fat, of which 44% was saturated fat).

Similarly, Seyssel et al[13] reported *SIRT1* and *SIRT3* expression to be significantly increased after 56 days of hyperlipidic overfeeding (usual diet plus 760 kcal from fat per day).[13] However, they suggest that SIRT1 activity decreased, given that NAD^+ concentrations were reduced and PGC-1α acetylation was increased after overfeeding. SIRT1 is activated by NAD^+ bioavailability, and when activated, it is responsible for PGC-1α deacetylation.[13]

High-fat dietary interventions

In the study by Lopez-Moreno et al,[37] conducted in adults with metabolic syndrome, the intervention groups that received a high-MUFA diet (38% energy from fat; 20 E% from MUFAs) or a low-fat, high-complex-carbohydrate diet supplemented with long-chain n-3 PUFAs (28.0% energy from fat, supplemented with 1.24 g of n-3 PUFAs daily) showed increased expression of *SIRT1* in PBMCs when compared with baseline after 12 weeks of intervention. In addition, after long-term adaptation (12 weeks) to the corresponding intervention diet, study participants were subjected to a fat challenge consisting of a fat overload (breakfast containing 65% fat) in order to assess the postprandial response of *SIRT1* mRNA. After 4 hours, when compared with fasting values at week 12, *SIRT1* expression was increased in the high-MUFA group and decreased in the group that received

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Table 2 **Summary of human studies investigating the role of lipid consumption on SIRT1 expression**

Reference	Study design	Characteristics of participants	Characteristics of intervention			Sample analyzed	Results[a]
			Type	Diet	Duration		
Seyssel et al (2014)[13]	Single-arm clinical trial[b]	n: 39 Sex: 0 F; 39 M Mean age: 34 ± 4 y Mean BMI: 25.3 ± 3.1 kg/m^2 Healthy individuals	Overfeeding	Hyperlipidic overfeeding: supplementation with 70 g of lipids (46.3% SFAs and 44.7% MUFAs)	8 wk	Skeletal muscle (20 individuals)	↑ *SIRT3* mRNA ↑ *SIRT1* mRNA
Toledo et al (2018)[39]	Single-arm clinical trial[b]	n: 26 Sex: 5 F; 21 M Mean age: 25 ± 5 y Mean BMI: 25.5 ± 2.4 kg/m^2 Healthy individuals	Overfeeding	Hyperlipidic overfeeding (40% of baseline energy requirements): 44% energy from fat (17.6 E% SFAs, 16.3 E% MUFAs, 10.1 E% PUFAs)	8 wk	Skeletal muscle	↑ *SIRT1* mRNA
Bergouignan et al (2012)[36]	Crossover clinical trial[b]	n: 11 Sex: 5 F; 6 M Mean age: 35 ± 9 y BMI: 29.6 ± 7.2 kg/m^2 Healthy individuals	Dietary interventions	Dietary interventions: Low-fat meal: 20% energy from fat (6 E% SFAs, 8–12 E% MUFAs, 3–5 E% PUFAs) High-fat meal: 50% energy from fat (16 E% SFAs, 20–30 E% MUFAs, 8–12 E% PUFAs)	2 d	Skeletal muscle	↔ *SIRT1* mRNA (both interventions) ↔ SIRT protein (both interventions)
Lopez-Moreno et al (2017)[37]	Randomized clinical trial[b]	n: 75 Sex: NA Mean age: 56 ± 7 y Mean BMI: 35.1 ± 3.1 kg/m^2 Patients with MetS	Dietary interventions	Dietary interventions: High-fat diet: 38% energy from fat (16 E% SFAs) High MUFA diet: 38% energy from fat (20 E% MUFAs) LFHCC n-3 PUFA diet: 28% energy from fat (supplemented with n-3 PUFAs, 1.24 g/d) LFHCC diet: 28% energy from fat	12 wk	PBMCs	Long-term interventions: ↑ *SIRT1* mRNA for high MUFA and LFHCC n-3 ↔ *SIRT1* mRNA for LFHCC and high SFA Postprandial status: ↑ *SIRT1* mRNA for high MUFA ↓ *SIRT1* mRNA for LFHCC

(continued)

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Table 2 **Continued**

Reference	Study design	Characteristics of participants	Characteristics of intervention			Sample analyzed	Results[a]
			Type	Diet	Duration		
				(supplemented with sunflower oil as placebo, 1.0 g/d)			↔ *SIRT1* mRNA for LFHCC n-3 and high SFA
Alayón et al (2018)[38]	Crossover randomized clinical trial	n: 42 Sex: 0 F; 42 M Mean age: 40 ± 8.9 y Mean BMI: 26.6 ± 4.8 kg/m^2 Healthy individuals	Dietary interventions	Dietary interventions: High-fat meal: 59% energy from fat (18.8 E% SFAs, 13.5 E% MUFAs, 2.3 E% PUFAs) High-fat meal plus 15 mL of SIO: 65% energy from fat (19.4 E% SFAs, 20 E% MUFAs, 14.9 E% PUFAs)	2 d	PBMCs	↔ *SIRT1* mRNA (both interventions)
Saboori et al (2016)[41]	Double-blind, parallel, randomized, placebo-controlled clinical trial	n: 60 Sex: 0 F; 60 M Mean age: NA Mean BMI: 27.3 ± 0.8 kg/m^2 Patients with CAD	Supplementation	Supplementation: n-3 PUFAs (0.72 g EPA and 0.48 g DHA) Placebo: NA	8 wk	PBMCs	↔ *SIRT1* mRNA
Mazaherioun et al (2017)[40]	Double-blind, parallel, randomized, placebo-controlled clinical trial	n: 85 Sex: 32 F; 53 M Mean age: 51 ± 7 y Mean BMI: 29.2 ± 3.2 kg/m^2 Patients with T2DM	Supplementation	Supplementation: n-3 PUFAs (1.8 g EPA and 0.9 g DHA) Placebo: paraffin (2.7 g)	10 wk	PBMCs	↔ *SIRT1* mRNA

Abbreviations and symbols: BMI, body mass index; CAD, coronary artery disease; DHA, docosahexaenoic acid; E%, proportion of total energy intake; EPA, eicosapentaenoic acid; LFHCC, low-fat, high-complex-carbohydrate; MetS, metabolic syndrome; mRNA, messenger RNA; MUFA, monounsaturated fatty acid; n, number of participants; NA, not available; PBMC, peripheral blood mononuclear cell; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; SIRT 1, sirtuin 1; SIO, sacha inchi oil; T2DM, type 2 diabetes; ↑, increased; ↓, decreased; ↔, unchanged.

[a]Comparison with control or baseline (in single-arm clinical trials).

[b]Studies conducted with subgroups of previous studies.

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the low-fat high-complex-carbohydrate diet supplemented with n-3 PUFAs. Interestingly, the group that received the high-SFA diet had lower *SIRT1* expression in comparison with the other groups after both the long-term and the postprandial interventions.

Supplementation interventions

Neither daily supplementation with n-3 PUFAs (0.72 g of EPA and 0.48 g of DHA for 8 weeks) in patients with coronary artery disease[41] nor supplementation with n-3 PUFAs (1.8 g of EPA and 0.9 g of DHA for 10 weeks) in adults with type 2 diabetes melliltus[40] was able to modify *SIRT1* or *PGC1α* expression in PBMCs.

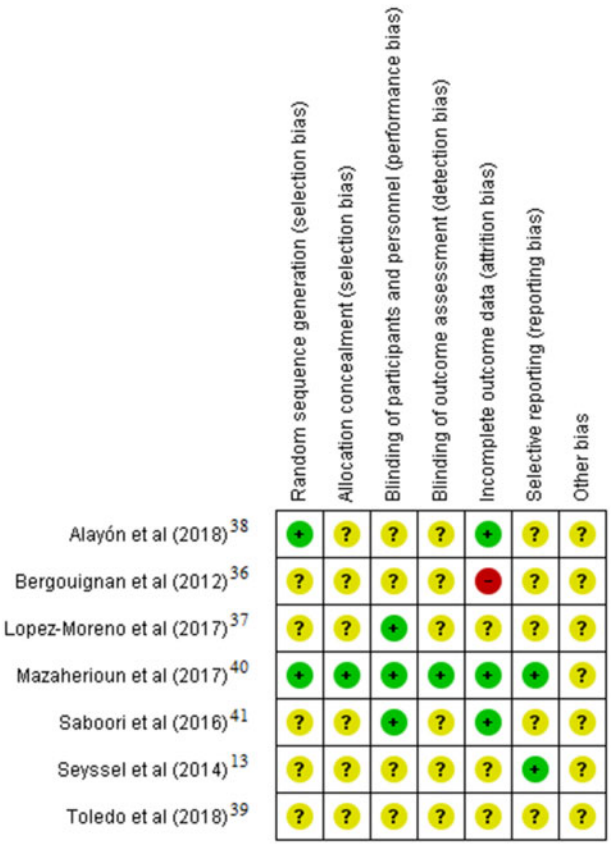

Figure 2 **Summary of risk of bias of each study included in the systematic review.**

DISCUSSION

To the best of knowledge, the present study is the first systematic review to analyze the effect of lipid consumption on human sirtuins. Currently, there is considerable interest in the exploration of dietary modulators of sirtuins, given the importance of sirtuins to health maintenance. This systematic review included 7 studies involving 338 individuals who were healthy or who had metabolic syndrome, type 2 diabetes mellitus, or coronary artery disease. These studies comprised 2 short-term studies and 5 long-term studies that used different types of interventions (supplementation, dietary intervention, and overfeeding) to examine the effects of different types of dietary fat (SFAs, MUFAs, and PUFAs) on sirtuins 1 and 3. However, there is limited evidence to establish how fatty acid intake affects the activity of human sirtuins.

Of the 7 members of the sirtuin family, SIRT1 has been studied most extensively and was evaluated in all studies included in this review, while SIRT3 was evaluated in only 1 study. SIRT1 is involved in the regulation of multiple essential cellular functions, such as mitochondrial biogenesis, glucose and lipid metabolism, DNA repair, apoptosis, stress resistance, and inflammation.[8,42–45] Consequently, alterations in SIRT1 expression or function have been associated with several chronic conditions, including cancer, diabetes, cardiovascular disease, insulin resistance, and metabolic syndrome.[26,46–48] SIRT3 is a major regulator of mitochondrial function.[49] Given its role in the control of inflammation, oxidative stress, and cellular metabolism, SIRT3 can be involved in several pathological processes. Accumulating evidence suggests that SIRT3 has a critical role in cardiovascular diseases such as hypertrophic cardiomyopathy, myocardial infarction,

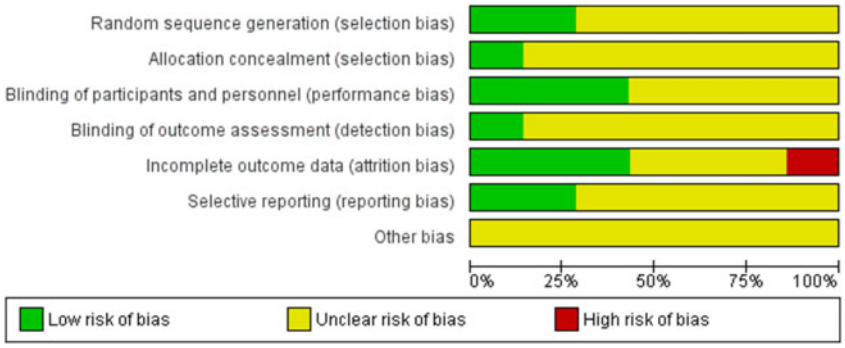

Figure 3 **Risk of bias of each item assessed, presented as percentages across all studies included in the systematic review.**

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ischemia-reperfusion injury, hypertension, atherosclerosis, and heart failure.[50–53] In addition, SIRT3 might regulate systemic inflammation by improving metabolic balance.[54]

The studies of short-term lipid intake included in this review demonstrated that 2 days of a high-SFA meal or high-fat diet does not promote any modification of *SITR1* mRNA or SIRT1 protein levels in the skeletal muscle or PBMCs of healthy individuals.[36,38] However, Bergouignan et al[36] demonstrated that the amount of acetylated PGC-1α in muscle decreased without a change in total PGC-1α content, indicating an improvement in SIRT1 activity after a high-fat diet vs an isocaloric low-fat diet. Thus, in healthy individuals, an increase in dietary fat intake from 20% to 50% (of which 20% to 30% were MUFAs) of total calories for 2 days might lead to an increase in skeletal muscle oxidative capacity, since PGC-1α is a transcription factor involved in the control of fat oxidation pathways.[39,55] This suggests an acute physiological adaptive response to excessive fat intake, possibly linked to increased activity of SIRT1.

In fact, high energy status, including high-fat diet feeding, decreases cellular NAD^+ levels, which reduces SIRT1 activity.[44] Moreover, fatty acids have been highlighted as activators or inhibitors of SIRT1. In vitro studies showed that the addition of PUFAs to cell cultures was able to increase *SIRT1* mRNA expression and SIRT1 protein levels as well as SIRT1 activity.[56–58] Similarly, mice fed a diet supplemented with PUFAs also showed an increase in *SIRT1* mRNA expression and SIRT1 protein levels.[59] However, in humans, Alayón et al[38] showed that the addition of 15 mL of sacha inchi oil, a vegetable oil containing high amounts of alpha-linolenic acid and linoleic acid, to a high-SFA meal was not able to modify *SIRT1* expression in PBMCs when compared with a high-SFA meal only. In that study, the experimental meals (100 g of buttered bread and sweetened coffee with or without 15 mL of sacha inchi oil) were similar in organoleptic characteristics but contained different amounts of energy (874 kcal vs 998 kcal), which is a key factor in modulation of sirtuin function. The high-SFA meal with sacha inchi oil had more calories than the control meal. Thus, the higher amount of energy available may have prevented the PUFAs in sacha inchi oil from modulating *SIRT1* expression.[38]

Caloric restriction, which increases NAD^+ levels, was the first method proven to increase SIRT1 activity.[60] NAD^+ acts as a positive modulator of SIRT1, whereas the accumulation of nicotinamide and nicotinamide adenine dinucleotide (NADH), the reduced form of NAD^+, leads to inhibition of SIRT1.[24] NAD^+ is synthesized via 2 major pathways, the NAD^+ de novo and the salvage pathways, both of which converge at nicotinic acid mononucleotide. In the de novo pathway, the nicotinic acid moiety of NAD^+ is synthesized from tryptophan via the kynurenine pathway.[61] In the NAD^+ salvage pathway, NAD^+ is generated through the recycling of its degradation products, such as nicotinamide. During caloric restriction, there is a decline in glycolytic rates in favor of respiratory metabolism as the main energy source. These alterations change the equilibrium of the reduced/oxidized forms of NAD towards NAD^+, thus increasing SIRT1 activity.[60] Unexpectedly, the 2 included studies that used long-term hyperlipidic overfeeding and conditions of excess nutrient intake showed an increase in expression of *SIRT1* and *SIRT3* mRNA in muscle.[13,39] Because the proportions of PUFAs, MUFAs, and SFAs provided in these overfeeding studies were similar, it is difficult to attribute any observed effect to the type of fatty acid used. Furthermore, the increase in *SIRT1* expression was not necessarily associated with improved SIRT1 activity. For example, Seyssel et al[13] showed PGC-1α hyperacetylation, decreased lipid oxidation rates, and reduced NAD^+ levels after 56 days of overfeeding, suggesting a lower deacetylase activity of SIRT1. Toledo et al[39] suggested an adaptive metabolic process in the face of an increase in available energy to explain the increase in *SIRT1* expression. Thus, an adaptative metabolic process might lead to an increase in the expression of *SIRT1* and *SIRT3* toward metabolic homeostasis to compensate for a possible reduction in sirtuin activity caused by chronic consumption of a hyperlipidic diet.

Currently, the best-characterized mechanism for sirtuin modulation by fatty acids shows a MUFA as a SIRT1 modulator. Lim et al[62] demonstrated that oleic acid stimulates the cAMP/protein kinase A (cAMP/PKA) signaling pathway and activates the SIRT1/PGC-1α transcriptional complex to modulate rates of fatty acid oxidation. This new lipid signaling/transcriptional cellular route is dependent on the activation of the cAMP/PKA signaling pathway that phosphorylates SIRT1 at Ser-434 and increases its deacetylase activity. Once activated, SIRT1 deacetylates PGC-1α, which increases the expression of fatty acid oxidation genes, leading to increases in complete oxidation of fatty acids (Figure 4[27–32,56–58,62–68]). These findings were supported by Lopez-Moreno et al,[37] who conducted a study in patients with metabolic syndrome. After long-term dietary intervention with a high-MUFA diet but not a high-SFA diet, patients showed an increase in *SIRT1* expression in PBMCs.[37] Similarly, increased levels of SIRT1 protein and increased expression of *SIRT1* mRNA after stimulation of hepatic cells with oleic acid (200μM and 500μM) were observed in vitro.[62,69,70]

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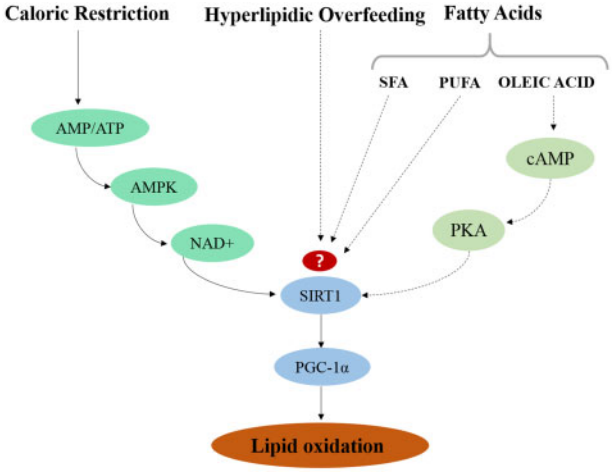

Figure 4 **Classical sirtuin modulators (solid lines) and new potential dietary sirtuin modulators (dotted lines) of SIRT1.** Under fasting conditions, SIRT1 is activated by NAD^+ and promotes PGC-1α activation through deacetylation. Once activated, PGC-1α increases the expression of target genes linked to the fatty acid oxidation pathway, thereby increasing lipid oxidation.[62,63] Current evidence suggests that sirtuins in humans also appear to be responsive to specific nutrient intake.[64] Lipids have been suggested as potential modulators of sirtuins in experimental and in vitro studies. Suppression of SFAs and improvement in SIRT1 function, both related to PUFAs, have been observed, but no mechanisms have been proposed yet.[27–32,56–58,65–68] On the other hand, MUFAs might activate SIRT1 via the cAMP/PKA pathway, which consequently promotes PGC-1α activation and, finally, improvement in lipid oxidation.[62] *Abbreviations*: cAMP, cyclic adenosine monophosphate; AMP, adenosine monophosphate; AMPK, AMP-activated protein kinase; ATP, adenosine triphosphate; MUFA, monosaturated fatty acid; NAD^+, nicotinamide adenine dinucleotide; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator 1-alpha; PKA, protein kinase A; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid; SIRT1, sirtuin 1.

In 2 randomized controlled trials of n-3 PUFA supplementation (1.2–2.7 g of EPA + DHA) for 8 to 10 weeks, no changes in *SIRT1* expression in PBMCs was observed in patients with cardiovascular disease or type 2 diabetes mellitus.[40,41] Similarly, no changes in *SIRT1* expression were observed in patients with metabolic syndrome who consumed a low-fat diet. However, when those patients were supplemented with n-3 PUFAs, *SIRT1* expression increased after 12 weeks of intervention.[37] Although in vitro and animal studies have demonstrated the ability of PUFAs to enhance *SIRT1* expression, no mechanism for modulation of sirtuins by PUFAs has yet been proposed. Furthermore, both cardiovascular disease and type 2 diabetes are associated with a severe decline in sirtuin function, especially SIRT1 function.[47,71–73] Levels of SIRT1 activity are lower in diabetic patients than in healthy individuals.[74] Insulin resistance and type 2 diabetes are both associated with inflammation, oxidative stress, and mitochondrial dysfunction. Inflammation and oxidative stress also promote pancreatic β-cell dysfunction, which contributes to the progression of type 2 diabetes.[75,76] SIRT1 may reduce inflammation and oxidative stress, thereby improving mitochondrial function and resulting in the protection of pancreatic β-cells and a reduction in insulin resistance.[76] Furthermore, SIRT1 was recently reported to have a protective effect against the pathogenesis of diabetic nephropathy by modulating metabolic inflammation, autophagy, apoptosis, and oxidative stress and suppressing inflammation through deacetylation of transcription factors.[75] Nissoli et al[77] provided the first evidence linking expression of SIRT1 to increased production of endothelial nitric oxide synthase. SIRT1expression is lower in patients with heart disease than in healthy individuals.[78,79] Moreover, sirtuins exhibit atheroprotective, antithrombotic, anti-inflammatory, and antioxidant effects.[46] Thus, it is plausible to suggest that the reduced sirtuin activity observed in chronic disease may decrease the modulatory effect of fatty acids such as PUFAs.

The studies included in this review exhibited substantial heterogeneity in trial design, characteristics of study participants, type of interventions, outcomes investigated, and duration of follow-up, which prevents definitive conclusions from being reached. Nevertheless, despite the limited evidence available, this review summarizes information about the relation between sirtuins and fatty acids in humans and represents an important step toward better understanding of these mechanisms. Because sirtuins play a role in various metabolic processes and, thus, may influence the development of chronic disease, the ability of dietary components, such as fatty acids, to modulate sirtuins warrants further investigation.

CONCLUSION

This review summarizes the most recent information about the relation between consumption of fatty acids and the activity of sirtuins. Currently, the ability of fatty acids to modulate sirtuin activity is best documented in preclinical studies. It is not yet possible to establish a specific effect of PUFA, MUFA, or SFA consumption on sirtuin function in humans. Thus far, the best-described mechanism highlights the ability of oleic acid to improve SIRT1 function and, consequently, to increase fatty acid oxidation by the SIRT1/PGC-1α pathway. Additional randomized clinical trials with homogeneous populations and better controls are needed to demonstrate whether fatty acid consumption may favorably modulate the activity of sirtuins. An improvement in sirtuin activity through dietary intake of fatty acids might not only protect against obesity by

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increasing fatty acid oxidation but also prevent the development of chronic disease, given the role of sirtuins in metabolic homeostasis.

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Declaration of interest. The authors have no relevant interests to declare.

Supporting Information

The following Supporting Information is available through the online version of this article at the publisher's website.

Appendix S1 **PRISMA 2009 checklist**

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