Addressing weight loss management in obese gout patients: guidance for future trials

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Abstract

Obesity is widely recognized as being associated with both the onset and advancement of gout, exerting a detrimental effect on health outcomes in society. In the realm of gout management, theoretical frameworks support weight loss as a beneficial strategy for people impacted by overweight or obesity. Existing empirical evidence is limited to a handful of predominantly observational studies with low methodological rigor. A recent exploratory clinical trial which included 61 people with obesity and gout randomly allocated participants to either an intensive diet group (n = 29) or a control diet group (n = 32). After 16 weeks, a significant difference in body weight change was observed between the intensive diet group and the control diet group [−7.7 kg (95% confidence interval −10.7 to −4.7)]. Although the results leaned towards favoring a low-energy diet, differences in changes in serum urate (SU) levels and fatigue between the groups could not be confirmed. For the majority of individuals who lose weight a key challenge is long term maintenance. Novel agents such as glucagon-like peptide-1 receptor agonists (GLP-1Ras) have a role in weight loss and its maintenance. In this manuscript we propose what we consider the ideal target trial for weight loss in gout. We envision a two-year randomized trial with participants allocated to either a GLP-1Ra or placebo and evaluated and monitored over a two-year period.

Keywords

Introduction

Gout is a prevalent condition affecting more than 41 million adults worldwide according to the Global Burden of Disease (GBD) estimates [1]. The primary pathological hallmark of gout involves the deposition of monosodium urate crystals in and around joints, which form in the presence of elevated serum urate (SU) [2]. Clinical manifestations of gout stem from the inflammatory response to these crystals, underscoring the pivotal role of treatment modalities aimed at lowering SU thereby leading to crystal dissolution. To the individual and society, the challenge posed by gout is further exacerbated by the presence of common comorbidities among people with gout, such as hypertension (75%), chronic kidney disease (CKD; 70%), obesity (53%), and cardiovascular disease (CVD; 10–14%). These co-morbidities significantly elevate the risk of morbidity and mortality [3]. Consequently, the latest American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology (EULAR) gout recommendations underscore the importance of systematic screening and treatment of comorbidities and cardiovascular risk factors, with a specific focus on addressing obesity [4, 5]. This paper aims to elucidate the associations between obesity, SU, and gout, and to define the imperative target trial evidence required to address the treatment of people with gout and concurrent obesity, building upon existing knowledge and urgently needed effectiveness trial data. We explore the pressing challenges and emerging hypotheses stemming from research opportunities facilitated by the approval of novel weight loss medications potentially applicable in this context.

Relationship between obesity, SU, and gout

There is a strong positive correlation between body mass index (BMI) and SU, for which there is at least some genetic basis [6]. BMI has been shown to be the most important modifiable risk factor for hyperuricemia, with a population attributable risk (i.e., the proportion of hyperuricemia cases attributable to overweight or obesity) of 44% [7]. Obesity is thought to increase SU by both decreasing renal urate excretion and increasing urate production. BMI is also associated with risk of gout; compared with individuals with a BMI of 21–22.9 kg/m^2, the age-adjusted relative risk of gout is 1.40 for a BMI of 23–24.9 kg/m^2, 2.35 for a BMI of 25–29.9 kg/m^2, 3.26 for a BMI of 30–34.9 kg/m^2, and 4.41 for a BMI of 35 kg/m^2 or higher [8].

Potential mechanisms for urate lowering with weight loss

The mechanisms underlying the impact of weight loss on SU levels remain incompletely elucidated. Early studies reported that weight loss increased renal urate excretion and decreased urate production [9, 10]. Insulin resistance is associated with increased SU levels, and weight loss may contribute to a reduction in SU through improved insulin sensitivity [11–13].

The role of weight loss in the management of gout is twofold. Firstly, gout is independently associated with higher prevalence of CKD, type 2 diabetes (T2D), CVD and dyslipidemia, even after adjusting for SU, age, and sex. Weight loss exerts beneficial effects on cardiometabolic comorbidities [14]. Reduction in SU does not provide the same benefits for these comorbidities and thus weight loss is an important component of overall care for people with gout [15]. Secondly, while the available evidence remains limited and predominantly observational, it indicates that weight reduction in individuals who are overweight or obese and have gout leads to a decrease in both SU and the frequency of gout flares [16]. Weight loss of > 7 kg and > 2 kg per week from either surgery or dietary modification results in a beneficial effect on SU in the medium-term/long-term and weight loss of > 3.5 kg shows beneficial effects on gout flares over medium-term/long-term follow-up. However, the optimal magnitude and intensity of weight loss have not been identified. Whether the effect of weight loss on gout flares is mediated by the reduction in SU or through a reduction in adipose tissue and adipocytes which are metabolically active and contribute to systemic inflammatory responses remains unknown [17]. Of importance, the effect of weight loss on other patient-reported outcomes such as health-related quality of life (HR-QoL), pain, patient global assessment, and subcutaneous tophi, all of which are Outcome Measures in Rheumatology (OMERACT) endorsed core

domains for gout studies, have not been examined. Finally, any harms or adverse effects have been poorly reported in weight loss studies to date [16, 18].

New therapies for weight loss and potential benefits for people with gout

While dietary and lifestyle interventions can be successful in weight loss, a major challenge remains to prevent weight regain in the long-term. Thus, when treating chronic conditions, such as gout and its co-morbidities, additional strategies are required to help maintain weight loss. Pharmacotherapy is one such additional approach [19]. The glucagon-like peptide-1 receptor agonists (GLP-1Ras), such as liraglutide and semaglutide, are analogs of GLP-1, a gut-derived peptide hormone that is secreted following ingestion of food. GLP-1Ras lower glucose by stimulating insulin secretion from the pancreas and are thus used for the treatment of T2D [20]. Effects of GLP-1Ras in the central nervous system result in a reduction in appetite, food cravings, and energy intake as well as increased satiety and improved eating control [21]. Through these mechanisms, GLP-1Ras contribute to both initial weight loss and maintenance of weight loss in people who are overweight or obese. In a recent systematic review and meta-analysis of GLP-1Ras for weight loss and cardiometabolic benefits in obese individuals without diabetes, GLP-1Ras led to statistically significant weight loss (mean difference, −8.8 kg). GLP-1Ras also significantly improved systolic blood pressure (mean difference, −4.1 mmHg), diastolic blood pressure (mean difference −1.4 mmHg), and lipid profiles [22]. The effect of GLP-1Ras on SU seems to be negligible and certainly less profound than the effects of specific urate-lowering therapies and sodium-glucose co-transporter-2 (SGLT2) inhibitors [23]. Nevertheless, GLP-1Ras would seem appropriate for people with gout through beneficial effects on weight reduction, cardiometabolic risk factors, and major adverse cardiovascular events (MACE) [14].

Rationale for a large randomized trial with extended follow-up period

In a recent proof-of-concept trial published Christensen et al. [24] demonstrated that weight loss is a credible potential strategy for managing concomitant obesity in people with gout. They explored the clinical implications of implementing an intensive hypo-energetic dietary intervention over a 16-week period among individuals with obesity and gout. The study, conducted through a randomized trial design, aimed to reveal the cause-and-effect relationship between the intervention and its clinical outcomes. The trial encompassed an intention-to-treat (ITT) population of 61 participants, who were randomly assigned to either the intensive diet group (utilizing the Cambridge Weight Plan®; 29 participants) or the control diet group (offered basic nutritional advice; 32 participants) for the duration of the 16 weeks. Predominantly male participants, with an average age of 60 years and a mean BMI of 36 kg/m^2, were enrolled. At the conclusion of the 16-week intervention period, the intensive diet group exhibited a significant reduction in body weight (−15.4 kg) compared to the control group (−7.7 kg), with a difference between groups of 7.7 kg [95% confidence interval (CI): 4.7 to 10.7]. Although not reaching statistical significance, favorable trends were observed with reductions in SU and fatigue among participants in the intensive diet group. However, no discernible benefits were noted regarding pain levels or the occurrence of gout flares in this proof-of-concept trial. The researchers acknowledge that the 16-week duration is unlikely to be adequate to detect changes in gout flares, noting that in studies of urate-lowering therapies there is a delay between reduction in SU and reduction and cessation in gout flares [24]. Nonetheless, Christensen et al. [24] anticipate observing meaningful effects on patient-important outcomes within two years. By collecting data over a more extended period, the researchers would potentially be able to evaluate the persistence of any observed effects on weight loss and determine whether significant reductions in other patient important outcomes such as flares occur over time.

Since large, rigorously conducted randomized trials are the cornerstone of evidence-based rheumatology, it is unfortunate that the ability to perform them is difficult. Large trials present numerous challenges, including high costs due to extensive resource requirements for personnel, infrastructure, and data management. They are time-consuming, often spanning several years, with potential delays in recruitment and data collection.

Comparison of new weight loss compounds vs. placebo in individuals with gout and obesity

Herein we propose a preliminary protocol for an urgently needed weight loss in gout clinical trial, envisioning ideal conditions where participants, time and funding are unlimited. We propose that a preliminary trial protocol can offer valuable guidance on trial design, including the utilization of the "Core Outcome Set" established for gout trials [18], while generating the anticipated benefits of once-weekly GLP-1Ra drugs in gout [25].

Study design

In the outlined double-blind trial, our objective is to target a minimum sample size of 600 obese adults (BMI ≥ 30 kg/m^2) diagnosed with gout and having experienced at least one gout flare within the past six months. Participants will be randomly assigned, in a 1:1 ratio, to receive either GLP-1Ra or placebo administered via subcutaneous injection on a weekly basis, along with lifestyle intervention, for a duration of 104 weeks.

Participants and interventions

Eligible participants will be aged > 18 years, have obesity defined as a BMI ≥ 30 kg/m^2, meet the 2015 EULAR/ACR gout classification criteria exhibit an SU level of ≥ 0.36 mmol/L (6.0 mg/dL) at screening, and have at least one self-reported gout flare in the past 6 months [26]. Participants will be permitted to use urate-lowering therapy (ULT), but they will be instructed not to alter the type or dose of ULT during the first 52 weeks of the trial. After week 52 ULT escalation to achieve target urate will be permitted. Exclusion criteria will include the presence of other inflammatory diseases or cancer, as well as participation in other trials, including pharmacological studies or weight loss trials. Depending on random group allocation, the GLP-1Ra drug and identically appearing placebo will be initiated at the lowest dose, followed by dose escalation until reaching the target dose. The GLP-1Ra and placebo we are aiming for will most likely be administered via subcutaneous injection on a weekly basis. Maintaining blinding in a trial involving GLP-1Ras can be challenging, particularly when considering the anticipated speed of weight change. This can make it difficult for participants and investigators to remain unaware of treatment allocation. Participants on active treatment might experience more rapid or more significant weight changes compared to those on placebo, potentially revealing their group assignment. As weight loss becomes apparent, it could influence other outcomes measured in the trial, such as improvements in patient-reported outcomes, which could inadvertently unblind participants or investigators. Participants unable to tolerate the maximum dose will have the option to receive a lower dose at the investigator's discretion and will be encouraged to attempt reescalation to the maximum dose at least once. Throughout the full two-year trial period, the GLP-1Ra drug (and placebo) will be discontinued if participants become or plan to become pregnant, or if pancreatitis develops. Investigators are encouraged to adhere to evidence-based guidelines in managing gout and associated comorbidities. In the event of diabetes onset during the trial, patients will generally be advised to continue with the assigned trial medication. Ensuring adherence to ULT in a gout trial, particularly when comparing a GLP-1Ra to placebo, involves several strategies to effectively promote, monitor, and measure adherence: (i) promotion of adherence: this includes participant education, motivational support, regular communication, and providing incentives; (ii) monitoring of adherence: utilizing tools such as medication diaries to track compliance; and (iii) measurement of adherence: employing methods to accurately assess adherence rates and patterns. These strategies are essential for maintaining the integrity of the trial outcomes and ensuring valid comparisons between the GLP-1Ra and placebo treatments.

Outcomes and endpoints

Hypothesis testing will be used to address the uncertainty in assessing the treatment effect based on the chosen primary endpoint. Here, the co-primary endpoint will serve as the basis for the main statistical inference and conclusions of the trial. Outcome measures will involve multiple analyses, including confirmatory secondary, key secondary, and exploratory analyses. The OMERACT initiative has successfully

established a core set of outcome measures for clinical trials in gout [18]. We should collect, analyze, and report all the following in the main publication: pain due to gout [assessed using a visual analog scale (VAS)], joint swelling (measured through physical examination and imaging), patient global assessment (assessed with a VAS), activity limitation [using the Health Assessment Questionnaire-Disability Index (HAQ-DI)], HR-QoL [assessed using the Short Form Health Survey (SF-36)], tophus burden (number, sites, and maximum diameter of the largest tophus, dual energy CT volume), and SU levels. We will systematically collect the frequency of self-reported gout flares over the whole study period. Finally, cost effectiveness will be calculated as cost per quality-adjusted life-year (QALY) gained. To derive QALYs from SF-36, we will convert SF-36 scores to a utility measure using a mapping function; using mapping algorithms to convert SF-36 scores into utility values, such as those derived from the EQ-5D. The reporting of cost-effectiveness analyses will aim to provide decision-makers with information on the value for money of healthcare interventions, considering both their costs and effects.

The co-primary endpoints will consist of the proportions of participants achieving weight reductions of at least 10% and the proportion of participants achieving SU concentrations < 0.36 mmol/L (6 mg/dL) at 52 weeks. The rationale for selecting two distinct and specific time points (with 52 weeks allocated for the primary endpoint) is firmly rooted in the biomedical nuances of gout research [27]. Initially, our efficacy emphasis lies on the reduction of body weight and the reduction of SU to < 0.36 mmol/L among participants; the relevance of these efficacy measures is expected to transition into effectiveness. Attaining these objectives is anticipated to facilitate favorable long-term clinical outcomes, as outlined by the confirmatory secondary endpoints. Confirmatory endpoints are defined as those that are pre-specified in the clinical trial protocol and are intended to provide robust evidence to support the primary objective of the trial. Confirmatory secondary endpoints will include the percentage change in body weight, the proportions of participants having a gout flare from week 52 to 104, and the change from baseline to week 104 in SU levels, fatigue, HR-QoL, physical function/mobility, tophus burden, and pain intensity.

Key secondary endpoints should be applied to provide supportive evidence and additional insights beyond the primary hypothesis. While they help to understand the broader effects of the intervention and can include various outcome measures related to efficacy and safety, they do not carry the same weight as confirmatory endpoints in the regulatory decision-making process. Among the benefits associated with GLP-1Ra, a reduced risk of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke has been previously reported [14]. Consequently, in a 2-year trial like the one we propose herein, MACE should be a composite of death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, and death from any cause, all assessed in a time-to-first-event analysis.

Harms and laboratory markers

Randomized trials should measure, and report benefits and harms of health interventions. Prospectively collected data about harms in the outlined trial will be important to inform knowledge synthesis and future patient and provider decisions [28]. Treatment-emergent adverse events, serious adverse events, and mortality will be assessed throughout the entire follow-up period (up to 2 years from baseline). Selected adverse events (e.g., cardiovascular events, acute pancreatitis) and deaths should be reviewed by an independent external event adjudication committee. Metabolic measures should include changes in systolic and diastolic blood pressure, high sensitivity C reactive protein, total cholesterol, HDL cholesterol, LDL cholesterol, glycated hemoglobin, and triglycerides.

Sample size and power considerations

For disorders like gout with concomitant obesity, there are two different features that are so critically important to the disease under study that an experimental intervention will not be considered effective without demonstration of a treatment effect on both disease features. Multiple primary endpoints become co-primary endpoints when demonstrating an effect on both endpoints is critical to concluding that an experimental intervention (i.e., GLP-1Ra) is effective (i.e., superior to placebo). The proposed co-primary endpoint is a hierarchical outcome: at the 52-week assessment, we will first determine whether a

significantly higher proportion of participants achieve a substantial weight reduction defined as ≥ 10% from baseline. Only if this condition is met, we will test whether more participants reach the SU target. Thus, the effect of randomization to GLP-1Ra on SU will be considered conceptually supported only if there is a statistically significant difference in the number of participants who achieve significant weight loss. After 52 weeks, we conservatively estimate that approximately half of the participants (50%) in the experimental intervention group (GLP-1Ra) within the ITT population will achieve a substantial reduction in body weight, compared to an optimistically estimated 20% of participants in the control group. To detect such a large magnitude, we would need only 104 patients in the ITT population (approximately 52 per group) to attain a statistical power of 90%. Achieving SU levels below the target threshold [< 0.36 mmol/L (6 mg/dL)] at 52 weeks, we anticipate a success rate of 75% among participants randomly assigned to the experimental intervention (GLP-1Ra), compared to 60% in the ITT population receiving placebo [27]. To detect an effect size like that, we would need 406 patients in the ITT population (approximately 203 per group) to attain a statistical power of 90%.

For pragmatic reasons, the proposed trial is designed with a sample size of 600 patients in the ITT population. Although this may seem excessive, our objective is to ensure sufficient power to detect differences in the following confirmatory and key secondary endpoints evaluated at 104 weeks: percentage change in body weight, proportions of participants experiencing a gout flare between weeks 52 and 104, and changes from baseline to week 104 in fatigue, HR-QoL, physical function/mobility, tophus burden, pain intensity, proportion requiring ULT dose escalation after week 52, proportion achieving SU < 0.36 mmol/L at week 52 stratified by baseline SU and proportion achieving SU < 0.36 mmol/L at week 52 stratified by baseline BMI and SU. The superiority tests of GLP-1Ra compared to placebo for the primary and confirmatory secondary endpoints are conducted using a fixed-sequence statistical strategy. This approach evaluates each endpoint in a predefined hierarchical order, all at a 5% significance level, proceeding to the next endpoint only if the previous one demonstrates statistically significant superiority (P-value < 0.05). The effective power is determined by multiplying the respective marginal powers sequentially, assuming the independence of endpoints. As the two primary endpoints are part of this statistical testing hierarchy, the demonstration of significant superiority of GLP-1Ra over placebo is required for each primary endpoint.

Randomization, allocation concealment, and blinding

Stratified random assignment will be conducted based on sex (male compared with female), morbidly obese class (BMI ≥ 40 kg/m² compared with BMI < 40 kg/m²), and current ULT status at study enrollment. A computer-generated random assignment sequence will be generated to create 8 separate random assignment schedules (2 × 2 × 2) prior to enrollment, allocating patients in permuted blocks of 2 to 6 to either the GLP1-RA or placebo group. An independent data manager will input the random assignment sequence into the electronic case report file (eCRF) system. At week 0, the attending healthcare professional will initiate the "random assignment button" in the eCRF system to assign patients to one of the experimental arms. The entire procedure will be conducted in a blinded manner for all participants, investigators, clinical staff, academic personnel, and administrative trial staff. Administering identically appearing drugs in the trial ensures that they are physically indistinguishable from one another in terms of appearance, smell, and other sensory attributes. This practice aims to prevent participants and investigators from discerning which treatment each participant is receiving based solely on the drug's characteristics. Participants will receive the GLP-1Ra or placebo via subcutaneous injection once weekly. A double-blind design is essential for a placebo-controlled trial involving a GLP-1Ra to minimize bias: (i) if participants are aware of their treatment allocation, their expectations and behavior might impact the outcomes, potentially altering diet or exercise habits; (ii) if researchers know the treatment assignments, their expectations could unintentionally affect their interactions with participants, the interpretation of results, or the recording of outcomes. The use of identically appearing drugs helps uphold the blinding of the study, thereby mitigating the potential for participant or investigator performance bias to influence outcomes. Consequently, any observed differences in outcomes between treatment groups can be attributed to the effects of the treatment itself rather than external factors.

Statistical analysis

The endpoints that establish the effects of the experimental intervention (GLP-1Ra) and form the basis for concluding that the study meets its objective are designated as the primary endpoint family. When there is a single prespecified primary endpoint, there are no multiplicity issues related to determining that the study achieves its objective. In our suggested trial, the determination of effectiveness depends on success in both co-primary endpoints. Consequently, there are no multiplicity issues related to our choice of co-primary endpoints, as there is only one path to a successful outcome for the trial, thereby avoiding concerns of type I error rate inflation [29]. All 95% CIs and *P*-values will be two sided. We will not apply explicit adjustments for multiplicity, rather we will analyze the confirmatory secondary outcomes in a prioritized order (e.g., "gatekeeping procedure") [30]. The superiority of GLP-1Ra to placebo for the primary and secondary endpoints will be assessed in hierarchical order, with a claim of superiority at a significance level of 5% (two-sided) required before testing of subsequent endpoints in the hierarchy. The analyses of the secondary outcomes will be performed in sequence until one of the analyses fails to show the statistically significant difference, or until all analyses have been completed at a statistical significance level of 0.05.

The main analyses will be based on the ITT population [31]. This principle asserts the effect of a treatment policy (that is, the planned treatment regimen), rather than the actual treatment given (i.e., it is independent of treatment adherence). Maintaining follow-up with participants who discontinue randomized treatment can pose challenges, yet it holds significance as these individuals may exhibit systematic differences compared to those who continue with treatment. A trial that neglects to pursue follow-up after treatment cessation cannot uphold the ITT principle [32]. Therefore, individuals assigned to a treatment group (GLP-1Ra or placebo) should be diligently followed, evaluated, and analyzed as part of that respective group, regardless of their adherence to the prescribed treatment regimen (i.e., irrespective of withdrawals and crossover occurrences).

Continuous and categorical endpoints in a trial like this will highly likely be analyzed using analysis of covariance (ANCOVA) and logistic regression, respectively, with randomized treatment as a factor, stratifying factors, and the baseline value as covariates. The results will be presented by group, along with the differences between them using least squares means and odds ratios, each accompanied by 95% CIs. For continuous outcomes, missing data will be addressed through a multiple imputation approach, where each sampled complete dataset will be analyzed. This process will yield a series of estimates, which can be combined using Rubin's formula to obtain overall estimates [33]. For categorical efficacy endpoints, missing data will be handled by non-responder imputation in the main analyses.

We expect that a cost-effectiveness analysis (CEA) will be reported as part of a broader economic evaluation (i.e., secondary analyses following the main analysis and manuscript). The reporting of CEAs in a randomized trial, such as the one outlined here, will adhere to established guidelines such as the CHEERS (Consolidated Health Economic Evaluation Reporting Standards) statement [34].

In summary, this proposed 104-week trial will evaluate both the efficacy and utility of a novel weight loss approach as compared with sham as an adjunct to lifestyle intervention for reducing body weight plus SU and meeting other related endpoints in adults with gout and obesity.

Caveats and concerns

Looking ahead, we believe weight loss interventions hold significant promise in optimizing gout management, particularly among overweight individuals. Given the well-established link between obesity, elevated SU, and gout flares, achieving sustainable weight reduction should be prioritized as a therapeutic goal. Emerging data suggest that weight loss may reduce SU levels and could thereby decrease the frequency of gout flares. In this context, GLP-1Ras, already widely used in the treatment of T2D and for promoting weight loss, represent a particularly promising addition to the therapeutic landscape. This raises the exciting possibility that GLP-1Ra drugs could play a significant role in long-term management of gout, especially in people struggling with obesity, a common comorbidity in this population. By incorporating GLP-1Ra drugs into the treatment paradigm for gout, we may be able to address not only hyperuricemia but

also the underlying metabolic contributors to disease severity. We propose a visionary future research strategy that is urgently needed; the potential impact of such a strategy could transform the standard of care for people with both gout and obesity, offering a more comprehensive and effective approach to disease management.

A potential limitation of this trial could arise if some participants do not achieve target SU by week 52. We have therefore allowed for ULT dose escalation to achieve target urate in those participants who fail to achieve target urate by that time point.

As part of the trial design, it may be valuable to consider integrating the Gout Assessment Questionnaire (GAQ) as an optional tool to assess the broader patient experience, particularly the emotional and psychological impacts of gout. While the GAQ is not currently endorsed by OMERACT, it could provide additional insights into patient-reported outcomes, complementing the primary and confirmatory outcomes focused on physical symptoms like joint pain and tophi burden. Furthermore, participants could be asked to maintain a flare diary, where they record the onset, duration, and severity of gout flares. This approach allows for real-time data collection, reducing recall bias and capturing fluctuations in symptoms more accurately. Such diaries have been shown to enhance the ecological validity of flare reporting, enabling more precise tracking of treatment efficacy across the study period. However, they are frequently incomplete and other methods for collecting flare data are also required. Given recent evidence from the large-scale SELECT trial that GLP-1Ra drugs reduce the risk of major cardiovascular events, based on death from cardiovascular causes, nonfatal myocardial infarction, and stroke [14], it is reasonable to question whether obese individuals with gout or their healthcare providers would agree to a two-year placebo. Patients may be reluctant to accept randomization to placebo in a trial where cardiovascular benefits are purported, potentially complicating recruitment and trial feasibility. However, as with trials that stop early for benefit, concluding that we have high-certainty evidence for a cardiovascular benefit requires careful consideration. Ethical concerns regarding the withholding of an active treatment with established benefits could also arise, especially if participants become aware of the evidence.

Before the outlined trial is ready for implementation, the need for a Data Safety Monitoring Board (DSMB) should be considered. DSMBs are responsible for overseeing participant safety and trial integrity, which typically includes conducting interim analyses to monitor efficacy, safety, or futility. These analyses, guided by pre-specified stopping rules, help determine whether the trial should continue, be modified, or be stopped early. In this case—applying a new mode of action for managing gout in individuals with concomitant obesity—monitoring for serious adverse events or safety concerns would be crucial. If such concerns arise, the DSMB might recommend halting the trial to protect participants. Additionally, if interim results suggest that the trial is unlikely to demonstrate a significant difference between groups, the DSMB may recommend stopping early to conserve resources and avoid exposing participants to unnecessary interventions. The application of stopping rules through interim analyses will need to be discussed with ethics committees prior to trial commencement, ensuring adherence to ethical standards while maintaining scientific rigor. However, these analyses must be carefully planned and interpreted to avoid overstating benefits, harms, or drawing premature conclusions.

Conclusion

Obesity is a common comorbidity associated with both hyperuricemia and gout. The presence of obesity is also important given the association of gout with hypertension, T2D, and CVD. Weight loss is a critical modifiable risk factor for these conditions and may also benefit people with gout by contributing to a reduction in SU levels and gout flares. Sustained weight loss through behavioral modification is challenging and newer therapies that contribute to weight loss may have a role. Trials such as the one proposed will be important to determine the benefits, harms, and cost effectiveness of weight loss in people with gout.

Abbreviations

BMI: body mass index

CI: confidence interval

CVD: cardiovascular disease

DSMB: Data Safety Monitoring Board

eCRF: electronic case report file

GLP-1Ras: glucagon-like peptide-1 receptor agonists

HR-QoL: health-related quality of life

ITT: intention-to-treat

OMERACT: Outcome Measures in Rheumatology

SU: serum urate

T2D: type 2 diabetes

ULT: urate-lowering therapy

Declarations

Author contributions

RC: Conceptualization, Investigation, Writing—original draft, Writing—review & editing. TH: Investigation, Validation, Writing—review & editing. MBM: Writing—review & editing. HG: Conceptualization, Writing—review & editing. HB: Conceptualization, Supervision, Writing—original draft, Writing—review & editing. LKS: Conceptualization, Investigation, Writing—original draft, Writing—review & editing. All authors read and approved the submitted version.

Conflicts of interest

Robin Christensen who is the Associate Editor of *Exploration of Musculoskeletal Diseases* had no involvement in the decision-making or the review process of this manuscript. TH and MBM: declare that they have no conflicts of interest. HG has formerly been employed by NOVO. HB has received research grants and speaker's fees from NOVO. LKS has received royalties from Up-to-Date.

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Consent to participate

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Consent to publication

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