WEIGHT LOSS FOR OVERWEIGHT AND OBESE INDIVIDUALS WITH GOUT: PROTOCOL FOR A SYSTEMATIC REVIEW AND META-ANALYSIS

Sabrina M. Nielsen[1], Else M. Bartels[1], Julie Bolvig[1], Marius Henriksen[1,2], Eva E. Wæhrens[1,3], Henrik Gudbergsen[1], Henning Bliddal[1], Arne Astrup[4], Filip K. Knop[5], Lars E. Kristensen[1], Robin Christensen[1].

Affiliations:

1: The Parker Institute, Copenhagen University Hospital, Bispebjerg & Frederiksberg, Copenhagen, Denmark.

2: Department of physical and occupational therapy, Copenhagen University Hospital, Bispebjerg & Frederiksberg, Copenhagen, Denmark.

3: The Research Initiative for Activity Studies and Occupational Therapy, General Practice, Department of Public Health, University of Southern Denmark, Odense, Denmark.

4: Department of Nutrition, Exercise and Sports, Faculty of Science, University of Copenhagen, Copenhagen, Denmark.

5: Department of Biomedical Sciences, University of Copenhagen, Copenhagen, Denmark.

Contact address:

Robin Christensen, MSc, PhD; Biostatistician

Professor of clinical epidemiology, adj.

Head of Musculoskeletal Statistics Unit, The Parker Institute,

Copenhagen University Hospital, Bispebjerg & Frederiksberg

Nordre Fasanvej 57

DK-2000 Copenhagen Frederiksberg

Denmark

Phone: +45 3816 4165

Fax: +45 3816 4159

E-mail: robin.christensen@regionh.dk

ABSTRACT

Background: Gout is the most common form of inflammatory arthritis. The overarching management principle of this crystal-deposition disease is to reduce serum uric acid (sUA) levels, allowing monosodium urate (MSU) crystals to dissolve, leading to reduced symptoms, and, possibly, cure of the disease. It has been suggested, that overweight and obesity is the strongest modifiable risk factor for gout and hyperuricaemia, and weight loss interventions are commonly recommended in the management of gout. However, the effectiveness of weight loss in gout has to our knowledge not previously been evaluated in a systematic review.

Objective: The objective of this systematic review is to determine the benefits and harms associated with weight loss in overweight and obese individuals with gout.

Methods/design: Eligible studies will be acquired through a systematic search of six databases; Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library), MEDLINE via Ovid from 1946, EMBASE via Ovid from 1974, Web of Science via Web of Knowledge from 1900, ClinicalTrials.gov, and World Health Organization International Clinical Trial Registry Platform portal (ICTRP). Eligibility criteria will be all types of clinical trials, i.e. randomised controlled trials (RCTs) and non-randomised studies (NRS), quantitatively estimating the effect of any intervention where a weight reduction is reported in adult (≥18 years), overweight and/or obese (i.e., body mass index ≥ 25 kg/m^2) patients with gout. The study selection, data extraction and bias assessment will be conducted by one reviewer supported by other reviewers. Risk of bias will be assessed using risk of bias tools from Cochrane Collaboration for RCTs and ACROBAT-NRSI for NRS. If the studies are sufficiently homogeneous, the data will be summarised in a meta-analysis, using standardised mean differences or risk ratios with 95% confidence intervals and estimation of statistical heterogeneity.

Perspectives: Our review will be the first to evaluate the effects of weight loss in overweight and obese individuals suffering from gout. The results will have important implications for future research strategies, by providing insights into which kind of further research is required to establish the value of weight loss for overweight and obese individuals with gout. The results will be disseminated as an article in a peer-reviewed scientific journal.

Systematic review registration: PROSPERO, CRD42016037937.

Keywords: Systematic review, Randomised controlled trials, Observational trials, Gout, Overweight, Obese, Weight loss.

BACKGROUND

Description of the condition

Gout is the most common form of inflammatory arthritis [1,2]; it constitutes an excruciatingly painful inflammatory disease of the joints and causes morbidity, disability and poorer quality of life [3-5]. The reported prevalence of gout worldwide ranges from 0.1% to approximately 10%, and the incidence ranges from 0.3 to 6 cases per 1,000 person-years [6]. Gout is a crystal-deposition disease that results from chronic elevation of uric acid levels above the saturation point for monosodium urate (MSU) crystal formation [7-10]. Thus, elevated serum uric acid (sUA), i.e. hyperuricaemia, represents the base for developing gout flares.

Initial presentation is mainly severely painful episodes of peripheral joint synovitis (acute self-limiting 'attacks'), but joint damage and deformity, chronic usage-related pain and subcutaneous tophus deposition can eventually develop. Typical presentations - for example, rapid onset of severe pain with swelling, erythema and marked tenderness in a first metatarsophalangeal joint, peaking within 12–24 h, and then completely resolving within 1–2 weeks, generally allow for a very high likelihood of an accurate clinical diagnosis of gout, although other forms of crystal-induced arthritis, trauma, sepsis and psoriatic arthritis may also be considered as differential diagnoses [6]. Both prevalence and incidence of gout are increasing in many developed countries [6]. The cause is a combination of genetic and dietary factors [11], and it occurs more commonly in those who eat large amounts of meat and certain seafoods, consume excess alcohol, and/or are overweight [6].

Description of the intervention

The general management principle is to reduce sUA levels, allowing MSU crystals to dissolve, leading to the elimination of acute episodes of inflammation, the disappearance of tophi, and, possibly, cure of the disease [12,13]. Treatment with nonsteroidal anti-inflammatory drugs (NSAIDs), steroids, or colchicine improves symptoms [12,13]. Once the acute attack subsides, levels of sUA are usually lowered via lifestyle changes, and in those with frequent attacks, allopurinol or probenecid provides long-term prevention [13].

It has been estimated that dietary causes account for about 12% of gout, and likely include an association with the consumption of alcohol, fructose-sweetened drinks, meat, and seafood [14]. Further, it has been suggested that obesity is the strongest modifiable risk factor for gout and hyperuricaemia [15,16]. Current understanding of the lifestyle factors associated with gout is largely derived from large, cross-sectional, epidemiological studies. Despite the lack of (causal) evidence supporting lifestyle interventions in the treatment of gout per se, several guidelines exist recommending lifestyle modifications [17], including the guidelines from the Dutch College of General Practitioners in 2002 [18], the European League Against Rheumatism (EULAR) in 2006[19], the British Society of Rheumatology (BSR) in 2007 [20], the Japanese Society of Gout and Nucleic Acid Metabolism in 2011 [21], an update of EULAR in 2011 [22], American College of Rheumatology (ACR) in 2012 [23], the Italian Society of Rheumatology recommendations for the management of gout in 2013 [24], and the Multinational Evidence, Expertise, Exchange Initiative (3e) in 2013 [25]. Together with general lifestyle advice, education concerning the need for compliance with lifelong urate-lowering therapy has been deemed essential [14].

How the intervention might work

In population-based studies, body mass index (BMI) has been shown to be strongly positively correlated with sUA levels [26,27], and obesity to be associated with the development of hyperuricaemia and the risk of incident gout [16]. Insulin resistance is associated with obesity [28] as well as with gout [29], and, interestingly, clearance of uric acid has been shown to be inversely correlated with insulin resistance [30]. However, it remains unclear, if insulin resistance promotes hyperuricaemia or *vice versa* [31]. One theory is that uric acid inhibits insulin signalling by increasing the production of reactive oxygen species, which may cause insulin resistance. This has been demonstrated *in vivo* and *in vitro* in animal models [32,33]. Another theory is that insulin resistance and ensuing hyperinsulinaemia cause hyperuricaemia by insulin-induced enhancement of renal tubular sodium-hydrogen exchanger expression, thereby facilitating secretion of hydrogen and reabsorption of not only sodium, bicarbonate, and chloride, but also organic anions such as urate [2]. In line with this, induced hyperinsulinaemia has been shown to acutely reduce clearance of uric acid [34]. Weight reduction enhances insulin sensitivity and lowers insulin [35,36], and we speculate that this may reduce sUA levels and the symptoms of gout.

Why it is important to do this review

Despite the fact that lifestyle interventions such as weight loss are commonly recommended in the management of patients with gout, the evidence for effectiveness in clinical studies has to our knowledge not previously been evaluated in a systematic review. The results of this review could be important knowledge for clinical practice and will definitely provide insights into what kind of research is required to establish the value of weight loss for overweight and obese individuals with gout.

OBJECTIVES

The primary objective of this systematic review is to determine the benefits and harms associated with weight loss in overweight and obese individuals with gout in terms of pain, physical function, quality of life, flare events and safety. Furthermore, we will have an explicit focus on quality of the weight loss intervention (including magnitude and intensity) [37] to see whether a dose-response relationship exists at the study (i.e., group) level.

METHODS

Types of studies

Evidence from existing randomised trials may not be sufficient to answer the question whether weight loss is effective in overweight individuals with gout. Therefore, this systematic review will attempt to include non-randomised studies (NRS) as well. Clinical trials, whether randomised and/or controlled or not, cohort studies, and cross-sectional studies, will be considered potentially eligible for inclusion; i.e., quantitative studies that estimate the effect (harm or benefit) following weight loss in at least 10 gout patients, which do not use randomisation to allocate units (individuals or clusters of individuals) to comparison groups. This includes studies where allocation occurs during the course of usual treatment decisions or peoples' choices: such studies are often called "observational". There are many types of such NRS, including cohort studies, case-control

studies, controlled before-and-after studies, interrupted-time-series studies and controlled trials in which intervention groups are allocated using a method that falls short of full randomisation (i.e., "quasi-randomised" studies).

Types of participants

Adult (aged 18 years or older) and overweight or obese patients (author-described or with a BMI ≥25 kg/m^2, as defined by the World Health Organisation's (WHO) international BMI classifications [38]) with diagnosed gout (author-described or meets 1977 ACR criteria for gout [39] or other criteria as specified in the study).

Types of interventions

Any intervention where a weight reduction is reported explicitly (whether it is intentional or unintentional) will be considered eligible. The weight reduction will need to be the only difference in terms of intervention from the defined control group. Thus any concomitant treatments (medication, exercise, behavioural therapies, etc.) have to be identical in the treated and the control group, ensuring that any clinical benefits (or harms) are likely caused by a difference in change of body weight, independently of any possible interactions (incl. effect modifiers) that might have influenced the outcome of gout.

Types of outcomes

1. Joint pain: mean change in pain score on a visual analogue scale (VAS) or numerical rating scale
2. Tophus/tophi
3. Physical function (i.e. activity and participation): as measured by disease-specific and/or generic instruments (such as the Health Assessment Questionnaire Disability Index (HAQ-DI))
4. Health-related quality of life (HRQoL): as measured by generic instruments (such as the Medical Outcomes Study Short-Form-36 Survey (SF-36))
5. Serum urate change: mean change in sUA
6. Serum urate normalisation: sUA reduction to < 0.36 mmol/L (6.1 mg/dL)
7. Serious adverse events (SAEs, defined as adverse events that are fatal, life-threatening or require hospitalisation) AND withdrawals due to adverse events (WDdtAEs)
8. Patient global assessment, e.g. VAS
9. Body weight: change in bodyweight
10. Gout attacks: patient-reported gout attack frequency

The outcomes include the essential domains for outcomes for chronic gout recommended by the 2010 Outcome Measures in Rheumatology Meeting (OMERACT 10) [40,41].

For the purpose of this review, if feasible, we plan to group trials into those of short-term (less than three months), medium term (three to 12 months) and long-term (more than 12 months) duration. We will present the above listed outcomes (at the latest time point) in a 'Summary of findings' table.

Search methods for identification of studies

Electronic searches

We will search the following databases for controlled studies using the search strategy presented below:

1. Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library)
2. MEDLINE via Ovid from 1946
3. EMBASE via Ovid from 1974
4. Web of Science via Web of Knowledge from 1900
5. ClinicalTrials.gov
6. World Health Organization International Clinical Trial Registry Platform portal (ICTRP)

The search strategies for the bibliographic databases are outlined in appendix 1.

Searching other resources

We will search the ACR and EULAR conference abstracts from 2014 and 2015. We will hand-search the reference lists of included articles and relevant reviews to identify any additional studies not retrieved by the aforementioned search strategy.

Selection of studies

Three reviewers (SMN supported by JB/EMB) will assess all retrieved trials to identify those that fulfilled the criteria for inclusion in this systematic review. We will retrieve all potentially relevant articles in full text for closer examination. Disagreement about study inclusion or exclusion will be resolved by consensus or by discussion with a fourth reviewer (RC) if needed.

Data extraction and management

Two reviewers (SMN supported by RC) will extract the following relevant information from included trials using a predefined data extraction form: study design, characteristics of the study population (age, gender, presence or absence of concurrent urate lowering medication use or tophi), lifestyle/pharmacological interventions, control interventions, outcome measures (mean and standard deviation for continuous outcomes, number of events and participants for dichotomous outcomes), timing of outcome assessment, and methodological domains relevant to the assessment of internal validity. We will establish consensus by referring back to the original articles, and a third reviewer (MH) will be consulted if necessary.

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

Two reviewers (SMN supported by RC) will assess risk of bias for each included study using the criteria outlined by the Cochrane Collaboration, using the Risk of Bias tool for randomised controlled trials [42] and the ACROBAT-NRSI (A Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies of Interventions)

for the evaluation of risk of bias in the results of NRS that compare the health effects of two or more interventions.

Both the Cochrane risk of bias tool for randomised trials and the ACROBAT-NRSI focus on studies' internal validity, For both types of studies, we define bias as a tendency for study results to differ systematically from the results expected from a good randomised trial, conducted on the same participant group, that had no flaws in its conduct (for example, a large trial that achieved concealment of randomised allocation; maintained blinding of patients, health care professionals and outcome assessors to intervention received throughout follow up; ascertained outcomes in all randomised participants; and reported intervention effects for all measured outcomes). Such bias is distinct from issues of generalisability (applicability) to types of individual who were excluded from the study. For example, restricting the study sample to individuals free of comorbidities may limit the utility of its findings because they cannot be generalised to clinical practice, where comorbidities are common. We will resolve any disagreements by discussion and/or by involving another reviewer.

Measures of treatment effect

We plan to summarise the data in a meta-analysis only if there is sufficient homogeneity in clinical and setting characteristics (i.e., PICOTs). For continuous data, we will analyse results as mean differences (MD) between the intervention and comparator groups, with corresponding 95% confidence intervals (CIs). However, when different scales are used to measure the same conceptual outcome (i.e., construct for example, function or pain), we will apply standardised mean differences (SMDs) instead, with corresponding 95% CIs. SMDs will be calculated per default by dividing the MD by the standard deviation and subsequently apply the Hedges's small-sample adjustment, resulting in a unit less measure of treatment effect. For dichotomous data, we will calculate a risk ratio (RR) with corresponding 95% CI.

Unit of analysis issues

For studies containing more than two intervention groups, making multiple pair-wise comparisons between all possible pairs of intervention groups possible, we will include the same group of participants only once in the meta-analysis (to prevent inflated sample sizes). In the event that crossover trials are identified in which the reporting of continuous outcome data precluded paired analysis, we will include data from the first period only in the analysis. Where outcomes are collected at multiple follow-up times, within the short-term, medium-term and long-term time frames, we will give preference to extract the last endpoint.

Dealing with missing data

Where data are missing or incomplete we will search for further information from the study authors. In cases where individuals are missing from the reported results and no further information are achieved from the study authors, we assume the missing values had a poor outcome: For dichotomous outcomes measuring adverse events (e.g., number of withdrawals due to adverse events) we calculate the withdrawal rate using the number of

patients who received treatment as the denominator (worst-case analysis); For dichotomous outcomes measuring benefits (e.g., patient-reported reduction in gout attack frequency) we calculate the worst-case analysis using the number of randomised subjects as the denominator. For continuous outcomes (e.g., pain) we will calculate the MD or SMD based on the number of patient's analysed at the time point. If the number of patients analysed is not presented for each time point, we will use the number of randomised patients in each group at baseline. Where possible we will compute missing standard deviations from other statistics such as standard errors, confidence intervals or P values, according to the methods recommended in the Cochrane Handbook for Systematic Reviews of Interventions. If standard deviations cannot be calculated, they will be imputed (e.g. from other studies in the meta-analysis).

Assessment of heterogeneity

Prior to planned meta-analysis we will assess studies for clinical homogeneity with respect to type of therapy, control group, outcomes and study setting. For any studies judged as clinically homogeneous we plan to estimate statistical heterogeneity using the inconsistency (I^2) index, with the following as a rough guide for interpretation: 0% to 40% might not be important, 30% to 60% may represent moderate heterogeneity, 50% to 90% may represent substantial heterogeneity and 75% to 100% considerable heterogeneity. In cases of considerable heterogeneity (defined as $I^2 \geq 75\%$) we will explore the data further, including possibly stratified analyses, in an attempt to explain the heterogeneity.

Assessment of reporting biases

In order to determine whether reporting bias was present we will evaluate whether the protocol for the study was published before recruitment of study patients was started. For studies published after 1 July 2005 we will screen ICTRP. We will evaluate whether selective reporting of outcomes is present (outcome reporting bias). We will compare the fixed-effect estimate against the random-effects model to assess the possible presence of small-sample bias in the published literature (i.e. in which the intervention effect appears more beneficial in smaller studies); in the presence of small sample bias the random-effects estimate of the intervention is more beneficial than the fixed-effect estimate.

Data synthesis

Where studies are sufficiently homogeneous to make it clinically meaningful for them to be pooled we perform meta-analysis using a random-effects model, regardless of the I^2 results. We will perform the analyses and produce forest plots using the statistical software R version 3.2.3 (R Foundation for Statistical Computing).

Subgroup analysis and investigation of heterogeneity

Where sufficient data are available we plan to perform the following subgroup analyses:

1. Acute versus chronic gout

2. Presence or absence of concurrent urate-lowering medication use

3. Presence or absence of tophi

Thus, ideally we would like to extract the main outcome for the above subgroups within each trial.

We will perform meta-regression analyses to explore the expected dose-response phenomena. Restricted Maximum Likelihood (REML)-based (i.e. random-effects) meta-regression analysis [43] will be applied in order to answer the specific question raised by the secondary hypothesis – whether the absolute magnitude and intensity (magnitude over time) of weight loss is associated with the quantitative changes in pain and function; this will performed using the statistical software R, version 3.2.3 (R Foundation for Statistical Computing).

Sensitivity analysis

If sufficient studies exist we will perform sensitivity analyses to assess the impact of any bias attributable to inadequate or unclear treatment allocation (including studies with quasi-randomised designs) and inadequate blinding of study participants, personnel and outcome assessors.

PERSPECTIVES AND DISSEMINATION

The results of this review could provide important knowledge/information for clinical practice, helping overweight and obese gout patients receiving evidence-based treatment. Further, it will have important implications for research strategies, by providing insights into which type of further research is required to establish the value of weight loss for overweight and obese individuals with gout.

The results will be disseminated as at least one scientific article in a peer-reviewed scientific journal, and will be communicated via scientific meetings. Papers will be drafted by the primary reviewer (SMN) and revised by all the co-authors.

OTHER ASPECTS

Contributions

Study concept and design: SMN, EMB, LEK, RC.

Drafting on the protocol: SMN, EMB, RC.

Search strategy: EMB, SMN.

Critical revision of the protocol for important intellectual content and final approval before submission: All authors.

Obtained funding: HB, LEK, RC.

Competing interests

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