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a systematic review of longitudinal studies

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EXTENDED REPORT

Weight loss for overweight and obese individuals with gout: a systematic review of longitudinal studies

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ABSTRACT

Objectives Weight loss is commonly recommended for gout, but the magnitude of the effect has not been evaluated in a systematic review. The aim of this systematic review was to determine benefits and harms associated with weight loss in overweight and obese patients with gout.

Methods We searched six databases for longitudinal studies, reporting the effect of weight loss in overweight/obese gout patients. Risk of bias was assessed using the tool Risk of Bias in Non-Randomised Studies of Interventions. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation.

Results From 3991 potentially eligible studies, 10 were included (including one randomised trial). Interventions included diet with/without physical activity, bariatric surgery, diuretics, metformin or no intervention. Mean weight losses ranged from 3 kg to 34 kg. Clinical heterogeneity in study characteristics precluded meta-analysis. The effect on serum uric acid (sUA) ranged from −168 to 30 µmol/L, and 0%–60% patients achieving sUA target (<360 µmol/L). Six out of eight studies (75%) showed beneficial effects on gout attacks. Two studies indicated dose–response relationship for sUA, achieving sUA target and gout attacks. At short term, temporary increased sUA and gout attacks tended to occur after bariatric surgery.

Conclusions The available evidence is in favour of weight loss for overweight/obese gout patients, with low, moderate and low quality of evidence for effects on sUA, achieving sUA target and gout attacks, respectively. At short term, unfavourable effects may occur. Since the current evidence consists of a few studies (mostly observational) of low methodological quality, there is an urgent need to initiate rigorous prospective studies (preferably randomised controlled trials).

Systematic review registration PROSPERO, CRD42016037937.

INTRODUCTION

Gout is a common form of inflammatory arthritis,[1 2] with an age-standardised global prevalence of 0.08% and is higher in developed countries.[3] Gout is a crystal-deposition disease resulting from chronic elevation of serum uric acid (sUA) above the saturation point for monosodium urate (MSU).[4–7] Initial presentation is severely painful episodes of peripheral joint synovitis (acute 'attacks'), but joint damage and subcutaneous tophus deposition may develop.[8] The general management principle is to reduce sUA levels, allowing MSU crystals to dissolve, leading to the elimination of acute attacks, disappearance of tophi and possibly cure of the disease.[9–11]

Body mass index (BMI) is strongly positively correlated to sUA levels,[12 13] and weight loss is a commonly recommended treatment for gout.[14–23] Furthermore, weight loss from bariatric surgery is associated with reduced incidence of hyperuricaemia and gout.[24] The mechanism by which weight loss can lower sUA levels is poorly understood. Some suggest that improved insulin resistance results in less insulin-enhanced reabsorption of organic anions such as urate,[2] and a study demonstrated decreased sUA in overweight patients receiving either weight loss from low-energy diet or an insulin-sensitising agent.[25] However, a study of severe obese patients receiving bariatric surgery found no association between reduced sUA levels and improved insulin resistance,[26] making a relationship questionable.

Guidelines recommending weight loss for gout patients[14–23] are based on evidence from only few clinical studies,[27 28] one population-based study[29] and indirect evidence from studies on non-gout subjects. The evidence for effectiveness in clinical studies has to our knowledge not previously been evaluated in a systematic review. Therefore, the primary objective of this systematic review was to determine the benefits and harms associated with weight loss in overweight and obese individuals with gout. Furthermore, we had an explicit focus on the weight loss intervention (including magnitude and intensity) to see whether a dose–response relationship exists at the study (ie, group) level.

METHODS

Protocol

A protocol adhering to the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols 2015 statement[30] was registered online (PROSPERO: CRD42016037937) and published on www.parkerinst.dk.

Search strategy

We searched four bibliographic databases on 26 April 2016; MEDLINE via Ovid from 1946, EMBASE via Ovid from 1974, Web of Science via Web of Knowledge from 1900, Cochrane Central

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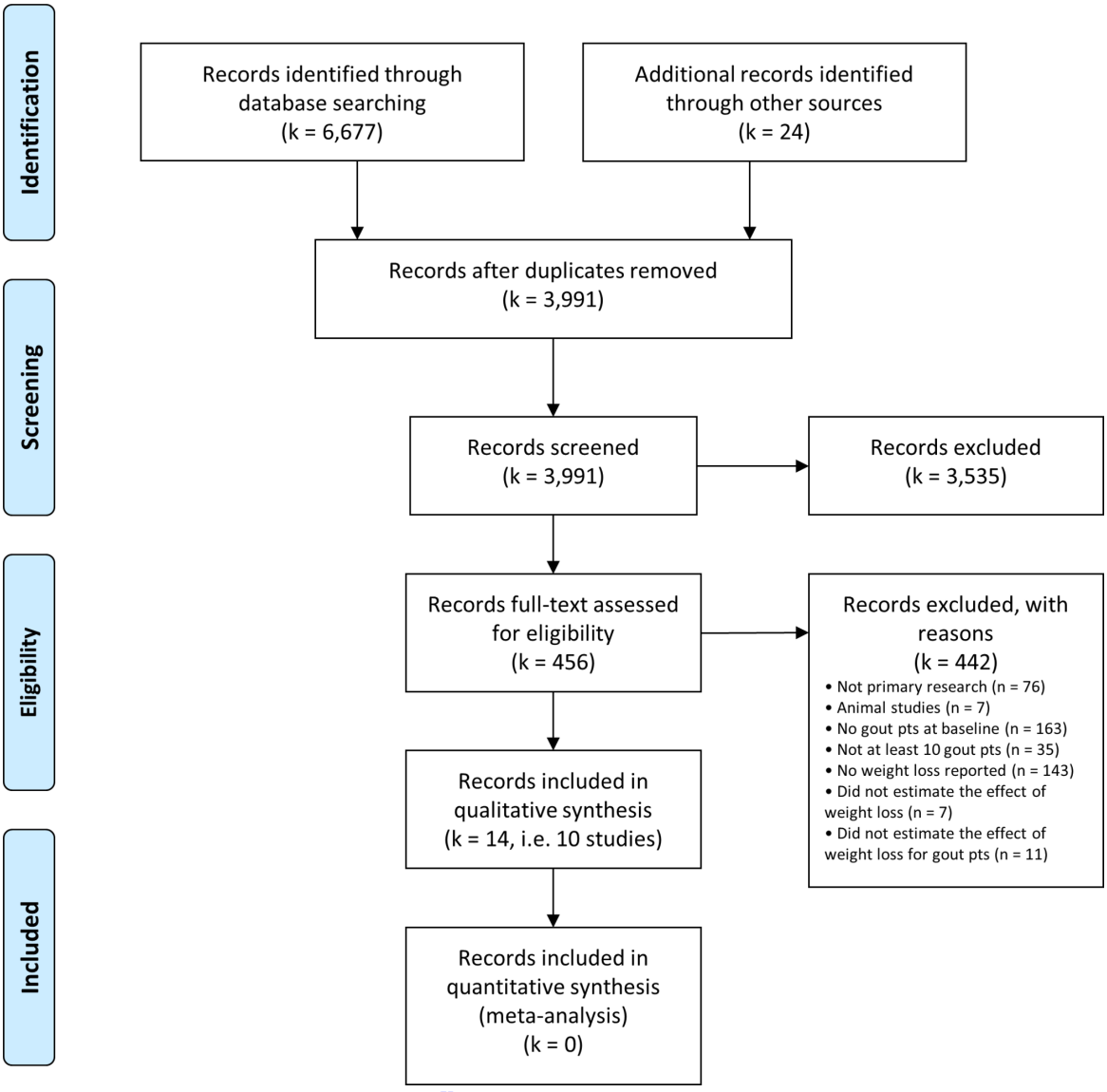

Figure 1 PRISMA flow diagram. Modified from Moher *et al*.[75] pts, patients.

Register of Controlled Trials (CENTRAL, The Cochrane Library), as well as ClinicalTrials.gov and WHO International Clinical Trial Registry Platform portal (search strategy presented: online supplementary text S1). We screened reference lists of relevant articles, as well as the American College of Rheumatology (ACR) and European League Against Rheumatism conference abstracts from 2014 and 2015, the ACR conference abstracts from 2016 and content experts were asked if they were aware of any other relevant studies.

Study selection

Anticipating only few randomised controlled trials (RCTs), we also included longitudinal observational studies (non-randomised studies) that quantitatively estimated the effect following weight loss. Studies needed to include ≥10 adult and overweight/obese patients (author described or BMI ≥25 kg/m^2[31]) with diagnosed gout (author described or meeting the 1977 ACR criteria for gout[32]). Eligible interventions included those where a weight reduction was reported explicitly, whether intentional or unintentional. The weight reduction was required to be the only difference in terms of intervention from the defined control group. Two reviewers (SMN supported by EMB) assessed the records. Disagreements were resolved by consensus or by discussion with a third reviewer (RC).

Data extraction and management

Two reviewers (SMN supported by RC) extracted the data. Prespecified outcomes included essential outcome domains for chronic gout[33 34]: (1) joint pain; (2) tophus/tophi; (3) physical function; (4) health-related quality of life (HRQoL); (5) sUA change; (6) Achieving sUA target (ie, sUA reduction to <360 μmol/L (6 mg/dL)); (7) serious adverse events (SAEs, defined as adverse events that are fatal, life-threatening or require hospitalisation); (8) withdrawals due to adverse events (WDdtAEs); (9) patient global assessment; (10) wody weight change; and (11) gout attacks (any measure).

Assessment of risk of bias in included studies (internal validity)

Two reviewers (SMN supported by RC) assessed risk of bias using the tool Risk of Bias In Non-Randomised Studies of Interventions[35 36] for evaluation of the risk of bias in non-randomised studies comparing health effects of two or more interventions.

Table 1 Characteristics of the included studies

	Study characteristics		Characteristics of gout pts						
Author, year, (multiple publication)	Study population	Intervention	No. of pts	Females, n pts	Age, years	BMI, kg/m^2	Disease duration, years	Urate-lowering medication use, n pts	Presence of tophi, n pts
Nguyen *et al*, 2016 [44] (Sherwin *et al* 1981 [47])	Men with a high cardiovascular risk profile and no gout at baseline of the MRFIT* study (n=11 896). 408 developed gout during the 7-year follow-up period.	This substudy of MRFIT uses a subpopulation, stratifying the risk of recurrent gout attacks for the BMI change in gout pts.	408†	0 (0)	NA	NA	NA	NA	NA
Dalbeth *et al*, 2014 [27] (Dalbeth, *et al* 2013 [42])	Pts with T2D and BMI ≥35 kg/m^2 who met presurgery weight loss requirements during part 1 (72 included, 60 completed). Included gout pts.	(Part 1) Presurgery weight loss (dietetic advice, set goals to establish a regular exercise programme and lose 5–10 kg, in addition to Optifast VLCD programme 4 weeks prior to surgery). (Part 2) Bariatric surgery (laparoscopic sleeve gastrectomy)	12	5 (42)	49 (8)	48.5 (5.4)	6.4 (7)	9 (75)	NA
Romero-Talamás *et al*, 2014 [46]	Gout pts with obesity (n=155).	I: Bariatric surgery (Roux-en-Y gastric bypass, gastrectomy, or adjustable gastric banding)	99	75 (75)	52.1 (10.3)	49.5 (11.9)	NA	53 (56)	NA
		C: Non-bariatric surgery (laparoscopic cholecystectomy, open cholecystectomy, cholecystectomy with another contaminant procedure or laparoscopic Heller myotomy).	56	34 (61)	63.3 (11.9)	36.8 (9.8)	NA	23 (42)	NA
Zeng *et al*, 2012 [49] *(In Chinese, RCT)*	Overweight men with gout, not using urate-lowering medication or having tophi (67 randomised, 61 completed the study).	I: High protein	30	0 (0)	61.5 (14.5)	27.0 (1.3)	NA	0 (0)	0 (0)
		C: Low purine	31	0 (0)	61.3 (11.2)	27.2 (1.6)	NA	0 (0)	0 (0)
Perez-Ruiz *et al*, 2011 [45] (*unpublished data*)	Gout pts with 5 years of compliance to urate-lowering therapy, and no tophi or resolution of all tophi prior to withdrawing urate-lowering therapy (n=211).	Withdrawal of urate-lowering therapy, stratified according to weight loss: lost >5% weight	25‡	1 (4)	NA	NA	7.4 (6.4)	25 (100)	0 (0)
		Withdrawal of urate-lowering therapy, stratified according to weight loss: no weight loss	167‡	7 (4)	NA	NA	7.2 (6.4)	167 (100)	0 (0)
Zhu *et al*, 2010 [29] (Sherwin, *et al* 1981 [47])	Men with a high cardiovascular risk profile and sufficient data from the MRFIT* study (n=12 379). Included gout pts.	This substudy of MRFIT uses a subpopulation, stratifying the changes in sUA for baseline BMI, weight change and other variables.	NA†	0 (0)	NA (All: 46 (range, 35–57))	NA	NA	NA	NA
Barskova *et al*, 2009 [40] *(In Russian)*	Gout pts (30 included, 23 completed).	Metformin (1500 mg/day)	23	2 (7)	51 (range, 43–54)	32.6 (5.2)	6 (range, 4–11)	0 (0)	8 (27)
Friedman *et al*, 2008 [43]	Pts received gastric bypass and experiencing postoperative gout attacks.	Bariatric surgery (gastric bypass and preoperative preparation, that is, clear liquid diet with protein supplementation 4–7 days and mechanical bowel preparation 2 days).	21	6 (29)	52 (range, 32–73)	49.6 (range, 36.1– 63)	NA	NA	NA
Dessein *et al*, 2000 [28] (Terkeltaub, *et al*, 2001 [48])	Gout pts. without tophi (n=13).	Diet recommendations (calorie restriction with specified macronutrient proportions, replacing refined carbohydrates with complex ones and replacing saturated fats with monosaturated and polyunsaturated ones).	13	0 (0)	50§ (5.6; range, 38–62)	30.5§¶ (8.1)	7§(10.2; range, 0.5–38)	0 (0)	0 (0)
Brandstetter *et al*, 1986 [41] (*In German*)	Gout pts with hyptertension (n=22)	I: Allopurinol, diet (low purine) and celiprolol (betablocker) and chlorthalidone (diuretic). C: Allopurinol, diet (low purine) and celiprolol .	11+11 (both groups)	7 (32)	52§ (range, 28–68)	26.0**	NA	NA	NA

The results are reported as mean (SD) or number (%), unless otherwise indicated.
*The original study (MRFIT) [39] randomised pts (n=12 866) to intervention (smoking cessation, weight reduction by caloric intake reduction and increased physical activity, nutritional counselling and antihypertensive treatment) or control.
†May include gout pts that were not overweight at baseline.
‡Due to loss of data in the study, the number of pts in the groups were 25 and 167 at baseline, and 29 and 163 at latestfollow-up.
§Median.
¶One had normal BMI.
**No BMI were reported, so BMI were calculated from data on height (median, 179 (range, 162–199)), and weight (median, 83.2 (range, 58–105)).
Allopurinol, diet (low purine) and caliprolol.
BMI, body mass index; C, control treatment; I, intervention; MRFIT, The Multiple Risk Factor Intervention Trial; NA, no data available; pts, patients; RCT, randomised controlled trial; sUA, serum uric acid; T2D, type 2 diabetes.

Post hoc, we decided to also use this tool for assessing studies with only one study group, by assuming that a virtual control group not receiving any intervention and experiencing no effect on any outcome was available, and for assessing RCTs, making comparisons possible. We resolved disagreements by discussion.

Important confounders of interest and cointerventions possibly affecting the effect of weight loss were not specified at protocol stage but prior to the risk of bias assessment (online supplementary text S2).

Reporting bias in individual studies was further investigated by comparing the constructed outcome reporting matrix,[37] with the protocols (if available).

Statistical analyses and evidence synthesis

None of our planned meta-analyses were conducted due to indisputable clinical heterogeneity in study characteristics (PICOTs). Instead it was decided post hoc that data for each study would be presented for all time points in a summary of findings table and the latest time point as changes from baseline would be summarised for each study in a summary of findings and GRADE evidence profile table. Based on the tables, we qualitatively considered the impact of follow-up time, that is, short-term (<3 months), medium (3–12 months) and long-term (>12 months), acute versus chronic gout, presence versus absence of concurrent urate-lowering medication use, presence versus absence of tophi, the dose–response phenomena of weight loss in magnitude and intensity (ie, magnitude over time) and the impact of bias. A graph showing the relationship between weight loss and sUA was constructed post hoc.

Dealing with missing data

Where data were missing or incomplete, we searched for information from the study authors and from additional records for the study. No imputations were carried out for patients lost at follow-up. Missing body weights were estimated from BMI, assuming a height of 1.70 m. Missing SDs were calculated from other statistics such as standard errors, or estimated from other studies investigating gout patients; for sUA, we used a SD for change from baseline of 137 μmol/L.

Assessing the quality of the evidence

We assessed the quality of the evidence with the GRADE approach,[38] starting at low quality of evidence, since the evidence was primarily based on observational studies and subsequently down-rated or up-rated the evidence.

RESULTS

Study selection

We identified 3991 records after removal of duplicates, forwarding 456 for full-text assessments after screening (figure 1). After excluding 442 records (see online supplementary text S3), we identified 14 records describing 10 studies for inclusion in the systematic review.[27–29 39–49]

During the study selection and data extraction, authors of 18 studies[27–29 40 43–46 49–58] were contacted; three responded[27 44 45] and provided additional information, including unpublished data for Perez-Ruiz *et al*.[45]

Study characteristics

The studies were comprised of one RCT[49] and nine non-randomised studies (table 1). Gout patients were a subgroup in three of the studies,[27 29 44] of which one study initially only included non-gout patients but did a subanalysis on recurrent gout attacks for those who developed gout during follow-up.[44] The studies included between 12 and 408 gout patients, including 0%–75% females. The average age and BMI ranged from 49 to 63.3 years, and 26.0 to 49.6 kg/m^2, respectively. Case definitions of gout included the use of the 1977 ACR criteria in one study,[42] diagnosis confirmed by detecting crystals in three studies,[28 40 45] asking 'Have you been told by your physician that you have gout?' in two studies,[29 44] medical history and documentation of previous gout attacks in one study,[43] documented episode(s) or evidence of medication use in one study,[46] or not specified in two studies[41 49] (online supplementary table S1). Comorbidities selected in the studies, besides overweight, included type 2 diabetes,[27] hypertension[41] and a high cardiovascular risk profile.[29 44]

Interventions included intentional weight loss from dietary changes with or without increased physical activity,[27 28] bariatric surgery[27 43 46] and unintentional weight loss from high protein diet,[49] diuretics[41] and metformin.[40] Three studies[29 44 45] stratified according to weight or BMI reduction, using no reduction as control. Four studies had no control group.[27 28 40 43] Follow-up ranged from 4 weeks to 7 years, and a mean weight loss of 3–34 kg at latest follow-up was reported.

Effect of weight loss

No data were available for joint pain, HRQoL or patient global assessment (outcome matrix: online supplementary table S2). One study[45] provided data on tophi, reporting none for both groups at baseline and follow-up, and one study[27] provided data on physical function measured by Short Form-36 physical functioning domain, reporting diminished function with the values 43.3 (SD 21.8), 24.6 (SD 28.2), 10.8 (SD 12.8) at baseline, 6 months and 1.5 years, respectively. One study[40] reported four WDdtAEs from metformin, and one study[27] did not report any SAEs in gout patients. On sUA, achieving sUA target and gout attacks, eight, five, and eight studies provided data, respectively (table 2).

The effect on mean sUA ranged from −168 μmol/L to 30 μmol/L (−2.8 mg/dL to 0.5 mg/dL) at latest follow-up (table 3). Studies with the largest (and fastest) weight loss showed in general the largest decrease (figure 2).[27 28 46] Furthermore, a dose–response relationship was shown by Zhu *et al*[29] with a weight loss of ≥10 kg being associated with a change in sUA of −37 μmol/L. It should be noted that non-gout and non-overweight patients were included in their analysis as well. At short term, Dalbeth *et al* (part 2)[27] reported an immediate postoperative mean sUA of 510 (SD 130) μmol/L, that is, an increase of 70 μmol/L from bariatric surgery, and at latest follow-up, sUA had dropped to 330 (SD 90) μmol/L. In that period, three out of seven patients terminated urate-lowering medication, that is, the decrease may truly be larger. Three studies showed no effect on sUA; Perez-Ruiz *et al*[45] and Dalbeth *et al* (part 1),[27] both with a concurrent decrease in urate-lowering medication, and Brandstetter *et al*,[41] where the weight loss may partly be due to diuretics and hence truly lower. Barskova *et al*[40] showed a decrease in sUA from a weight loss of only 3 kg. However, the use of metformin can have affected the results.

The proportion achieving sUA target (<360 μmol/L) ranged from 0% to 60% reduction in patients with raised sUA. Furthermore, a dose–response relationship was shown by Zhu *et al*[29] with approximately three times higher odds of achieving sUA target with loss of ≥10 kg body weight during 7 years compared with not losing weight. It should be noted that non-overweight gout patients were included in their analysis as well. The 0% and

Table 2 Study findings

Author, year, (multiple publication)	Group: time point	Body weight, kg	Body weight change from baseline, kg	sUA, µmol/L	Achieving sUA target*, n pts	Gout attacks
Nguyen *et al*, 2016[44] (Sherwin *et al* 1981[47])	<−5% BMI: 12 months	NA	NA	NA	NA	Recurrent, OR 0.61 (0.32 to 1.16)†
	−3.6 to −5% BMI: 12 months	NA	NA	NA	NA	Recurrent, OR 0.94 (0.43 to 2.06)†
	No change: 12 months	NA	NA	NA	NA	Recurrent, OR 1.00 (reference)†
	+3.6 to +5% BMI: 12 months	NA	NA	NA	NA	Recurrent, OR 1.43 (0.75 to 2.72)†
	>+5% BMI: 12 months	NA	NA	NA	NA	Recurrent, OR 1.60 (0.89 to 2.89)†
Dalbeth *et al*, 2014[27] (Dalbeth *et al* 2013[42])	Baseline (part 1)	139.8 (23.8)	–	410 (70)	2 (17)	2 (17) pts had ≥1 in 3 months
	6 months (part 1/2)	134.3 (24.3)	−5.5 (5.2)	440 (90)	2 (17)	0 (0) pts had ≥1 in 6 months
	6 months, 2 weeks (part 2)	NA	NA	510 (130)	NA	NA
	1.5 years (part 2)	100.3 (16.3)	−34 (11.0)	330 (90)	8 (67)	3 (25) pts had ≥1 in follow-up
Romero-Talamás *et al*, 2014[46]	I: Baseline	143‡	–	546 (120)	NA	20 (24) pts had ≥1 in 12 months
	I: 1 month	132‡	−11‡	NA	NA	NA (18) pts had ≥1 in 1 month
	I: 13 months	101‡	−31‡	336 (150)	NA	NA (8) pts had ≥1 in 12 months
	C: Baseline	106‡	–	462 (120)	NA	10 (18) pts had ≥1 in 12 months
	C: 1 month	105‡	−1‡	NA	NA	NA (2) pts had ≥1 in 1 month
	C: 13 months	104‡	−2‡	420 (96)	NA	NA (11) pts had ≥1 in 12 month
Zeng *et al*, 2012[49] *(In Chinese)*	I: Baseline	74.5 (3.50)	–	486 (41)	NA	All (100) had ≥1 in 6 months; 33 episodes
	I: 6 months	65.8 (4.44)	−8.7	420 (37)	NA	17 episodes; 48% fewer gout attacks
	C: Baseline	72.7 (3.26)	–	486 (41)	NA	All (100) had ≥1 in 6 months; 36 episodes
	C: 6 months	69.3 (7.78)	−3.4	467 (42)	NA	28 episodes; 22% fewer gout attacks
Perez-Ruiz *et al*, 2011[45] (*unpublished data*)	Lost weight: baseline	81.0 (11.0)	–	263 (59)§	23 (92)§	0 (0)§ pts with gout attacks at withdrawal
	Lost weight: mean 34 (26) months	77.8 (11.0)	−3.2 (5.6)	298 (59)§	27 (93)§	5 (17)§ pts with gout attacks during follow-up
	No weight loss: baseline	81.9 (8.6)	–	491 (95)§	150 (90)§	0 (0)§ pts with gout attacks at withdrawal
	No weight loss: mean 32 (28) months	84.3 (9.9)	2.4 (4.3)	509 (90)§	146 (90)§	80 (49)§ pts with gout attacks during follow-up
Zhu *et al*, 2013[29] (Sherwin *et al* 1981[47])	≤−10 kg: 7 years	NA	(range, ≤−10)	Change, −37 (−40 to −35)‡‡	OR 3.19 (1.99 to 5.09)**	NA
	−5 to −9.9 kg: 7 years	NA	(range, −9.9 to −5)	Change, −19 (−20 to −17)‡‡	OR 2.33 (1.75 to 3.11)**	NA
	−1 to −4.9 kg: 7 years	NA	(range, −4.9 to −1)	Change, −7 (−9 to −6)‡‡	OR 1.53 (1.24 to 1.89)**	NA
	No change: 7 years	NA	(range, −0.9 to 0.9)	Change, 0 (reference)‡‡	OR 1.0 (reference)**	NA
	+1 to +4.9 kg: 7 years	NA	(range, 1 to 4.9)	Change, 5 (4 to 7)‡‡	OR 1.01 (0.80 to 1.27)**	NA
	+5 to +9.9 kg: 7 years	NA	(range, 5 to 9.9)	Change, 17 (16 to 19)‡‡	OR 0.65 (0.45 to 0.95)**	NA
	≥+10 kg: 7 years	NA	(range, ≥10)	Change, 26 (23 to 29)‡‡	OR 0.58 (0.31 to 1.08)**	NA
Barskova *et al*, 2009[40] *(In Russian)*	Baseline	94‡	–	570 (110)	0 (0)	3†† (range, 1 to 6) pr. patient in 12 months
	6 months	91‡	−3‡	435 (91)	NA	NA
	12 months	91‡	−3‡	443 (107)	11 (48)	1†† (range, 0–2) pr. patient in 12 months
Friedman *et al*, 2008[43]	Baseline	143‡	–	NA	NA	NA
	6 months	NA	NA	NA	NA	7 (33%) pts had an attack during 6 months
Dessein *et al*, 2000[28] (Terkeltaub *et al* 2001[48])	Baseline	91.1†† (23.5)	–	570†† (100)	1 (8)††¶	2.1†† (SD, 0.8) pr. month (in 4 months)
	16 weeks	83.4†† (22.0)	−7.7†† (range: 0 to −21)	470†† (90)	7 (54)††¶	0.6†† (SD, 0.7) pr. month

Continued

Table 2 Continued

Author, year, (multiple publication)	Group: time point	Body weight, kg	Body weight change from baseline, kg	sUA, µmol/L	Achieving sUA target*, n pts	Gout attacks
Brandstetter *et al*, 1986[41] *(In German)*	I: Baseline	89.9 (10.9)	–	316 (46)	NA	NA
	I: 4 weeks	89.1 (10.6)	−0.8	368 (55)	NA	NA
	I: 3 months	87.3 (9.6)	−2.6	364 (29)	NA	NA
	I: 6 months	84.2 (8.4)	−5.7	320 (61)	NA	NA
	C: Baseline	77.0 (14.0)	–	297 (54)	NA	NA
	C: 4 weeks	77.0 (13.8)	0	304 (98)	NA	NA

The results are reported as means (SD) or number (%), unless otherwise indicated.
*Achieving sUA target, that is, sUA <360 µmol/L (6 mg/dL).
†Multivariable OR of recurrent gout attacks according to BMI change. Based on a conditional logistic regression adjusted for BMI, age, education, alcohol and coffee intake, presence of hypertension and diuretic use measured during the 12 months before the incident gout attack. It should be noted that non-overweight gout patients were included as well in the analysis.
‡Estimated from the BMI assuming a height of 1.70 m.
§Due to loss of data, the number of patients in the groups were 25 and 167 at baseline, and 29 and 163 at last follow-up.
¶Note that Dessein *et al* uses a cut-off of ≤510 µmol/L.
**Multivariable OR of achieving sUA target of ≤360 µmol/L according to the weight loss. Based on a conditional logistic regression adjusted for time-varying covariates, that is, age, congestive heart failure, hypertension, diuretic use, serum creatinine level, alcohol intake and dietary variables (intake of fructose, caffeine, total protein, polyunsaturated fat, monounsaturated fat, saturated fat and fibre). Reported with corresponding 95% CIs. It should be noted that non-overweight gout patients were included as well in their analysis.
††Median.
‡‡Based on linear mixed model adjusted for baseline covariates (race, education level and weight categories), and time-varying covariates, that is, age, congestive heart failure, hypertension, diuretic use, serum creatinine level, alcohol intake and dietary variables (intake of fructose, caffeine, total protein, polyunsaturated fat, monounsaturated fat, saturated fat and fibre). Reported with corresponding 95% CIs. It should be noted that non-overweight and non-gout patients were included as well in their analysis.
AEs, adverse events; BMI, body mass index; I, intervention group; C, control group; n, number; pts, patients; sUA, serum uric acid.

Table 3 Summary of findings and GRADE evidence profile

Quality assessment								No. of patients	Weight loss information		Effect		Quality
Studies with data	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Other	Study	Weight loss/ No weight loss	Weight loss, kg (% of body weight)	Weight loss pr. month (% of body weight)	Effect on outcome	Overall conclusion	GRADE rating
Serum uric acid (µmol/L)													
7	Serious (–1)	Not serious	Not serious	Not serious	Not serious	Dose response (+1)	Nguyen	NA/NA	–	–	NA	Weight loss results in a decrease of sUA after medium/long follow-up.	Low ⊕⊕◯◯
							Dalbeth (part 1)	12/0	5.5 kg (3.9)	0.9 kg (0.7)	30* (–48 to 108)		
							Dalbeth (part 2)	12/0	34 kg (24.3)	2.8 kg (2.0)	–110* (–188 to –32)		
							Romero-Talamás	99/56	29 kg† (23)	2.4 kg (1.8)	–168 (–213 to –123)		
							Zeng	30‡/31	3.6 kg (4.8)	0.6 kg (0.8)	–47 (–66 to –27)		
							Perez-Ruiz	25§/167§	5.6 kg (6.9)	0.2 kg (0.2)	17 (-40 to 73)		
							Zhu	NA/NA	–	–	Dose–response relationship between weight change and sUA change¶		
							Barskova	23‡/0	3 kg† (3.2)	0.3 kg (0.3)	–127* (–183 to –71)		
							Friedman	21/0	NA	NA	NA		
							Dessein	13/0	7.7 kg** (8.4)	2.1 kg (2.3)	–100*†† (–174 to –26)		
							Brandstetter	11‡/11	5.7 kg (6.9)	1.0 kg (1.1)	–2 (–116 to 113)		
Achieving serum uric acid target that is, sUA<360 µmol/L													
4	Serious (–1)	Not serious	Not serious	Not serious	Not serious	Large effect (+1) Dose response (+1)	Nguyen	NA/NA	–	–	NA	Weight loss results in a higher chance of achieving sUA target after medium/ long follow-up.	Moderate ⊕⊕⊕◯
							Dalbeth (part 1)	12/0	5.5 kg (3.9)	0.9 kg (0.7)	0% (0/10) reduction in pts with raised sUA*		
							Dalbeth (part 2)	12/0	34 kg (24.3)	2.8 kg (2.0)	60% (6/10) reduction in pts with raised sUA*		
							Romero-Talamás	99/56	29 kg† (23)	2.4 kg (1.8)	NA		
							Zeng	30‡/31	3.6 kg (4.8)	0.6 kg (0.8)	NA		
							Perez-Ruiz	25§/167§	5.6 kg (6.9)	0.2 kg (0.2)	1% reduction in pts with raised sUA		
							Zhu	NA/NA	–	–	Dose–response relationship between weight change achieving serum uric acid target**		
							Barskova	23‡/0	3 kg† (3.2)	0.3 kg (0.3)	48% (11/23) reduction in pts with raised sUA*		
							Friedman	21/0	NA	NA	NA		
							Dessein	13/0	7.7 kg **(8.4)	2.1 kg (2.3)	50% (6/12) reduction in pts with raised sUA*‡‡		
							Brandstetter	11‡/11	5.7 kg (6.9)	1.0 kg (1.1)	NA		

Continued

Table 3 Continued

Quality assessment								No. of patients	Weight loss information		Effect		Quality
Studies with data	Study limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Other	Study	Weight loss/ No weight loss	Weight loss, kg (% of body weight)	Weight loss pr. month (% of body weight)	Effect on outcome	Overall conclusion	GRADE rating
Gout attacks													
8	Serious (–1)	Not serious	Not serious	Not serious	Not serious	Dose response (+1)	Nguyen	NA/NA	–	–	Dose–response relationship between BMI change and recurrent gout attacks**	Weight loss results in fewer gout attacks after medium/long follow-up.	Low ⊕⊕◯◯
							Dalbeth (part 1)	12/0	5.5 kg (3.9)	0.9 kg (0.7)	0 pts had ≥1 attack 6 months (At baseline two pts had ≥1 attack in 3 months)*		
							Dalbeth (part 2)	12/0	34 kg (24.3)	2.8 kg (2.0)	Three pts had ≥1 attack in 12 months (At baseline for part 2, 0 pts had ≥1 attack in 6 months)*		
							Romero-Talamás	99/56	29 kg† (23)	2.4 kg (1.8)	RR of 0.72 for ≥1 attack at follow-up		
							Zeng	30‡/31	3.6 kg (4.8)	0.6 kg (0.8)	39% fewer attacks at follow-up		
							Perez-Ruiz	25§/167§	5.6 kg (6.9)	0.2 kg (0.2)	RR of 0.35 for ≥1 attack at follow-up		
							Zhu	NA/NA	–	–	NA		
							Barskova	23‡/0	3 kg† (3.2)	0.3 kg (0.3)	33% fewer attacks*††		
							Friedman	21/0	NA	NA	33% (7/21) pts had attacks*§§		
							Dessein	13/0	7.7 kg** (8.4)	2.1 kg (2.3)	71% fewer attacks*††		
							Brandstetter	11‡/11	5.7 kg (6.9)	1.0 kg (1.1)	NA		

Modified from table made with GRADEpro (computer program on www.gradepro.org), McMaster University, 2014. Effect on outcome was calculated as change from baseline to latest follow-up for NRS with one group, difference in changes for NRS with two groups and difference between groups at follow-up for RCTs, unless otherwise indicated. Effects on outcomes are presented as means (95% CI), numbers or RRs.
*Studies with only one group, hence the effect is not a contrast between groups.
† Weight loss estimated from BMI.
‡ On average a weight loss was seen for these pts as a group. Hence, some individuals may not have lost weight.
§Due to loss of data in the study, the number of pts in the groups were 25 and 167 at baseline, and 29 and 163 at last follow-up, respectively. For calculation of 95% CI, a mean, that is, 26 and 165, was used.
¶It should be noted that non-overweight and non-gout patients were included as well.
**It should be noted that non-overweight gout patients were included as well.
††Based on medians.
‡‡Dessein[28] used a cut-off of ≤510 µmol/L.
§§For this study, no comparison (such as a comparison group or a measurement before the intervention) was provided. Hence, the number is the absolute number.
BMI, body mass index; GRADE, The Grading of Recommendations Assessment, Development and Evaluation; NRS, non-randomised study; pts, patients; RCT, randomised controlled trial; RR, risk ratio; sUA, serum uric acid.

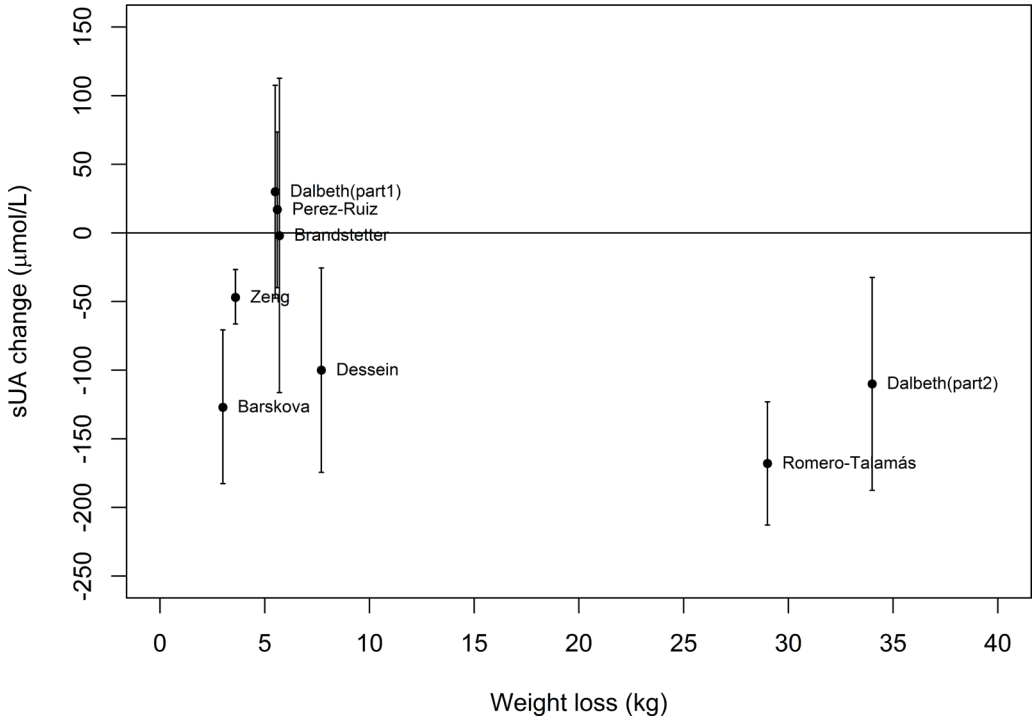

Figure 2 Relationship between weight loss and serum uric acid at latest follow-up. Estimates are shown with 95% confidence intervals. sUA, serum uric acid.

1% reduction in patients with raised sUA reported by Dalbeth *et al* (part 1)[27] and Perez-Ruiz *et al*,[45] respectively, are consistent with no change in sUA. Furthermore, achieving sUA target reported by Dessein *et al*[28] may be overestimated due to using a higher sUA cut-off of 510 µmol/L.

All studies, except two,[27 43] with data on gout attacks, showed a beneficial effect, and Dessein *et al*[28] reported 71% fewer attacks. Furthermore, a dose–response relationship was shown by Nguyen *et al*.[44] It should be noted that non-overweight patients were included in their analysis as well. Dalbeth *et al* (part 2)[27] reported an increase from zero patients experiencing ≥1 attack during 6 months to three patients during 12 months. This is possibly due to including the immediate postoperative phase where attacks could be a consequence of the increased sUA. Likewise, Romero-Talamás *et al*[46] report a possible increase from 24% experiencing ≥1 attack during 1 year at baseline to 18% during 1 month at 1-month follow-up, and a subsequently decrease to 8% during 1 year at last follow-up.

Only one study[40] included patients with tophi at baseline, therefore the impact on tophi could not be assessed.

Risk of bias assessment

The most frequent risk of bias was 'Bias due to confounding', with four studies rated critical due to studying one group without adjustment for confounders.[28 40 42 43] Five studies were rated serious (figure 3), and only the RCT[49] was rated low risk of bias. All studies were rated serious risk for 'Bias due to departures from intended interventions' (see possible confounders and cointerventions in online supplementary table S3). Reporting bias was suspected for two studies reporting change in BMI instead of change in weight.[40 46] Protocols were only found for two substudies[29 44] of one main study[39 47] and three studies reported no published protocol.[27 44 45]

Quality of the evidence using GRADE

For a beneficial effect of weight loss at medium-term/long-term follow-up, we evaluated the overall quality of evidence to be low for sUA, moderate for achieving sUA target and low for gout attacks.

DISCUSSION

Overall, we found low to moderate quality of evidence for beneficial effects of weight loss for overweight gout patients in terms of sUA, achieving sUA target and gout attacks. No or few data were available on our remaining prespecified outcomes. We did not find evidence for the optimal magnitude and intensity of weight loss. However, our data suggest that a weight loss of >7 kg and/or >2 kg per week from either surgery or diet results in a beneficial effect on sUA at medium-term/long-term follow-up based on three studies[27 28 46] and that weight loss of >3.5 kg showed beneficial effects on gout attacks at medium-term/long-term follow-up based on six studies.[27 28 40 45 46 49] However, with the present quality of evidence, further research may change these findings. WDdtAEs and SAEs were poorly reported. At short term, weight loss from bariatric surgery showed temporarily increased sUA levels and gout attacks, that is, a harmful effect, in the immediate postoperative period based on two studies.[27 46]

It is well known that there is a higher risk of gout attacks during the first months of urate-lowering therapy, postsurgery and starvation.[59] One hypothesis is that dramatic changes in sUA, rather than absolute level, triggers gout attacks.[60] In line with this, a study[61] comparing gout patients experiencing postoperative gout attacks with those who did not, find that the first group had higher presurgical sUA and a more rapid and larger decrease in sUA 3 days after surgery. Dalbeth *et al*[27] reported a drastic increase 2 weeks after surgery, which they suggested was due to renal dysfunction associated with major surgery, or metabolic effects from fasting or rapid weight loss (catabolic state),

Author, year and outcome	1. Bias due to confounding	2. Bias in selection of participants into the study	3. Bias in classification of interventions	4. Bias due to departures from intended interventions	5. Bias due to missing data	6. Bias in measurement of outcomes	7. Bias in selection of the reported result
Nguyen, 2016*							
Gout attacks	Serious	Moderate	Moderate	Serious	Moderate	Serious	Low
Dalbeth, 2014* (part 1)							
Physical function, SF36 PF	Critical	Serious	Moderate	Serious	Moderate	Serious	Low†
sUA and achieving sUA target	Critical	Serious	Moderate	Serious	Moderate	Low	Low
Body weight	Critical	Critical	Moderate	Serious	Moderate	Low	Low
Gout attacks	Critical	Serious	Moderate	Serious	Moderate	Serious	Low
SAEs	Critical	Serious	Moderate	Serious	Moderate	Serious	Low
Dalbeth, 2014* (part 2)							
Physical function, SF36 PF	Critical	Low	Low	Serious	Moderate	Serious	Low†
sUA and achieving sUA target	Critical	Low	Low	Serious	Moderate	Low	Low
Body weight	Critical	Low	Low	Serious	Moderate	Low	Low
Gout attacks	Critical	Low	Low	Serious	Moderate	Serious	Low
Romero-Talamás, 2014							
sUA	Serious	Low	Low	Serious	NI	Moderate	Moderate
Body weight (i.e. change in BMI)	Serious	Low	Low	Serious	NI	Moderate	Serious
Gout attacks	Serious	Low	Low	Serious	NI	Serious	Moderate
Zeng, 2012							
sUA	Low	Low	Low	Serious	Moderate	Low	Moderate
Body weight	Low	Low	Low	Serious	Moderate	Low	Moderate
Gout attacks	Low	Low	Low	Serious	Moderate	Serious	Moderate
Perez-Ruiz, 2011							
sUA and achieving sUA target	Serious	Low	Moderate	Serious	Low	Moderate	Low
Presence of tophi	Serious	Low	Moderate	Serious	Low	Low	Low
Body weight	Serious	Low	Moderate	Serious	Low	Low	Low
Gout attacks	Serious	Low	Moderate	Serious	Low	Serious	Low
Zhu, 2010*							
sUA and achieving sUA target	Serious	Moderate	Moderate	Serious	Moderate	Low	Moderate
Barskova, 2009							
sUA and achieving sUA target	Critical	Low	Low	Serious	Moderate	Low	Moderate
Body weight (i.e. change in BMI)	Critical	Low	Low	Serious	Moderate	Low	Serious
Gout attacks	Critical	Low	Low	Serious	Moderate	Serious	Moderate
WDdtAEs	Critical	Low	Low	Serious	Moderate	Serious	Moderate
Friedman, 2008							
Gout attacks	Critical	Low	Low	Serious	Low	Serious	Moderate
Dessein, 2000*							
sUA and achieving sUA target	Critical	Low	Low	Serious	Low	Low	Moderate
Body weight	Critical	Low	Low	Serious	Low	Serious	Moderate
Gout attacks	Critical	Low	Low	Serious	Low	Serious	Moderate
Brandstetter, 1986							
sUA	Serious	Low	Low	Serious	Low	Low	Moderate
Body weight	Serious	Low	Low	Serious	Low	Low	Moderate

Critical: Critical risk of bias is present. Serious: Serious risk of bias is present. Moderate: Moderate risk of bias is present. Low: Low risk of bias is present. NI: No information available.

Figure 3 Risk of bias summary figure. Similar outcomes has been put together in the figure but has been assessed separately. *Multiple publications existed. A primary publication was chosen. †Potentially serious risk of bias, since physical function was not reported in the article, but assessed low since data were provided from the author through email contact. BMI, body mass index; sUA, serum uric acid.

and they report one case of postoperative gout attack together with severe hyperuricaemia. Other factors increasing sUA levels are fasting,[62–64] dehydration[65] and tissue hypoxia.[66] Fasting-associated increase in sUA is likely due to tissue breakdown.[67 68] In line with this, daytime fasting during Ramadan, without weight loss, compared with non-fasting did not increase sUA or gout attacks in gout patients.[69]

Increased sUA seems to be related to decreased estimated glomerular filtration rate (eGFR).[70 71] This is probably related to sUA affecting blood pressure,[72] which may be caused by

increased vascular stiffness.[73 74] Reducing sUA may therefore have beneficial effect on susceptibility towards cardiovascular disease and diminished renal function.

In our study, we lacked evidence for many prespecified outcomes important to patients. Serum uric acid was among the most frequently reported outcomes and is recommended as a treatment target,[15–19 21–23] since elevated sUA is considered to cause the disease. Gout attacks in this study is not well defined and was reported in various ways and over various follow-up times. Therefore, stating fewer gout attacks following weight loss is not very specific and not necessarily assessable in smaller study sizes, or when attacks were not systematically assessed. At least three studies[27 43 45] did not point at reduced frequency of attacks, of which Friedman *et al*[43] did not report any baseline and Perez-Ruiz *et al*[45] did show less increase compared with control. Other studies can mask increasing number of attacks by reporting number of patients experiencing ≥1 attack over various follow-ups. Therefore, one could consider rating the evidence for gout attacks further down for indirectness.

Limitations of our methods include no independent double study selection, data extraction or risk of bias assessment. A limitation of investigating weight loss per se is that weight loss can be a consequence of many different interventions, that is, cointerventions, or conditions. Hence, it was impossible to ensure the weight reduction to be the only difference in terms of intervention from the comparison group, resulting in the inclusion of a wide variety of study settings. This is also observed as for which variables have been measured longitudinally. The included cohort studies stratifying according to weight loss may include unintentional weight loss for example, from illness, which is not relevant as intervention. Adding this to the fact that the majority of our included studies did not have a comparison group introducing non-controllable confounding, we cannot be sure that weight loss is accountable for all the effects observed. As a result, the implementation of weight loss intervention in clinical practice cannot be specified from the included studies. Taking the limitations of the available evidence into account, one may suggest, in order to address the effect of weight loss on sUA, that there currently is a need to perform a systematic review and meta-analysis of data not only for gout patients.

In conclusion, the available evidence is in favour of weight loss for overweight gout patients at medium-term/long-term follow-up on sUA, achieving sUA target and gout attacks. However, the evidence is of low, moderate and low quality, respectively. Harms were poorly reported. However, gout attacks might occur at short term when initiating treatment. We believe that there is an urgent need to initiate rigorous prospective studies (preferably RCTs) to provide more trustworthy estimates of gout-related benefits and harms including the effect on joint pain, tophi, physical function, HRQoL, adverse events and patient global assessment. Future research should aim at identifying the optimal magnitude and intensity of weight loss, the preferred method of weight loss, including prevention of flare, which cointerventions result in a better effect, and which gout patients will benefit the most, for example, grouped according to type (and possibly severity) of overweight and comorbidities.

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