Title:

Weight loss as treatment for gout in patients with concomitant obesity: Protocol for a proof-of-concept randomised, non-blinded, parallel-group trial

Short title:

Weight loss for obese individuals with gout

AUTHORS/COLLABORATORS (TBD)

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INTRODUCTION

Background

Gout is an increasingly common disorder {Zhu, 2011 #25} characterised by elevated serum urate (SU) and by acute and chronic arthritis causing severe disability and pain. Long-term management of gout focuses on urate-lowering therapy (ULT), and keeping SU under its solubility threshold. When SU is kept under the threshold for solubility, the frequency of gout flares will decrease and the urate crystals dispositioned in the joints will dissolve. New therapeutic management of gout has in recent years emerged. However, despite the potential for effective treatment, gout management remains suboptimal {Richette, 2017 #14}. According to the overarching principles, and latest EULAR recommendations - emphasizing the need to address comorbidities - in the management of gout, every person with gout should be systematically screened for associated comorbidities and cardiovascular risk factors, including kidney impairment, coronary heart disease, heart failure, stroke, peripheral arterial disease, smoking, hyperlipidaemia, hypertension, diabetes, and obesity {Neogi, 2011 #28;Dalbeth, 2016 #29}. Appropriate management of these comorbidities is an integral part of the management of gout {Richette, 2017 #14}.

Epidemiological data link obesity and other components of the metabolic syndrome to the development of gout. Both conditions share pathogenetic mechanisms and the development of one disease increases the risk of the other and may trigger the onset of a vicious circle {Roddy, 2010 #19}. In addition, insulin resistance (IR) has been closely connected to gout {Vuorinen-Markkola, 1994 #8}. Insulin stimulates the renal tubular sodium hydrogen exchanger facilitating secretion of hydrogen and reabsorption of not only sodium, bicarbonate, and chloride but also organic anions such as urate. This constitutes a putative mechanism by which IR and hyperinsulinemia cause hyperuricemia {Facchini, 1991 #9;Puig, 1999 #7}. However, the hypothesis that a beneficial effect of weight loss in these patients is caused by a change in insulin resistance is currently controversial {Richette, 2016 #15}. Hypertension and dyslipidaemia as part of the metabolic syndrome has been linked to gout. Epidemiological studies support the alleged association between SU and hypertension and find that uric acid is an independent risk factor for developing hypertension. Consistency is found in a large number of prospective observational studies {Dyer, 1999 #30;Goldstein, 1993 #31;Imazu, 2001 #32;Jossa, 1994 #33;Krishnan, 2007

#34;Nagahama, 2004 #35;Nakanishi, 2003 #36;Taniguchi, 2001 #37}. Gout has also been associated with both increased very-low-density lipoprotein (VLDL) triglycerides {Matsubara, 1989 #38;Rasheed, 2014 #39} as well as low levels of high-density lipoprotein (HDL)-cholesterol {Choi, 2007 #40}. In hyperuricaemic individuals there is also a strong linear relation between, total cholesterol, triglycerides, LDL cholesterol and apolipoprotein-B levels and an inverse relationship with HDL and SU{Peng, 2015 #41}. A causal link between gout and hypertension/gout and dyslipidemia has yet to be discovered.

Rationale

In conclusion, there is some physiological evidence, although sparse, that weight loss in patients with gout reduces both SU and number of gout flares {Dessein, 2000 #11;Nicholls, 1972 #10}. Despite the scarcity of data regarding the effects of weight loss in gout, international guidelines recommend dietary intervention and weight loss as a core management strategy in patients with concomitant gout and obesity {Sivera, 2014 #4}. Medical treatment strategies have focused on either treatment of the acute inflammatory response of flares or long term reduction of SU by either inhibiting its production with xanthine oxidase inhibitors or increase renal excretion with uricosuric agents {Sivera, 2014 #4}. To date, no treatment strategy has targeted the basic dysmetabolic mechanisms linking obese patients with gout.

The Parker Institute has previously designed and applied a well-documented weight loss program running over 16 weeks (CAROT study) that effectively results in a significant weight loss (average ~12% of body weight) in obese (body mass index [BMI] >30 kg/m^2) patients with knee osteoarthritis with beneficial improvements in knee pain and function {Christensen, 2012 #6;Christensen, 2013 #5;Christensen, 2017 #1;Christensen, 2015 #3}.

Evidence-based research (reviewing previous studies)

The evidence-based research principles aims to reduce waste in research by promoting no new studies without the systematic review of existing evidence and the efficient production, updating, and dissemination of systematic reviews {Lund, 2016 #13}.

A recent systematic review from the Parker Institute, published previously this year in the *Annals of Rheumatic Diseases*, indicates that the available evidence is in favour of weight loss for people with gout {Nielsen, 2017 #20}. In the study, six databases were searched for longitudinal studies, initially resulting in 3,991 potentially eligible studies, of which 10 were included. The included studies were very heterogeneous; only one was a randomised controlled trial, and four of the studies had no comparator group. The interventions included diet with/without physical activity, bariatric surgery, diuretics, metformin, or no intervention. This heterogeneity precluded meta-analysis. In the included studies, mean weight losses ranged from 3 to 34 kg. Only sparse data on gout outcomes was available. The effect on SU ranged from -168 to 30 µmol/L, and 0% to 60% of patients achieved SU less than the therapeutic target for gout (<360 µmol/L). Six out of eight studies (75%) showed beneficial effects with reduction in the frequency of gout flares. Two studies indicated a dose-response relationship between weight change and SU, achieving SU target and gout flares, respectively. Furthermore, it should be noted, that shortly after bariatric surgery, one study showed a temporary increase in SU, and another showed a temporary increase in the number of gout flares. Other possible harmful effects were poorly reported. In the systematic review, risk of bias was assessed using ROBINS-I and the quality of evidence was assessed using GRADE, and Nielsen et al. concluded that the available evidence is in favour of weight loss for overweight/obese people with gout, with low to moderate quality of evidence for effects on SU, achieving SU target, and gout flares {Nielsen, 2017 #20}.

Objective and aim

To explore the short term clinical and laboratory effects related to a rapid diet-induced weight loss in obese individuals with gout. The aim with the current study is to address whether or not there is a difference in success rate in weight reduction, SU levels, and possible side-effects between the 2 approaches in the "short-term", by comparing a weight loss group to an ongoing no-treatment (usual care) group.

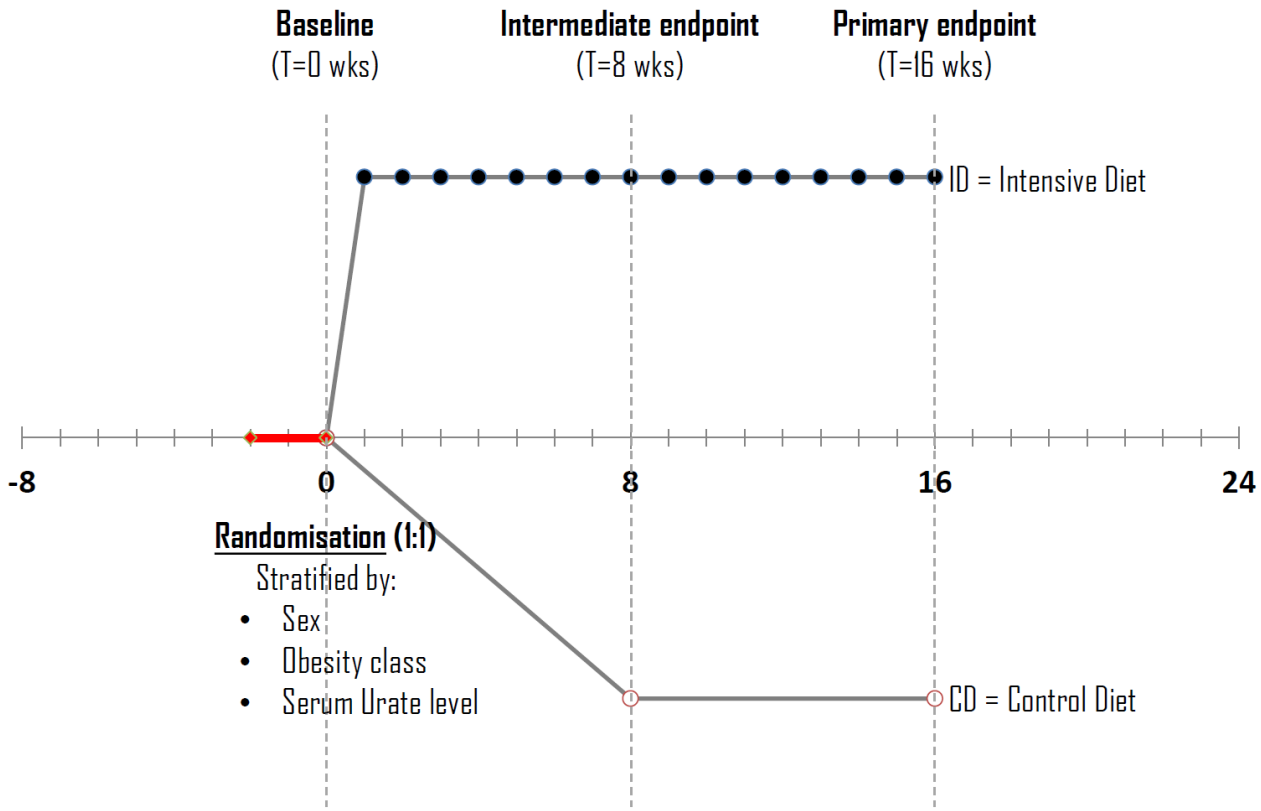

Figure 1. Illustration of the trial design including visits at the dietitian clinic illustrated as filled (ID)/unfilled circles (CD); primary endpoint assessed after 16 weeks. The period from week -2 to 0 indicate the screening and enrolment phase. Week 0 indicate the point of group allocation (stratified randomisation).

METHODS

Trial design and registration

The study is designed as a 16 (8+8) week pragmatic proof-of-concept randomised, non-blinded, parallel-group trial; the trial design is illustrated in **Figure 1**. The protocol will be registered with ClinicalTrials.gov (NCT03664167) before enrolling the first participants.

Participants and study setting

Participants will be recruited in the period March 2018–September 2018 from the out-patient clinics at the Parker Institute, Bispebjerg and Frederiksberg Hospital and the Department of

Rheumatology, Herlev-Gentofte Hospital, Denmark, through advertisements in newspapers and on the website of the Parker Institute. Additionally, local general practitioners will be informed about the possibility to assign patients to the project. All participants will be pre-screened via telephone using a series of standard questions about eligibility according to criteria of inclusion and exclusion. This study aims at being as pragmatic and inclusive as possible with few exclusion criteria.

Key inclusion criteria will be as follows: Participants will be included if they are above 18 years AND have a Body Mass Index (BMI) of at least 30 kg/m^2 AND per expert opinion have gout AND meet the 2015 American College of Rheumatology/EULAR gout classification criteria {Neogi, 2015 #2}, and with SU ≥5 mg/dL: The presence of monosodium urate monohydrate (MSU) crystals in a symptomatic joint/bursa (ie, synovial fluid) or in a tophus is a sufficient criterion for classification of the subject as having gout, and does not require further scoring. The domains of the recent gout classification criteria include clinical (pattern of joint/bursa involvement, characteristics and time course of symptomatic episodes), laboratory (serum urate, MSU-negative synovial fluid aspirate), and imaging (double-contour sign on ultrasound or urate on dual-energy CT, radiographic gout-related erosion).

In laymen terms: Males or females above 18 years with a diagnosis of gout, BMI ≥30 kg/m^2, with at least one self-reported gout flare in the previous 12 months will be eligible for study inclusion. A complete list of exclusion criteria is presented in **Table1**.

Table 1.	Complete list of exclusion criteria
1	Pregnant or breastfeeding.
2	A history or suspicion of drug abuse within the past 5 years.
3	Active muscle disease, cancer, previous kidney disease, and/or fatty liver
4	An estimated creatinine clearance <30 mL/min calculated by the Cockcroft-Gault formula using ideal body weight.
5	An investigational therapy within 8 weeks or 5 half-lives (whichever is longer) prior to the screening visit.
6	Any other medical or psychological condition which, in the opinion of the investigator and/or medical monitor, might create undue risk to the patient or interfere with the patient's ability to comply with the protocol requirements, or to complete the study.

Interventions

All the participants who sign informed consent will be randomly assigned to either 16 (8+8) weeks of low-energy diet (LED; 3.4 MJ/day; i.e., the Intensive Diet [ID] group) OR a corresponding 16-week conventional hypo-energetic, high protein diet (app. 5 MJ/day) defined as a control group (i.e., conventional diet [CD] group).

Intensive Diet (ID) Group: The first phase of the study consists of an 8-week weight reduction programme where the participants initiate an LED diet-only, with 3.4 MJ/day (810 kcal per day) in a supervised dietary programme (products provided by The Cambridge Weight Plan). Participants will attend the nutrition department at the Parker Institute weekly. They will be weighed on a decimal scale and given nutritional and dietetic instructions by an experienced dietitian in sessions of 1–2 h. The LED programme consists of powdered formula mixture dissolved in skimmed milk and water. All participants allocated to the ID group are assigned to an initial supervised dietary weight loss program and receive a hypo-caloric formula diet containing 800 to 1000 kcal/day. The formula diet consists of ready-to-use meal bars and powders to mix with water to make shakes, soups, or porridge. The initial weight loss programme consists of an 8-week period with full meal replacement by a standard liquid energy intake protocol. To facilitate compliance with the programme, participants will be scheduled for weekly facility-based group sessions with 6-8 participants led by a dietician. The recommendations for daily nutrient intake will be met during this period {Christensen, 2012 #6;Christensen, 2011 #16}. In our

previous study on weight loss for obese individuals with knee OA {Christensen, 2011 #16}, we observed an average weight loss during the 8-week period of ~12 kg (11%).

The second phase (ID Group) of the study (week 8-16), will consist of an 8 weeks' fixed energy diet programme using 5 MJ/day (1,200 kcal per day) incorporating two diet products daily. Participants will continue to attend the groups to which they were initially allocated. The participants will be taught to make diet plans with five to six small meals a day. The principles of the diet will be in line with the current guidelines for healthy eating issued by the Danish National Board of Health, i.e. low-fat, low-sugar and high-fibre. Participants will be encouraged to eat at least 300 g vegetables and two pieces of fruit daily. Participants will receive a list of recommended food items and instructions on how to use a food shopping guide promoting low-fat and high-fibre products. The emphasis of these guidelines is to encourage consumption of whole grains, vegetables and fruits that induce satiety because they may be eaten in relatively large amounts.

In general, the cognitive behavioural therapy provided with the dietary approach focuses on long-term lifestyle modifications; educational themes are: energy expenditure and energy balance, macronutrients, satiety, digestion, motivation and diet planning. The group treatment provides a combination of empathy, social support. In both phases of the study, the dietitian will aim to maximise adherence by reinforcing positive dietary changes and addressing barriers to adherence.

Conventional Diet (CD) Group: The programme will consist of a presentation by the same dietitian as for the ID group, who will provide nutritional advice in a 2 h session at baseline (week 0), and in week 8. At these sessions the dietitian will recommend eating ordinary foods in amounts which will provide the patients with approximately 5 MJ/day (1,200 kcal per day). The follow-up meeting at week 16 will not influence the outcome. Thus, during the 16 week trial, the CD group will attend three sessions altogether with a total of approximately 4h of instruction.

At the end of the study (16 weeks) all participants, both ID group and CD group, will be offered voluntary follow-up consultations with a dietician at the Parker Institutes outpatient clinic.

Outcomes

Table 2 illustrates the time points at which the outcomes are assessed during the 'Weight Loss for Gout' study.

Table 2. Protocol schedule of forms and procedures					
VARIABLE	Screening (approx. -2 wks)	Enrolment	Baseline (0 wks)	Intermediate (8 wks)	Endpoint (16 wks)
Secretariat: Information Motivational appraisal Eligibility criteria/Screening (phone)	X				
Informed consent		X			
Demographics and clinical features:					
Age, years		X			
Male, y/n		X			
Ethnicity, n (%)		X			
Duration of gout, years		X			
Height, cm		X			
Body mass index, kg/m^2		X	X	(X)	(X)
Flares* in the preceding year, count		X			
Presence of palpable tophi, y/n		X		X	X
Comorbidities:					
History of kidney stones, y/n		X			
History ofgall stones, y/n		X			
Cardio Vascular Disease, y/n		X			
Diabetes, y/n		X			
Hypertension, y/n		X			
Hyperlipidaemia, y/n		X			
Urate Lowering therapy:					
Allopurinol, y/n		X			X
Febuxostat y/n		X			X
Probenecid y/n		X			X
Benzbromarone, y/n		X			X

Anti-inflammatory prophylaxis:					
NSAIDs, y/n		X			X
Prednisone, y/n		X			X
Colchicine y/n		X			X
Concurrent medication:					
Diuretics y/n		X			X
Aspirin y/n		X			X
Antihypertensive medication y/n		X			X
Lipid lowering agents y/n		X			X
Diabetes medication y/n		X			X
Blood tests (lab. work):†					
Creatinine, mg/dL		X		X	X
eGFR, mL/min/1.73m^2		X		X	X
Serum urate, mg/dL		X		X	X
Total cholesterol, mmol/L		X		X	X
LDL cholesterol, mmol/L		X		X	X
HDL cholesterol, mmol/L		X		X	X
Triglycerides, mmol/L		X		X	X
HbA1c, mmol/mol		X		X	X
Fasting glucose, mmol/L		X		X	X
Physical examination (Nurse):					
Flares* in the last 8 weeks, count			X	X	X
Body weight, kg			X	X	X
Waist circumference, cm			X	X	X
Hip circumference, cm			X	X	X
Systolic blood pressure, mmHg			X	X	X
Diastolic blood pressure, mmHg			X	X	X
Pulse, bpm			X	X	X
**Metabolic syndrome, y/n			X	X	X
Touch screen (PROMs) :					
SF-36 health survey, score			X	X	X
Activity limitation (HAQ), score			X	X	X
Pain (VAS), mm			X	X	X
Patient global (VAS), mm			X	X	X

Fatigue (VAS), mm			X	X	X
Physical examination (MD):					
ACR/EULAR gout classification		X			
Gout according to expert opinion		X			
Swollen joint count, 0-66		X		X	X
Tender joint count, 0-68		X		X	X
Palpable tophi count		X		X	X
Randomisation (after confirming written informed consent)			X		
Imaging:					
Radiographs: Most symptomatic (index) joint		X			
Dual energy CT of most symptomatic joint		X			
Ultrasonography of most symptomatic joint and 1 metatarophangeal joint, knee: intercondylar cartilage and quadriceps and patella tendon and triceps tendon			X	X	X
Harms and adverse events‡ (AEs):					
Withdrawal, y/n				X	X
Withdrawal due to AEs, y/n				X	X
Number of serious adverse events, count				X	X
Death, y/n				X	X

*Gout flares will be self-reported flares requiring treatment as has been used in other studies of gout treatment {Becker, 2005 #23}.

†The intensive weight loss (ID) group will, for safety reasons have blood tests drawn each week the first 4 weeks.

‡Will be collected according to the MedDRA standards (the Medical Dictionary for Regulatory Activities: A pragmatic, medically valid terminology with an emphasis on ease of use for data entry, retrieval, analysis, and display, as well as a suitable balance between sensitivity and specificity within the regulatory environment).

**The metabolic syndrome is defined according to the ATP III 2005.

Primary endpoint:

The primary endpoint will be change in bodyweight (measured in kilograms) from baseline to the week 16 visit in the intention-to-treat (ITT) population. Also the proportion of participants losing more than 5% and more than 10% of baseline weight will be assessed to facilitate interpretation.

Key secondary endpoints:

Other major outcome measures include absolute reduction in SU at the final visit (16 weeks); the proportion of participants reaching and maintaining target SU levels, defined as 8 weeks and 16 week visits with SU<6 mg/dL, respectively; the percentage reduction in SU at final visit (week 16); the proportion of individuals with any gout flare in the first-, and last 8 weeks following randomisation, respectively; the number of gout flares during the trial period for each patient; functional status (HAQ); pain from their gout (VAS); patient global (VAS); fatigue (VAS); swollen joint count (SJC); tender joint count (TJC); change in number of tophi from baseline; and 36-Item Short Form Health Survey (SF-36: MCS and PCS apply); Gout flares will be self-reported flares requiring treatment as has been used in other studies of gout treatment {Becker, 2005 #23}.

Exploratory endpoints

Other exploratory endpoints will include a more detailed mapping of SU and creatinine levels from the repetitive blood samples taking on the intensive diet group.

Furthermore a research biobank of blood samples and synovial fluid will be made for the purpose of investigating the inflammatory response by cytokine profiling prior to and during the weight loss. The blood samples will be drawn at the same time as the blood samples for the study in general and will therefore not result in increased discomfort or risk for the patients. There will be drawn approximately 28 ml per visit resulting in total 196ml over 16 weeks – this equals less than half what is in a normal donor blood sample. The joint aspirations will be done if the patient have a flare that requires treatment – a prespecified amount of synovialfluid is not possible to give beforehand as the joint will be emptied and the sample therefor will vary. The samples will be analysed together when all patients are included and no later than 5 years after study start, after which the remaining blood will be destroyed. The samples will be stored in the local and approved biobank at the Parker Institute.

Anthropometric outcome measures: Waist circumference will be measured with a tape measure in cm midway between the lower rib and iliac crest according to WHO recommendations. Body weight will be measured on digital scales (TANITA BW-800, Frederiksberg Vægtfabrik, Frederiksberg, Denmark). Height is measured to the nearest 0.01 m; BMI is calculated by a person's weight (in kilograms) divided by the square of his/her height (in meters). Pulse and blood pressure (BP) will be measured three times and lowest value recorded. All measurements will be done at baseline and after 8 and 16 weeks (except height; only assessed at baseline).

Metabolic syndrome: The metabolic syndrome (MS) definition is based on the National Cholesterol Education Program Adult Treatment Panel (ATP III 2005) - MS is present when three or more of the following conditions occur simultaneously: 1) abdominal obesity defined by waist circumference 102 cm (men), 88 cm (women); 2) dyslipidaemia: triglycerides (TG) ≥ 1.695 mmol/l; 3) dyslipidaemia: high density lipoprotein (HDL) cholesterol < 1.036 mmol/L (men), < 1.295 mmol/L (women); 4) BP > 130/85 mmHg or use of medication for hypertension; 5) fasting plasma glucose ≥ 5.55 mmol/L or use of medication for hyperglycaemia.

Patient-reported outcome measures: In the Rheumatology clinic, self-administered Patient-Reported Outcome Measures (PROMs) are an important part of the overall evaluation of these patients: Functional status (Health Assessment Questionnaire [HAQ]); pain Visual Analogue Scale (VAS, from their gout/ target peripheral joint/bursa); patient global (VAS); fatigue (VAS), and the SF36. In this project several questionnaires are applied in the self-assessment process based on a computerised method of data collection based on touch-screen which will likely decrease the risk of error {Waehrens, 2015 #26 ;Gudbergsen, 2011 #27}.

Imaging:

X-Rays: X-ray of the most symptomatic joint will be performed according to local imaging standards in 2 planes and used to visualise potential gout characteristics

Dual energy CT (DE-CT) Scan: Dual energy CT scan of the most symptomatic joint as well as the contralateral joint will be performed at the same day of the X-ray in order to visualise potential gout crystals in the joint.

Ultrasound: In the ultrasound examination the most symptomatic joint will be assessed. Furthermore the 1 metatarophangeal joint, knee joint (intercondylar cartilage and quadriceps and patella tendon) and triceps tendon will be examined bilaterally. The features to be assessed are: double contour of the cartilage (DC), tophi in the joint and surrounding tissues and in tendons, erosions, synovialhypertrophy and Doppler activity (increased flow) {Chowalloor, 2014 #45;Durcan, 2016 #44;Naredo, 2014 #43;Terslev, 2015 #42}.

Power and sample size considerations

Using SAS Power and Sample Size (Copyright © 2013 by SAS Institute Inc., Cary, NC, USA) it was calculated assuming that the standard deviation (SD) of weight change at week 16 would be 6.0 kg {Christensen, 2011 #16}, that, 60 patients (30 in each group) would provide 89% confidence (power=0.888) to detect a clinically relevant 5 kg difference (p=0.05, two-sided) in mean bodyweight change between individuals allocated to intensive or conventional diet. If a drop-out rate of up to 20% (i.e., 6 patients in each group) is assumed, the trial will still have an acceptable power (>0.80) to detect a 5 kg difference between the groups.

Among the key secondary outcome measures is the mean change in SU at the final visit: Assuming a common SD of 1.6 mg/dL {Stamp, 2017 #21}, a total sample size of 60 gout patients (randomised 1:1) will have a sufficient statistical power (81.5%) to detect a mean difference of 1.2 mg/dL {Stamp, 2017 #21}.

Patient-Reported Outcome Measures (PROMs): With 60 patients in total, the trial will have sufficient power to detect a statistically significant effect size (i.e. standardised mean difference [SMD]) corresponding to a large clinical effect (SMD=0.8; power=86.1%).

Recruitment and participant timeline

Participants with a diagnosis of gout who may be considered for inclusion will be identified from routine care at The Parker Institute (adjacent to the department of Rheumatology) as well as the department of Rheumatology at Gentofte hospital, both in the Capital Region of Denmark. Additionally, potentially eligible participants will be recruited through advertisements in newspapers and on the website of the Parker Institute; local general practitioners will be informed about the possibility to refer participants to the project.
Persons indicating a willingness to participate will be contacted by the study secretariat by phone. Information on the project will be given verbally and the potential participants' eligibility according to key inclusion and exclusion criteria will be appraised. Subsequently the written information material will be sent either as regular mail or as e-mail. The potential participants will afterwards be invited to a private conversation with an investigator (or his/her delegate) in the outpatient clinic, ensuring that the participants will receive both verbal and written information about the project including

- Participation on the project is voluntary
- Participants have the right to 24 hours reflection time before deciding to sign the informed consent or not.
- Participants have the right to bring next of kin or another person of the participant's choice with him/her to the conversation appointment.
- Participants can at any time and without giving any reason, withdraw from the project – this will not affect the participant's right to current or future treatment.

Further, the private conversation will include information on: aim, procedures, potential risks when participating in the project, procedures for random findings during the project, procedures for securing the participants privacy and data protection, information on the projects organisation, funding, as well as contact information on the primary investigator and other key investigators. The investigator will make sure that participants have received and understood the information given to them furthermore the investigator will make sure they are aware that they have 24 hours reflection time before signing the informed consent.

As described above, the inclusion and exclusion criteria for the study will attempt to ensure that the therapy would exclude as few patients as possible from participation and would be directly

relevant to health care practitioners. The primary study investigators will determine whether the eligibility criteria are fulfilled.

Randomisation and group allocation

After baseline measurements, the participants will be randomised to Intensive Diet (ID) or Conventional Diet (CD) group.

Sequence generation:

A computer-generated randomisation sequence will be produced, before any participants are enrolled, that allocate participants in permuted blocks of 2 to 4 to the ID or the CD group (1:1). The randomisation sequence will be prepared using SAS Proc Plan; after the list has been generated it will be concealed in a password-protected computer file only accessible by the data manager (CCH). Randomisation will be stratified according to gender (M vs F), baseline obesity class (<40 vs. ≥ 40 kg/m^2), and SU level (< 6 vs. ≥6 mg/dL). These eight mutually independent randomisation sequences (each including 60 "virtual patients") will be entered into the eCRF by the data manager (CCH).

Allocation concealment and implementation:

Individual allocations will be held in pre-specified virtually sealed (opaque), consecutively numbered envelopes (see sequence generation). From the computer-generated sequence generation the formalised group allocation is revealed when the physician clicks on the 'randomisation button', appearing at the baseline visit in the eCRF system. Upon allocation to one of the two groups the patient identifier is automatically coupled to specific dietary plan/schedule. Thus the entire randomisation and allocation process will be concealed for all investigators, clinical, academic, and administrative trial personnel.

Virtual envelopes will be opened sequentially by an un-blinded study nurse. This procedure will ensure that participants, study staff, and outcomes assessors are blinded to group allocations at least until the individual participant attends the nutrition department at the Parker Institute.

Blinding (masking)

The term "blinding" or "masking" refers to withholding information about the assigned interventions from people involved in the trial who may potentially be influenced by this knowledge. Blinding is an important safeguard against bias, particularly when assessing subjective outcomes. Participants included in the trial may respond differently (e.g. on patient-reported outcome measures) if they are aware of their treatment assignment (such as responding more favourably when they receive the new treatment). Lack of blinding may also influence compliance with the intervention, use of co-interventions, and risk of dropping out of the trial.

However, in view of the use of a formula (liquid) low energy diet in the intensive weight loss group, as well as more attention provided from the dietitians, blinding of staff or participants will not be feasible. As a consequence, the possible influence of performance bias on patient-reported outcomes will be discussed as a possible limitation.

Statistical methods

Data will be analysed according to a pre-established statistical analysis plan (SAP). Primary analyses will be done on a modified ITT population, which include all randomised individuals who had the respective variable assessed at baseline. All analyses will be analysed and reported as two-sided, done at a 5% significance level.

We will use analysis of covariance (ANCOVA) for the continuous outcome measures modelled using repeated-measures (mixed linear model) analysis. The statistical model will include diet group (ID/CD)as fixed effects, an interaction between time and diet group, and the respective variable (e.g. body weight at baseline) as assessed at randomisation as covariate. Furthermore, the possible impact on the effect size of the factors used for the stratified randomisation will be explored, i.e. sex (M/ F), obesity class (<40/≥40 kg/m^2), and SU level (< 6/≥6 mg/dL). We aim to assess whether data provide evidence of superiority of ID to CD group (primary objective). Thus, the primary null hypothesis is no difference between treatments at endpoint (week 16). Response variables (binary outcomes; e.g. the proportion of patients losing more than 5% of baseline weight) will be analysed with a logistic regression model, including the same fixed effects (covariates) as for the analyses of continuous outcomes.

Data monitoring

Careful conduct of the clinical trial according to this protocol has a major impact on the credibility of the results. Careful monitoring will ensure that difficulties are noticed early and their occurrence or recurrence minimised. There are two distinct types of monitoring that generally characterise RCTs: (1) The oversight of the quality of the trial, while the other type involves (2) Breaking the blinding to make treatment comparisons (that is, interim analysis). Both types of trial monitoring, in addition to entailing different staff responsibilities, involve access to different types of trial data and information, and thus different principles apply for the control of potential statistical and operational bias.

For the purpose of overseeing the quality of the trial, the checks include whether the protocol is being followed, the acceptability of data being accrued, the success of planned accrual targets, the appropriateness of the design assumptions, success in keeping patients in the trials, etc. To maintain the overall quality and legitimacy of the short term RCT, code breaks will occur only in exceptional circumstances when the PI's knowledge of the actual treatment (i.e., ID group) is absolutely essential for further management of the participant. The PI will monitor each participant for clinical and laboratory evidence of adverse events (AEs) on a routine basis throughout the trial. AEs, whether in response to a query, observed by site personnel, or reported spontaneously by the participant, will be recorded. The investigator will assess and record any AE in detail, including the date of onset, description, severity, duration and outcome, relationship of the AE to trial diet, and any action(s) taken. The PI will maintain the blind as far as possible. The actual allocation must NOT be disclosed to study personnel including other site personnel, monitors, corporate sponsors or project office staff; nor should there be any written or verbal disclosure of the code in any of the corresponding participant documents (i.e. except for the materials being provided directly from the dietitian).

We will NOT perform any "interim analyses". Interim analysis would involve the accruing of comparative treatment results. Interim analysis requires unblinding (that is, key breaking) access to treatment group assignment (actual treatment assignment or identification of group assignment) and comparative treatment group summary information. This would necessitate that the protocol (or appropriate amendments prior to the 1st analysis) contains statistical plans for the interim analysis to prevent certain types of bias.

Concomitant Medical Therapy

There are no restrictions to concomitant medical or physical therapy. The participants can at all times request a consultation with the investigator(s) or his/her delegates if the course of the gout is unsatisfactory. These consultations may result in treatment (as judged by the investigator), and will be recorded in the CRF. This does not exclude the participant from the trial.

Harms (collecting, assessing, and reporting of adverse events)

Safety assessments include ad hoc physical examination and medical history and adverse event (AE) updates and monthly complete blood counts, serum chemistry, and urinalysis. AEs will also be noted using non-leading questions at all clinic visits, including at baseline. All events will be coded according to the Medical Dictionary for Regulatory Activities as currently required by all regulatory authorities, including the US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products. Routine laboratory tests, including measurement of serum glucose levels for estimating effects on glucose homeostasis and administration of liver function tests, will be performed at baseline and together with each of the subsequent outcome assessments (i.e., at weeks 8, and 16).

Throughout the trial period we will also collect incidences corresponding to Serious Adverse Events (SAEs), as defined by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, document E2A: "*During clinical investigations, adverse events may occur which, if suspected to be medicinal product-related (adverse drug reactions), might be significant enough to lead to important changes in the way the medicinal product is developed (e.g., change in dose, population, needed monitoring consent forms). This is particularly true for reactions which, in their most severe forms, threaten life or function. Such reactions should be reported promptly to regulators*" {Ioannidis, 2004 #46}.

Any symptomatic exacerbation related to gout ("flares") will be regarded as an adverse event and its relation to the intervention will be assessed and treated according to best clinical practice. These are not restricted to the scheduled clinical visits, but can occur spontaneously.

ETHICS AND DISSEMINATION

Research ethics approval

We will obtain ethical approval from the local institutional Research Ethics Committee to conduct this single centre proof-of-concept randomised, non-blinded, parallel-group trial. Ethics committee approval and informed consent will be obtained; the participants will be informed that the control group will receive less attention but would be provided with some instructions and material to enable them to lose weight if compliant with a low-fat and energy reduced diet. The procedures followed will be in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) including the Independent Ethics Committee E6 Good Clinical Practice, and the Helsinki Declaration of 1975, as revised in 2000. All participants will be asked to provide written informed consent for the study, which will be approved by the ethics committee of the Capital Region of Denmark (H-18007292). The results of this study will be made publicly available via publication in scientific peer reviewed journal, independent of the trial findings.

Health research ethics – the interventions

There are no risks or predictable harms associated with the weight loss program that at worst is considered harmless. The knowledge gained by this trial is commensurate with the efforts and difficulties associated with participation. The intervention is considered to be justifiable from a health research ethical perspective.

Health research ethics – the outcomes

Body weight

The method is non-invasive and is not associated with any predictable risks. The procedure is considered to be justifiable from a health research ethical perspective.

Questionnaires

The method is non-invasive and is not associated with any predictable risks. The procedure is considered to be justifiable from a health research ethical perspective.

Ultrasound imaging

The method is non-invasive and is not associated with any predictable risks. The procedure is considered to be justifiable from a health research ethical perspective.

X-rays

The radiation dose is 0.12 mSievert, which is considerably less than the annual background radiation. The procedure is considered to be justifiable from a health research ethical perspective.

Dual energy CT

The radiation dose is 0.4 mSievert, which is 10-20% of the annual background radiation. The procedure is considered to be justifiable from a health research ethical perspective

Blood samples

Blood samples taken via an intravenous access will be sent to biochemistry laboratories for further examinations. When collecting blood, some patients may experience minor discomfort when the needle penetrates the skin and rarely a small bleeding occurs. The amount of blood collected during the entire study period is a maximum of 196 ml (28 ml per visit), which equals less than half of what is in a normal blood donor sample.

Joint aspirations

If patients experience a gout attack with accumulation of fluids, ultrasound guided aspirations from affected joints will be conducted (the joint will be emptied so the amount varies and cannot be specified beforehand). Aspiration of the synovial fluid requires insertion of a needle in the patient's joint. Patients may experience some discomfort when the needle penetrates skin and synovium. The proceduce will be done according to current standards for hygiene and aseptic injection technique. Penetrating the skin always carries the risk of infection, but the joint aspirations are standard care and the incidence of procedure related infections is very small. The procedure is considered to be justifiable from a health research ethical perspective.

Protocol amendments

None declared. However, any modifications to the protocol which may impact on the conduct of the study, potential benefit of the participants or may affect participant safety, including changes of study objectives, study design, study population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol.

Consent or assent

Additional consent provisions for collection and use of participant data and biological specimens in potential ancillary studies: Ancillary studies involve the collection or derivation of data for purposes that are separate from the main trial. The acquisition and storage of data and biological specimens for ancillary studies is increasingly common in the context of clinical trials. Specimens may be used for a specified subset of studies or for submission to biorepositories for future specified or unspecified research.

Confidentiality

Participant confidentiality

This study will be conducted under related legislation and regulations, including the Danish Act on Processing of Personal Data.

Participant medical information obtained by this study is confidential, and disclosure to third parties is prohibited.

With the participant's permission, medical information may be shared with his or her personal physician or with other medical personnel responsible for the participant's welfare.

If the data from this study are published, the presentation format will not include names, recognizable photos, personal information or other data which compromises the anonymity of participating participants.
All study-related information will be stored securely at the study site (The Parker Institute, Bispebjerg and Frederiksberg Hospital). All participant information will be stored in locked file cabinets in areas with limited access. All laboratory specimens, reports, data collection, process, and administrative forms will be identified by a coded ID number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. All local databases will be secured with password-protected access systems. Forms, lists, logbooks, appointment books, and any other listings that link participant ID numbers to other identifying information will be stored in a separate, locked file in an area with limited access.

Notification to the Danish Data Protection Agency
Because the study is carried out at hospital departments, it is regarded as "public" in accordance with the Data Protection Agency guidance. The study will be notified to the Data Protection Agency.

Insurance

The participants are insured by the Danish Patient Insurance Association. Financing and insurance issues are addressed in the written information material.

Declaration of interests

Financial and other competing interests for principal investigators for the overall trial and each of the trial investigators: This study had no financial competing interests. The Parker Institute is grateful for the financial support received from public and private foundations, companies and private individuals over the years. The Oak Foundation is a group of philanthropic organisations

that, since its establishment in 1983, has given grants to not-for-profit organisations around the world. Drs. R. Christensen, M. Henriksen, A. Astrup, and H. Bliddal report having previously received travel and/or research grants from the Cambridge Manufacturing Company to attend scientific meetings; holds no shares or share options in the company. Neither the investigators nor any of the other members of the project group has financial interest in the conduct or the results of the trial.

Access to data

All investigators will be given access to the cleaned data sets. Project data sets will be housed at the Parker Institute, Bispebjerg and Frederiksberg Hospital; all data sets will be password protected. To ensure confidentiality, data dispersed to project team members will be blinded of any identifying participant information.

Ancillary and post-trial care

Provisions, if any, for ancillary and post-trial care and for compensation to those who suffer harm from trial participation: Should this study provide apparent evidence for the effectiveness of weight reduction to patients with gout, it will be critical to provide access to the effective product(s) to study participants who were randomly allocated to the Conventional Diet (Control) group. In preparation for this study (protocol), discussions have begun with Cambridge Manufacturing Company to ensure such access (30 patients allowed 16 weeks of free products including support from the dietitians).

Dissemination policy

The results are to be reported according to the CONSORT guidelines {Moher, 2010 #22}: Negative, positive and inconclusive results will be disseminated in international peer-reviewed scientific journals at national and international conferences. Access to data can be granted on approval for a formal request to the trial steering committee. The scientific integrity of the project requires that the data from the 'Weight Loss for Gout' trial will be analysed study-wide and reported as such. All presentations and publications are expected to protect the integrity of the major objective(s) of the study; interim analyses will not be performed. Recommendations as to

the timing of presentation of such endpoint data and the meetings at which they might be presented will be given by the Trial Steering Committee. All papers and abstracts must be approved by the Trial Publications Committee before they are submitted. Substantive contributions to the design, conduct, interpretation, and reporting of the RCT are recognised through the granting of authorship on the final trial report. The ICMJE authorship guidance is intended to help enhance transparency and avoid disputes or misunderstanding after trial completion:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

In addition to being accountable for the parts of the work he or she has done, an author should be able to identify which co-authors are responsible for specific other parts of the work. In addition, authors should have confidence in the integrity of the contributions of their co-authors.

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