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Cherry Consumption and Decreased Risk of Recurrent Gout Attacks

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Objective. **To study the relationship between cherry intake and the risk of recurrent gout attacks among individuals with gout.**

Methods. **We conducted a case–crossover study to examine the associations of a set of putative risk factors with recurrent gout attacks. Individuals with gout were prospectively recruited and followed up online for 1 year. Participants were asked to provide the following information regarding gout attacks: the onset date of the gout attack, symptoms and signs, medications (including antigout medications), and exposure to potential risk factors (including daily intake of cherries and cherry extract) during the 2-day period prior to the gout attack. We assessed the same exposure information over 2-day control periods. We estimated the risk of recurrent gout attacks related to cherry intake using conditional logistic regression. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated.**

Results. **Our study included 633 individuals with gout. Cherry intake over a 2-day period was associated with a 35% lower risk of gout attacks compared with no intake (multivariate OR 0.65 [95% CI 0.50–0.85]). Cherry extract intake showed a similar inverse association (multivariate OR 0.55 [95% CI 0.30–0.98]). The effect of cherry intake persisted across subgroups stratified by sex, obesity status, purine intake, alcohol use, diuretic use, and use of antigout medications. When cherry intake was combined with allopurinol use, the risk of gout attacks was 75% lower than during periods without either exposure (OR 0.25 [95% CI 0.15–0.42]).**

Conclusion. **These findings suggest that cherry intake is associated with a lower risk of gout attacks.**

Gout is an excruciatingly painful inflammatory arthritis caused by the crystallization of uric acid within joints. Based on the National Health and Nutrition Examination Survey 2007–2008, the prevalence of gout in the US is estimated to be 3.9% among US adults, which translates into 8.3 million US adults (1,2). While the pathophysiology of gout is well-characterized and efficacious pharmacologic regimens are available, many patients with gout continue to experience recurrent gout attacks (3,4). Such attacks cause tremendous pain and are a major cause of morbidity.

Over the past few decades, cherries have garnered considerable public attention and interest from both patients and investigators as a potentially effective option in the prevention and management of gout. Small experimental studies in healthy human subjects and animals have demonstrated that cherry consumption lowers serum uric acid levels (5,6). Others have shown that cherry products contain high levels of anthocyanins (7–9), which possess antiinflammatory and antioxidant properties (8,10–12). Furthermore, some cherry producers have claimed that cherry products have the potential to reduce the pain associated with gout (13), and some patients use cherries as a strategy to avoid and/or treat gout attacks (14). However, to our knowledge, no study has assessed whether consumption of cherries lowers the risk of gout attacks, as reflected in warning letters sent to various cherry-based product manufacturers by the Food and Drug Administration about the lack of suffi-

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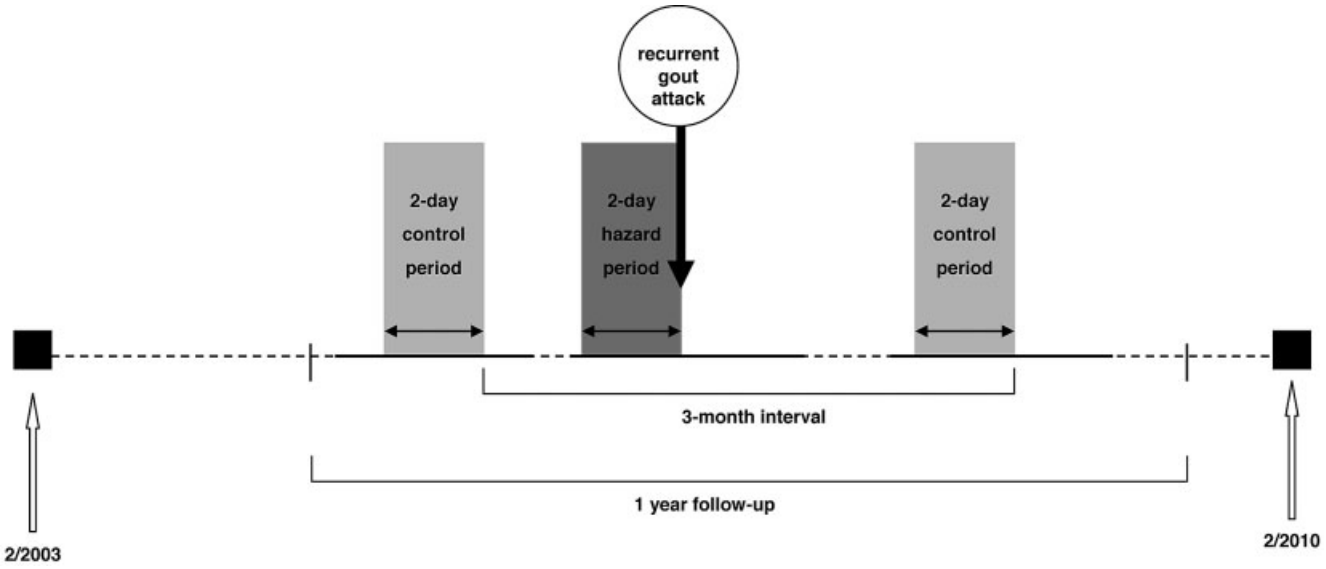

Figure 1. Case–crossover study design and timing of exposure measurements in relation to gout attacks. Individual patients were followed up for 1 year and monitored for recurrent gout attacks occurring at any time during the followup period. Hazard periods refer to the 2-day periods prior to the recurrent gout attack. One control period was selected every 3 months throughout the year, for a total of 4 control periods. Exposure to cherry intake and other factors that varied with time (potential confounders) were compared between hazard periods and control periods. The broken line (not to scale) indicates the time span of the study (February 2003 to February 2010).

cient data regarding their claims of disease-related benefits of cherry products (13).

To help address this relevant knowledge gap, we analyzed 633 gout patients who were prospectively recruited from across the US in an online gout study (15). In this study, we used a case–crossover design to quantify the relative risk of gout attack after cherry intake as compared with no cherry intake and its potential modification by allopurinol use and major gout risk factors.

PATIENTS AND METHODS

Study population and design. The Boston University online gout study is an ongoing internet-based, case–crossover study that was started in February 2003 with the primary aim of investigating purported triggers for recurrent gout attacks (15). The study design and timing of exposure measurements in relation to recurrent gout attacks are displayed in Figure 1. As previously described in detail (15), with this study design, each study participant serves as his or her own control, and self-matching eliminates confounding by risk factors that are constant within an individual but that would differ between study subjects during the study period (e.g., genetics, sex, race, education). Such a study design has been used successfully in many previous studies in which the effect of transient risk factors on the risk of an acute event was evaluated (e.g., triggering factors for myocardial infarction or motor vehicle collision) (16).

Subject recruitment. We constructed a study web site on an independent secure server in the Boston University School of Medicine domain (https//dcc2.bumc.bu.edu/gout). The study was advertised on the Google search engine by linking an advertisement to the search term "gout." Individuals who clicked on the study advertisement were directed to the study web site and were asked to provide the following information at study entry: sociodemographic characteristics, gout-related data (e.g., diagnosis of initial gout attack, age at onset, medication used for treatment of gout, and number of gout attacks in the last 12 months), and history of other diseases and medication use.

To be eligible for the study, a subject had to report gout diagnosed by a physician, have had a gout attack within the past 12 months, be at least 18 years of age, reside in the US, agree to the release of medical records pertaining to gout diagnosis and treatment, and provide electronic informed consent. To confirm the diagnosis of gout, we obtained medical records pertaining to the participant's gout history and/or a checklist of the features listed in the American College of Rheumatology (ACR) preliminary criteria for the classification of gout (17) completed by the subject's physician. Two rheumatologists (TN and DJH) reviewed all medical records and checklists and determined whether the participants had a diagnosis of gout according to the ACR criteria. Similar methods of gout diagnosis confirmation have been used in the Health Professionals Followup Study (18). This study was approved by the Institutional Review Board of Boston University Medical Campus.

Ascertainment of recurrent gout attacks. Data were collected regarding the onset date of the recurrent gout attack, anatomic location of the attack, clinical symptoms and signs (maximal pain within 24 hours or redness), and medications used to treat the attack (i.e., colchicine, nonsteroidal antiinflammatory drugs [NSAIDs], systemic corticosteroids, and intraarticular corticosteroid injections). Our method of identifying gout attacks is consistent with approaches used in acute and chronic gout trials (19–21) and the ACR/European League Against Rheumatism–supported initiative for defining gout attacks that includes only patient-reported elements (22). We further evaluated the robustness of our case definition by restricting recurrent attacks to those treated with at least one antigout medication (as listed above), those with podagra, those with maximal pain within 24 hours, those with redness, and those with combinations of these features (i.e., cases with ≥2, ≥3, or all 4 features).

Ascertainment of risk factors. Exposure to a set of putative risk factors during a 2-day period was assessed for each participant, including purported dietary factors, alcohol use, infections, immunizations, physical activity, geographic location, antigout medications, and purported alternative remedies, such as cherry products. Of note, cherry intake was one of the hypothesized exposures considered to be potentially relevant to the risk of gout attacks since the conception of the Boston University online gout study (Figure 1). Participants were asked the number of servings of cherries (i.e., the fruit), with 1 standard serving size being one-half cup or ~10–12 cherries, they had consumed on each of the 2 days prior to a gout attack (i.e., the hazard period). In addition, cherry extract use (yes or no) on each of the 2 days prior to the attack was assessed. The same list of exposure data was also collected at the following time points (i.e., control periods; 4 in total): at study entry and at 3, 6, and 9 months for those subjects who entered the study during an intercritical period, and at 3, 6, 9, and 12 months for those subjects who entered the study at the time of a gout attack (Figure 1). Other potential exposures that varied with time and that could be pertinent to gout attack risk were assessed in the same manner.

Statistical analysis. Since each person could have more than 1 hazard period and/or more than 1 control period and these were matched within a subject, we examined the relationship of cherry intake over the prior 2 days to the risk of gout attacks, using conditional logistic regression. In a multivariable regression model, we adjusted for purine intake and use of alcohol, diuretics, allopurinol, colchicine, and NSAIDs. To evaluate a potential dose-response relationship with the risk of gout attacks, we grouped cherry intake over 2 days into 5 categories: 0, 1, 2, 3, and ≥4 servings. We also evaluated the association with cherry extract intake alone, as well as with either cherry or cherry extract intake, using the same multivariable model. Finally, we assessed potential subgroup effects of cherry or cherry extract intake according to sex, body mass index (<30 kg/m^2 versus ≥30 kg/m^2), purine intake (median ≤1.7 gm versus >1.7 gm), use of alcohol (yes versus no), and treatment with diuretics (yes versus no), allopurinol (yes versus no), colchicine (yes versus no), and NSAIDs (yes versus no) over the prior 2 days. We determined the statistical significance of potential subgroup effects by testing the significance of interaction terms added to our final multivariable models. For all odds ratios (ORs), we calculated 95% confidence intervals (95% CIs). All *P* values are 2-sided. We used SAS 9.2 for all analyses.

Table 1. Characteristics of the 633 participants in the internet-based case–crossover study of gout*

Sex, male	494 (78.0)
Age, median (range)	54 (21–88)
BMI, median (range), kg/m^2	30.6 (14.7–69.9)
Race	
African American	19 (3.0)
White	558 (88.2)
Other	47 (7.4)
Refused to answer	9 (1.4)
Education	
Less than high school graduate	10 (1.6)
High school graduate	55 (8.7)
Some college/technical school	199 (31.4)
College graduate	157 (24.8)
Some professional/graduate school	70 (11.1)
Completed professional or graduate school	142 (22.4)
Annual household income, $	
<25,000	51 (8.1)
25,000–49,999	127 (20.1)
50,000–74,999	121 (19.1)
75,000–99,999	89 (14.1)
≥100,000	163 (25.8)
Refused to answer	82 (13.0)
Disease duration, median (range) years	5 (1–49)
Alcohol use	383 (60.5)
Treatments	
Diuretics	184 (29.1)
Allopurinol	285 (45.0)
NSAIDs	342 (54.0)
Colchicine	160 (25.3)

* Except where indicated otherwise, values are the number (%) of patients. BMI = body mass index; NSAIDs = nonsteroidal antiinflammatory drugs.

RESULTS

A total of 633 patients with gout completed both hazard-period and control-period questionnaires over a consecutive 12-month period between February 2003 and February 2010. Of them, 554 (87.5%) met the ACR preliminary criteria for the classification of gout. The characteristics of the participants are presented in Table 1. The average age of the participants was 54 years. Participants were predominantly men (78%), white (88%), and over half had received a college education. Subjects were recruited from 49 states and Washington, DC. Approximately 61% of the participants consumed alcohol, 29% used diuretics, 45% took allopurinol, 54% used NSAIDs, and 25% took colchicine during either the hazard or control periods.

During the 1-year followup period, we documented 1,247 gout attacks. Most gout attacks occurred

Table 2. Cherry or cherry extract intake in prior 2 days and risk of gout attacks*

Variable	Number of control periods	Number of hazard periods	Crude OR (95% CI)	Adjusted OR (95% CI)†
Cherries only				
No	1,318	1,074	1.0 (referent)	1.0 (referent)
Yes (any amount)‡	271	173	0.69 (0.54–0.89)	0.65 (0.50–0.85)
1 serving	71	53	0.92 (0.62–1.36)	0.98 (0.65–1.48)
2 servings	98	56	0.59 (0.40–0.89)	0.52 (0.34–0.79)
3 servings	35	16	0.48 (0.25–0.92)	0.39 (0.20–0.77)
≥4 servings	67	48	0.69 (0.44–1.09)	0.62 (0.38–1.00)
Cherry extract only				
No	1,520	1,212	1.0 (referent)	1.0 (referent)
Yes	69	35	0.59 (0.34–1.04)	0.55 (0.30–0.98)
Cherries or cherry extract				
No	1,278	1,052	1.0 (referent)	1.0 (referent)
Yes	311	195	0.68 (0.53–0.86)	0.63 (0.49–0.82)

* 95% CI = 95% confidence interval.
† Adjusted for purine intake and use of alcohol, diuretics, allopurinol, colchicine, and nonsteroidal antiinflammatory drugs.
‡ P for trend <0.003 for crude odds ratio (OR) and <0.001 for adjusted OR.

in the lower extremity (92%), particularly in the first metatarsophalangeal joint, and had features of either maximal pain within 24 hours or redness (89%). Approximately 90% of gout attacks were treated with colchicine, NSAIDs, systemic corticosteroids, intraarticular corticosteroid injections, or a combination of these medications. The median time between the onset of gout attack and completion of the hazard-period questions was 3 days.

Of the 633 participants included in the analysis, 224 (35%) reported ingesting fresh cherry fruit only, 15 (2%) cherry extract only, and 33 (5%) both fresh cherry fruit and cherry extract during hazard periods, control periods, or both. As shown in Table 2, cherry intake over a 2-day period was associated with a 35% lower risk of gout attacks compared with no intake (multivariate OR 0.65 [95% CI 0.50–0.85]). The risk of gout attacks tended to decrease with increasing cherry consumption up to 3 servings over 2 days; however, further intake did not appear to provide a greater protective effect. Cherry extract intake was associated with a 45% lower risk of gout attacks (multivariate OR 0.55 [95% CI 0.30–0.98]). When we additionally adjusted for caffeinated beverage intake and number of servings of vegetables consumed over the past 2 days, the results did not change materially (OR 0.65 [95% CI 0.50–0.85]).

When we limited the analysis to participants who met the ACR preliminary criteria for the classification of gout (n = 554), the multivariable OR of recurrent gout attacks was 0.65 (95% CI 0.50–0.85) for cherry intake over a 2-day period. In addition, when we varied the definition of recurrent gout attacks by requiring specific features individually or in combination, the results did not change materially. For example, when we limited the analysis to those that had ≥2 of the 4 features (antigout medication use, podagra, maximal pain within 24 hours, and redness) (n = 606), the multivariable OR was 0.63 (95% CI 0.48–0.82).

The inverse association with cherry intake persisted across subgroups divided by sex and body mass index. Multivariate ORs for cherry intake and the risk of recurrent gout attacks were 0.68 (95% CI 0.51–0.91) among men and 0.48 (95% CI 0.27–0.83) among women (P for interaction = 0.28). The corresponding ORs were 0.57 (95% CI 0.40–0.80) among obese individuals and 0.72 (95% CI 0.49–1.04) among nonobese individuals (P for interaction = 0.35).

Table 3 summarizes the combined effects of cherry intake and various gout-related risk factors or medications on the risk of gout attacks. Increase in alcohol consumption and purine intake as well as use of diuretics were associated with a higher risk of recurrent gout attacks, whereas use of allopurinol and use of colchicine were associated with a lower risk of gout attacks. There was no association between NSAID use and risk of recurrent gout attacks (Table 3). The effect of cherry intake on the risk of recurrent gout attacks tended to be stronger when cherries or cherry extract were consumed during periods of higher purine intake or alcohol abstention, and when diuretics or NSAIDs were not used. Notably, when cherry intake was combined with allopurinol use, the risk of gout attacks was

Table 3. Cherries or cherry extract intake in prior 2 days and risk of gout attacks in subgroups of patients divided by purine intake, alcohol consumption, use of diuretics, and use of antigout drugs*

Risk factors over 2 days	Cherry or cherry extract intake over 2 days†	Number of control periods	Number of hazard periods	Adjusted OR (95% CI)‡
Purine intake				
>1.7 gm (high)	No	536	604	1.00 (referent)
>1.7 gm (high)	Yes	152	119	0.60 (0.44–0.83)
≤1.7 gm (low)	No	742	448	0.46 (0.37–0.57)
≤1.7 gm (low)	Yes	159	76	0.32 (0.22–0.47)
Alcohol use				
Yes	No	622	495	1.00 (referent)
Yes	Yes	140	98	0.92 (0.70–1.20)
No	No	656	557	0.77 (0.53–1.10)
No	Yes	171	97	0.50 (0.34–0.74)
Diuretic use				
Yes	No	238	270	1.00 (referent)
Yes	Yes	65	58	0.74 (0.46–1.20)
No	No	1,040	782	0.37 (0.24–0.58)
No	Yes	246	137	0.22 (0.13–0.36)
Allopurinol use				
No	No	870	792	1.00 (referent)
No	Yes	205	150	0.68 (0.50–0.92)
Yes	No	408	260	0.47 (0.34–0.63)
Yes	Yes	106	45	0.25 (0.15–0.42)
Colchicine use				
No	No	1,097	930	1.00 (referent)
No	Yes	269	173	0.66 (0.46–0.97)
Yes	No	181	122	0.61 (0.47–0.80)
Yes	Yes	42	22	0.52 (0.27–0.98)
NSAID use				
No	No	954	770	1.00 (referent)
No	Yes	223	135	0.59 (0.44–0.79)
Yes	No	324	282	1.00 (0.78–1.30)
Yes	Yes	88	60	0.77 (0.49–1.19)

* OR = odds ratio; 95% CI = 95% confidence interval.
† Cherry or cherry extract intake during at least 1 of the prior 2 days versus no intake.
‡ Adjusted for purine intake and use of alcohol, diuretics, allopurinol, colchicine, and nonsteroidal antiinflammatory drugs (NSAIDs) in separate models for corresponding risk factors.

75% lower than without either exposure (OR 0.25 [95% CI 0.15–0.42]). None of these factors showed significant interaction with the effect of cherry intake (P for interaction > 0.17).

DISCUSSION

In this large study of prospectively recruited patients with preexisting gout, we found that cherry intake was associated with a 35% lower risk of recurrent gout attacks, and intake of cherry extracts showed a similar inverse association. These associations were independent of other risk factors, including factors that did not vary with time, such as genetics, sex, race, and education (by study design) and that varied with time, such as purine intake, alcohol consumption, and the use of antigout medications and diuretics. Interestingly, when cherry intake was combined with the use of allopurinol, the most commonly used urate-lowering drug, the risk of gout attacks was 75% lower than during the period without either exposure.

Several biologic mechanisms have been elaborated to link cherry consumption to the risk of gout attacks. A study conducted among 10 healthy women showed that consumption of cherries, but not other fruits, such as strawberries, grapes, or kiwi fruit, significantly reduced levels of both serum uric acid and plasma creatinine (5). These findings led investigators to speculate that cherries may exert their urate-lowering effect through increasing the glomerular filtration rate or reducing tubular reabsorption. In an animal study, in-

take of tart cherry juice significantly decreased the levels of serum uric acid in rats with hyperuricemia by inhibiting the hepatic activity of xanthine oxidase and xanthine dehydrogenase, suggesting that cherries may possess the capacity to reduce uric acid production (6). Cherries and cherry extract contain high levels of anthocyanins (7–9) that exert antiinflammatory effects either through inhibiting cyclooxygenase activity (8,10–12) or via scavenging of nitric oxide radicals (23). Thus, cherries may also have antiinflammatory properties against the series of inflammatory responses triggered by monosodium urate crystals. Although cherries contain vitamin C, the amount they include (~80 mg in 6 servings of cherries) (5) is likely to be too low to have an impact on the risk of gout, since the relevant vitamin C dosages associated with a reduction in serum uric acid levels and gout risk have been shown to be ~500 mg/day or higher (24–26).

Our findings suggest that these data on the potential influence of cherries on levels of serum uric acid (5) and potential antiinflammatory effects (8,10–12) may be translated into prevention of gout attacks among patients with preexisting gout. While urate-lowering therapy (e.g., allopurinol in >90% of cases in the US and Europe) can be efficacious in lowering levels of serum urate and the risk of gout when dosed appropriately and used compliantly, current practice standards limit urate-lowering therapy to specific indications, such as frequent gout attacks, tophaceous gout, and advanced gout, primarily due to rare but serious side effects (27). When these indications are not yet met, nonpharmacologic options, such as risk factor modifications, are the only acceptable preventive approach. Should our findings be confirmed in randomized clinical trials, cherries or cherry extracts could provide a novel nonpharmacologic option for preventing gout attacks. Furthermore, our findings regarding the combined use of cherries and allopurinol also suggest that cherries may add substantially to the effects of allopurinol in preventing gout attacks in gout patients.

Identifying potential triggers for recurrent gout attacks is challenging when using traditional study designs and recruiting methods. To address these issues, we adapted a case–crossover study design to examine a set of potential triggers, including cherry intake, in relation to the risk of recurrent gout attacks. This study design is highly adaptable to evaluating the effect of transient exposure as a trigger for acute disease onset, and self-matching of each subject minimizes bias in control selection and removes the confounding effects of the factors that are constant over the study period but differ between participants (e.g., genetic factors, sex, race, education) (28). We also used the internet as a platform to conduct the study. As our study and others have demonstrated, the internet is an efficient way to access a large number of potential participants and to collect information in real time (29,30), thereby minimizing recall bias.

The present study has some limitations. While the case–crossover study design is optimal for assessing the acute effects of cherry intake, it is not ideal for evaluating the long-term effects of habitual cherry consumption. Because cherry consumption was self-reported by questionnaire, some misclassification of exposure is possible despite our use of pictures to depict different serving sizes during our data collection. If gout attacks somehow triggered more recollection of cherry intake, it would have biased the potential protective effects of cherry intake toward null. Furthermore, our cherry effect estimates were independent of other well-established antigout measures, such as allopurinol, colchicine, and NSAIDs. Nevertheless, our study was observational; thus, we cannot rule out the possibility that unmeasured factors might have contributed to the observed associations.

We did not collect data on serum uric acid levels; thus, we were unable to assess whether cherry consumption decreased the risk of gout attacks even among subjects whose serum uric acid levels were below the therapeutic target levels (e.g., 6 mg/dl). However, when we limited our analysis to subjects who reported taking allopurinol on online questionnaires (n = 184), the risk of recurrent gout attacks was still decreased with cherry consumption, even though allopurinol use itself was associated with a lower risk of recurrent gout attacks. In our study, the antigout benefits of cherry consumption peaked at ~3 servings over a 2-day period and tended to attenuate at the next higher consumption level, although remaining protective. While certain opposing mechanisms, such as fructose included in sweet cherries, might play a role at certain levels of cherry consumption, as has been shown for oranges and apples (31,32), we cannot rule out random variations due to relatively small sample sizes in the highest consumption categories. Thus, these findings need be confirmed in future studies. Finally, we were unable to estimate the absolute rates of gout attacks using the case–crossover study design, and the distribution of cherry intake among the participants in our study may not be representative of a random sample of US patients with gout; however, the biologic effects of

cherry intake on gout attacks (as reflected in our OR estimates) should be similar.

In conclusion, our findings suggest that cherry intake is associated with a lower risk of gout attacks. Should our findings be confirmed in randomized clinical trials, cherry products could provide a novel nonpharmacologic option for the prevention of gout attacks.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Zhang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Zhang, Neogi, Chaisson, Hunter, Choi.
Acquisition of data. Zhang, Neogi, Chen, Chaisson, Hunter, Choi.
Analysis and interpretation of data. Zhang, Neogi, Chaisson, Hunter, Choi.

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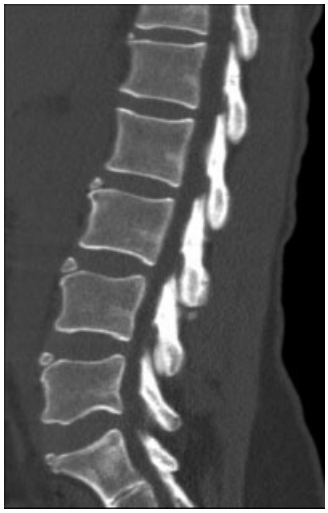
Clinical Image: Limbus vertebra



The patient, a 38-year-old woman with a 4-month history of low back pain, was referred to our care. She had no symptoms suggestive of inflammatory back pain, and results of the physical examination, including results of neurologic tests, were within normal ranges. Findings of motor and sensory conduction studies were also noted to be normal. Sagittal computed tomography scanning of her lumbar spine revealed well-corticated, triangular bone fragments on anterior and superior end plates of multiple vertebrae, a finding that is compatible with limbus vertebra. Limbus vertebra is a defect that usually occurs at the superior anterior margin of the lumbar vertebrae. The inferior and posterior margin and other regions of the spine are less frequently affected. Limbus vertebra is a consequence of a remote injury in an immature skeleton, thought to result from herniation of the nucleus pulposus through the ring apophysis prior to fusion, separating a small segment from the vertebral rim. While most reported cases of limbus vertebra have consisted of solitary involvement, to our knowledge, no formal study has addressed the prevalence of either solitary or multiple limbus vertebrae. Whereas anterior limbus vertebra is believed to be asymptomatic, posterior limbus vertebra has been reported to cause nerve compression. Limbus vertebra could be mistaken for a fracture, discitis, Schmorl's node, or tumor, resulting in unnecessary, even invasive, diagnostic procedures. This is most likely to occur when a patient presents with back pain, especially after trauma. Limbus vertebra is an incidental finding and typically not the cause of the pain; thus, it needs no medication or treatment. It is important to consider this defect in differential diagnosis.

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