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Nutritional recommendations for gout: An update from clinical epidemiology

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ABSTRACT

Objective: To present the evidence for nutritional lifestyle changes recommended for gout patients; an explicit focus will be on the evidence for weight loss in overweight gout patients based on a recent systematic review and to describe methodological details for an upcoming weight loss trial.

Methods: We did a pragmatic but systematic search in MEDLINE for current guidelines that had made an attempt to make nutritional recommendations for gout. The quality of the evidence for the nutritional recommendations was evaluated based on the guidelines’ own ratings and converted into a common simple version based on the GRADE system. The recently published systematic review on weight loss for gout, was based on six databases from which longitudinal studies that had quantified the effects following weight loss were included. The internal validity was assessed with the ROBINS-I tool and the quality of the evidence was assessed with the GRADE approach. Based on the results of the systematic review, a trial was designed, adhering to the principles of evidence based research.

Results: We included 17 guidelines. Most guidelines recommend avoiding or limiting alcohol intake (15; i.e. 88%), lose weight if relevant (12; 71%), and reduce fructose intake (11; 65%). The majority of the evidence for the nutritional recommendations was rated Moderate/Low or Very Low quality. Our recent systematic review on weight loss included 10 studies and found that the available evidence indicates beneficial effects of weight loss for overweight and obese gout patients, but the evidence is of low to moderate quality. As a consequence, researchers from the Parker Institute are launching a randomized trial to explore the short-term effects related to a diet-induced weight loss in obese gout patients.

Conclusions: The nutritional recommendations for gout are generally based on low quality evidence. In terms of weight loss as a management strategy, the available evidence is in favor of weight loss for overweight/obese gout patients. However, since the current evidence consists of only a few studies (mostly observational) of low methodological quality, the Parker Institute are now initiating a rigorous exploratory randomized trial. Similar efforts are needed for other nutritional management strategies for gout.

1. Introduction

Gout is the most common type of inflammatory arthritis and has been known for thousands of years [1]. Gout is caused by deposition of monosodium urate crystals in joints and various other tissues and appears in relation to chronic hyperuricemia. The main causal factors for primary gout seem to be diet and genetic polymorphisms of renal transporters of urate [1].

Throughout history gout has commonly been associated with rich foods and excessive alcohol consumption [2], and nutritional recommendations for gout have existed for a long time. In 1876, A. B. Gerrod was among the first ones to recommend reducing intake of purine-rich foods, such as meat and seafoods [2,3]. A little later, Professor Ebstein recommended moderate feeding, plenty of water, fruit such as cherries and strawberries, and to avoid alcohol [4,5].

Since then, the principles of evidence based medicine has been widely implemented [6] and influence the research practice as well as the development of treatment guidelines. However, when developing clinical guidelines, not only is the quality of the evidence supporting potential recommendations taken into account, but often also other...
factors such as costs, health care systems, as well as expert opinions [7]. This means that even though many guidelines are recommending nutritional lifestyle changes for gout, such as weight loss, the quality of the evidence supporting the recommendations may not necessarily be of high quality.

The aim of this review is to present the evidence for nutritional lifestyle changes recommended for gout patients. Furthermore, we will describe the evidence for weight loss for overweight and obese gout patients in detail by referring to our recent systematic review [8], as well as revealing some insights to a new randomized trial initiative exploring the effects of weight loss in obese gout patients.

2. Methods

2.1. Systematic search for guidelines

To get an overview of the evidence we did a pragmatic but systematic search for current guidelines that had done an attempt to make nutritional recommendations. The search was carried out on March 18, 2018 in MEDLINE (via PubMed) and included the search terms: (Recommendation*[ti] OR guideline*[ti]) AND (gout* OR podagra OR tophus OR tophi OR tophaceous OR urate OR uric acid OR hyperuricemia* OR hyperuricaemia* OR hyperuricemia* OR hyperuricaemia* OR arthritis urica). Other sources included screening reference lists and searching the library of The Guidelines International Network (G-I-N; http://www.g-i-n.net). We excluded guidelines for which a later update had been published, if their aim did not include to make nutritional recommendations, or if they were written in languages not using the latin alphabet (e.g. Chinese and Japanese). The study selection was conducted by one reviewer (SMN) and included screening of titles and abstracts, and subsequently, full text assessment.

2.2. Assessment of the quality of evidence for the nutritional recommendations

For each guideline, the quality of the evidence for the nutritional recommendations was evaluated based on the guidelines' own ratings. In order to make comparisons across guidelines using different methods for evaluating the quality of the evidence (e.g. Oxford’s levels of evidence, The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system etc. [9]), we converted the ratings so they approximated the levels of the GRADE system, with the levels High, Moderate/Low and Very Low, which, however, roughly corresponded to the old evidence hierarchy [10] i.e. evidence based on a) meta-analyses of randomized controlled trials (RCTs), RCTs, or good non-randomized trials, b) non-randomized trials, or observational studies, and, c) primarily expert opinions, respectively.

2.3. Evidence for weight loss from a systematic review

The systematic review on weight loss for overweight and obese gout patients [8] was carried out according to a predefined protocol (PROSPERO: CRD42016037937). This included a thorough search in four electronic databases and two trial registries. Longitudinal studies that had quantified the effects following weight loss were included. An effort was done not to exclude any publications due to language or not having access, so assistance from an experienced librarian and native speakers in Chinese, Japanese, Russian, and Bulgarian were utilized. Furthermore, authors were contacted if data was missing. The internal validity of the studies was assessed with the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool [11] and the quality of the evidence across the studies was assessed with the GRADE approach [9].
Table 1
Nutritional recommendations and quality of evidence from the guidelines included.

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a, high quality evidence; b, moderate/low quality evidence; c, very low quality evidence; x, no rating of evidence available.

3e Australia and NZ, 3e initiative Australia and New Zealand; 3e Austria, 3e initiative Austria; 3e initiative, 3e initiative multinational; 3e Portugal, 3e initiative Portugal; ACP, American College of Physicians; ACR, American College of Rheumatology; BSR, British Society of Rheumatology; Chinese METF, Chinese Multidisciplinary Expert Task Force; DEGAM, German College of General Practitioners and Family Physicians; DGRh, German Society for Rheumatology; EULAR, European League Against Rheumatism; JSGNM, Japanese Society of Gout and Nucleic Acid Metabolism; MOH, Ministry of Health Malaysia; NHG, The Dutch College of General Practitioners; ÖGR, Österreichischen Gesellschaft für Rheumatologie und Rehabilitation; SER, Spanish Society of Rheumatology; SIR, Italian Society for Rheumatology.
2.4. Designing a trial based on the systematic review

Based on the results of the systematic review on weight loss for overweight gout patients, a trial was designed in order to provide some of the evidence which are currently missing and thus adhering to the principles of ‘evidence based research’ [12]. The Parker Institute has a long history of running weight loss trials and have previously designed and applied a well-documented weight loss program running over 16 weeks (CAROT study) [13–15] that effectively resulted in a significant weight loss (average of approximately 12% loss of body weight) in obese (body mass index (BMI) > 30 kg/m²) patients with knee osteoarthritis with beneficial improvements in knee pain and function. The experiences gained from running previous weight loss trials was used when designing the trial for obese gout patients.

3. Results

3.1. Included guidelines

Our search resulted in 171 publications of which 17 guidelines [16–32] were included. Reasons for exclusion during full text assessment is stated in Fig. 1.

The included guidelines consist of both multinational initiatives, such as the 3e initiative [23] and EULAR [16], as well as many national initiatives. Table 1 summarizes the nutritional recommendations included in the guidelines, ignoring slightly different wording in the guideline publications. Most of the guidelines recommend avoiding or limiting alcohol intake (15 out of 17; i.e. 88%), to lose weight if relevant (12; 71%), to reduce fructose intake including fructose containing beverages such as fruit juices (11; 65%), to reduce purine intake such as meats, organ meats and seafoods (11; 65%), to reduce sugar intake including sugar sweetened beverages (8; 47%), to seek low-fat dairy products such as skim milk (8; 47%), and to seek vitamin C supplementation (4; 24%).

3.2. Evidence for the nutritional recommendations

Most of the guidelines have assessed the quality of the evidence for their nutritional recommendations. The majority of the evidence was rated Moderate/Low or Very Low quality (marked as ‘c’ or ‘b’, respectively, in Table 1). Only the recommendations, seeking low-fat dairy products and vitamin C supplementation, was reported to be supported by high quality evidence according to the British and Austrian guidelines [19,21]. Furthermore, it should be noticed, that the guidelines by the American College of Physicians (ACP) [17] and The Dutch College of General Practitioners (NHG) [31] do not make any nutritional recommendations. They explain this with insufficient evidence.

3.3. The evidence for recommending weight loss

The systematic review of weight loss for overweight and obese gout patients [8] resulted initially in almost 4000 publications, of which 10 studies were eligible for synthesis. The 10 studies included only one RCT, but its primary aim was not to investigate weight loss. In the studies, the mean weight loss ranged between 3 and 34 kg and weight loss was observed from diet, with and without physical activity, bariatric surgery, but also unintentionally from medication or no intervention. In the risk of bias assessment, none of the studies were rated low risk for all of the seven risk of bias domains, and some were even rated critical risk for the first bias domain (i.e. bias due to confounding). In addition to this, the included studies failed to report many of the outcomes that must be reported in all clinical trials on gout patients according to the organization Outcome Measures in Rheumatology (OMERACT) [34].

At latest follow up, almost all the studies reported beneficial effects on the outcomes, serum urate, achieving serum urate target (serum urate < 360 μmol/L), and gout attacks, and dose-response relationships were reported. However, at short term, two studies reported a temporary increase in serum urate and gout attacks following bariatric surgery. The quality of evidence was rated to be low, moderate and low, respectively, for the three outcomes, because we downgraded for study types, risk of bias, and upgraded for dose response relationships, and large reported effects. So the available evidence indicate beneficial effects of weight loss for overweight and obese gout patients, but the evidence is of low to moderate quality, meaning that rigorous prospective studies, preferably RCTs, are needed.

3.4. Designing a proof-of-concept randomized, non-blinded, parallel-group trial

Based on the existing sparse evidence it was decided that a prospective study was needed in order 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 study will be to address whether or not there is a difference in success rate in weight reduction, serum urate levels, flares, and other clinical outcomes, as well as possible side-effects, in short-term, when comparing an intensive diet group to a control diet group.

The study is designed as a 16 (8 + 8) week pragmatic proof-of-concept randomized, non-blinded, parallel-group trial; the trial design is illustrated in the appendix Fig. A.1. The protocol has been registered with ClinicalTrials.gov (NCT03664167) before enrolling any participants. The eligibility criteria will in broad terms include: both genders, above 18 years with a diagnosis of gout, BMI ≥ 30 kg/m², with at least one self-reported gout flare in the previous 12 months. All eligible patients who sign informed consent will be randomly assigned to either 8 weeks of full-meal replacement low-energy diet (LED; 3.4 MJ/day) followed by 8 weeks fixed energy diet program (5 MJ/day) defined as the intensive diet group or a corresponding 16-week conventional hypno-energetic, high protein diet (approximately 5 MJ/day) defined as the control diet group.

The outcomes measured and reported from the trial will as a minimum include all those recommended by the OMERACT [34]. Furthermore, in order to investigate whether a temporary increase in serum urate will follow a diet-induced weight loss, serum urate will be measured every week the first four weeks. Estimation of power and sample size suggested that 60 patients (30 in each group) would be appropriate, even with a drop-out rate of up to 20% (i.e., 6 patients in each group).

At this point, ethical approval has been obtained from the local institutional Research Ethics Committee to conduct this trial. When enrolling patients, 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. After the trial period all participants will be offered voluntary follow-up consultations with a dietician.

4. Discussion

From existing literature, we found an extensive number of guidelines recommending nutritional lifestyle changes, however, the recommendations are generally not based on high quality evidence. This applies to the most common recommendations such as avoiding/reducing alcohol intake, weight loss, fructose and purine intake. Furthermore, since many of the recommendations have existed for a very long time, e.g. reducing purine-rich foods and avoiding alcohol was recommended for almost 150 years ago, it may be surprising that no high-quality evidence seem to have been produced. Hence, our review indicates a potentially important gap in the evidence supporting the recommendations for nutritional lifestyle changes for gout.

Most nutritional lifestyle changes are inexpensive and safe,
however, recommending nutritional lifestyle changes without sufficient evidence to support a significant clinical effect may in many cases be problematic. Making and maintaining lifestyle changes often requires a substantial effort and can have a big impact on the life, including social life, of the individual patient, as well as being potentially demotivating if truly ineffective. In a qualitative study, patients reported lack of enjoyment of previously enjoyed activities associated with extremely restricted dietary lifestyle [35]. Another aspect to take into account is that some of the food items to be excluded could improve general health, including risk of common comorbidities in gout such as hypertension, kidney disease, obesity, diabetes, cardiovascular diseases [36]. For example, many types of fish should be avoided due to their high content of purines (including fatty fish with a high content of omega-3 fatty acids) [37], however a dietary pattern including fatty fish is recommended by the American College of Cardiology/American Heart Association (AHA/ACC) to reduce cardiovascular disease risk [38]. On the other hand, other recommendations for gout, may improve general health and risk of common comorbidities, such as intake of sugar-sweetened beverages [38]. However, keeping recommendations that do not improve gout symptoms may be misleading. Only two of the 17 guidelines acknowledge that the current evidence is insufficient to make recommendations on dietary changes [17,31].

At present, our recent systematic review on weight loss [8] is the only published systematic review dedicated to investigating weight loss for overweight and obese gout patients, despite the fact that weight loss is commonly recommended. Even though the systematic review includes a very thorough search, it gets to roughly the same conclusion as the guidelines and confirms that the evidence for weight loss is not sufficient yet. In addition to this, the included studies failed to report many of the outcomes recommended by the OMERACT [34], and hence the benefits and harms of weight loss have not been fully investigated yet. Future research should aim to close these gaps.

As part of such effort the proof-of-concept randomized, non-blinded, parallel-group trial was designed, anticipating to close several gaps in the existing evidence. The trial will be the only randomized trial investigating a traditional diet-induced weight loss intervention in gout patients, it will measure all outcomes recommended by the OMERACT, and it will investigate whether the temporary increase in serum urate observed from bariatric surgery are induced from diet-induced weight loss as well. Despite the sparse evidence available overall on the importance of nutritional lifestyle changes in the management of gout, we believe that obesity will be widely acknowledged as a risk factor for both the prevalence and incidence of gout, and we anticipate that obesity also have a negative impact as an effect modifier. Knowing how powerful a significant weight loss can be in other conditions, we speculate that it will also help gout patients achieve a significant improvement in symptoms, pain relief, physical function and health-related quality of life.

In general, adherence to medication is low in gout patients [39,40], and adherence to dietary recommendations tend to be even lower [41]. This may be an important challenge to consider when producing evidence for nutritional lifestyle changes. Since studies for improving adherence to dietary interventions in gout are currently lacking [40], this should be part of the research agenda as well. Knowing what evidence is currently missing, and seeking to produce such evidence is known as ‘evidence based research’ [12] and is the current recommended practice within medical research. This principle should be applied to all nutritional recommendations for gout, and producing high quality evidence for this area should be prioritized.

5. Conclusions

In conclusion, the current nutritional recommendations for gout are generally based on low quality evidence. The most frequent recommendations generally included (1) to avoid or limit alcohol intake, (2) to lose weight if relevant, (3) to reduce fructose intake including fruit juices, (4) to reduce purine intake including meats, organ meats and seafoods, (5) to reduce sugar intake, (6) to seek low-fat dairy products, and (7) to seek vitamin C supplementation. Evidence based research, including knowing what evidence is currently missing and seeking to produce such evidence, should be applied to all nutritional recommendations for gout, and producing high quality evidence for this area should be prioritized. The available evidence is in favor of weight loss for overweight gout patients, with low to moderate quality of evidence, and there is an urgent need for the trial that will be initiated at the Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark. Similar efforts are needed for other nutritional lifestyle interventions for gout.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.autrev.2018.05.008.

References


