# Correspondence

INSTRUCTIONS FOR LETTERS TO THE EDITOR

Editorial comment in the form of a Letter to the Editor is invited; however, it should not exceed 800 words, with a maximum of 10 references and no more than 2 figures (submitted as camera ready hard copy per Journal Guidelines) or tables and no subdivision for an Abstract, Methods, or Results. Letters should have no more than 3 authors. Full name(s) and address of the author(s) should accompany the letter as well as the telephone number, fax number, or E-mail address.

*Contact.* The Managing Editor, The Journal of Rheumatology, 920 Yonge Street, Suite 115, Toronto, Ontario M6J 3G7, CANADA. Tel: 416-967-5155; Fax: 416-967-7556; E-mail: jrheum@jrheum.com Financial associations or other possible conflicts of interest should always be disclosed.

## Silicone Gel Breast Implants

*To the Editor:*

The report of statistically increased risk of fibromyalgia (FM) in women whose silicone gel breast implants had ruptured received media attention despite its obvious serious flaws[1]. First, of women who chose to have implants for cosmetic reasons, the majority (only a minority received them after mastectomy) clearly differ in personality traits and characteristics and self-image from other women. Second, the authors of this study did not ascertain which women had commenced legal actions, and it is well known that the trial lawyers had coached the women's answers and their favorite physicians used questionnaires that were "loaded" (e.g., I have the following symptoms as a result of my breast implants...). Third, FM may have started out as a valid catch-all phrase to help in communication among clinicians, but it no longer has any validity except to designate women (and it is predominantly women who qualify) who evince symptom amplification, social maladjustment, hostility, and a propensity to voice their complaints. The symptoms exist without complaints in rural areas and stable communities, so that they reflect what 19th century sociology distinguished as the difference between community (with its peer oversight) and society (with social disorganization and poor integration). To state that FM is more common in women with ruptured breast implants is to say nothing of importance. From initial scares that breast implants led to scleroderma, human adjuvant disease, connective tissue disease, and atypical connective tissue disease to this assertion that the non-disease FM predominates is really the mountain laboring to produce a mouse. It's high time we disposed of the name and "disease" fibromyalgia, thus giving hope to disaffected sufferers who are being subjected to innumerable useless diagnostic tests and treatments, importuned by advocacy groups, and recruited by trial lawyers who know it is almost impossible to prove that a self-reported symptom that cannot be verified objectively does not exist. So it is with this study, which continues to attempt to justify US Food and Drug Administration restrictions that were not valid in the first place and represented an overreaction to media circuses (e.g., Connie Chung's notorious exposé) and misguided publications.

As a member of *The Journal*'s Editorial Board, I am dismayed that an article that goes to great lengths to analyze the findings leaves out the most important data: how many women consulted or were referred by lawyers and how many were diagnosed by physicians to whom they were referred by lawyers.

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REFERENCE

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*To the Editor:*

I read with interest the paper by Brown, *et al*[1] concerning silicone gel breast implant rupture and health status, but I question the appropriateness of the co-mingling of different implant rupture status categories. For critical analyses that led to their major findings, the authors presumably combined women who had intracapsular ruptured implants with women who had intact devices, and then they compared this group to those having ruptured implants with extracapsular silicone migration (I call this group extracapsular rupture). The right half of their Table 4 illustrates the comparison. Based on this categorization, the authors' main finding was that "these data suggest an association between extracapsular silicone from ruptured silicone breast implants and FM [fibromyalgia]."

What was the biological, clinical, and epidemiological rationale for combining these 2 groups? I argue it is better to classify implant status into 3 categories: intact, intracapsular rupture, and extracapsular rupture. Using this classification, one can compare the association between implants with extracapsular rupture to intact implants, and similarly, implants with intracapsular rupture to intact implants — these comparisons are biologically and clinically more relevant and, in my opinion, are the first place to start an epidemiologic analysis involving breast implant rupture. While Brown, *et al* did not present health outcome results for these 3 categories, they provided enough data to do this analysis. When I did, the data showed that fibromyalgia (FM) was indeed *not* associated with ruptured implants, neither for intracapsular nor extracapsular rupture.

From the authors' Table 4, I calculated the number of women in 3 rupture status categories: those with intact implants, those with apparently intracapsular rupture, and those with extracapsular rupture (Table 1). Following Brown, *et al*, Table 1 also displays the number of women by the 2 implant status comparisons the authors reported: (1) any ruptured implant (either intracapsular or extracapsular) versus intact implants, and (2) extracapsular rupture versus intracapsular rupture and intact. The odds ratio (OR), while not given in Table 4 by the investigators, between implant status and health outcome is shown for the 3 conditions the authors found as potentially associated with extracapsular silicone: FM, Raynaud's phenomenon, and "other connective tissue disease."

The OR between FM and extracapsular rupture (compared to intact devices) is 1.88 and not statistically significant. The OR between FM and intracapsular rupture (compared to intact devices) is 0.50 and also not statistically significant. The OR for any rupture versus intact devices is 0.87. It is obvious from Table 1 that the largest difference in FM risk is between extracapsular and intracapsular rupture. If a gradient in risk exists, these data seem to suggest a gradient for FM that is: intracapsular rupture < intact < extracapsular rupture. (While not statistically significant, these data surprisingly seem to point towards a FM risk for women with intracapsular rupture that is half that for women with intact implants, suggesting that intracapsular rupture may *protect* women against FM!) Intuitively, if an association exists between implant status and FM, one would hypothesize based on clinical reasoning that the true gradient would be: intact < intracapsular rupture < extracapsular rupture. Brown, *et al*'s data plainly depict no consistent association between ruptured implants of any type and FM when compared to intact devices.

The OR for the comparison the authors reported (i.e., extracapsular rup-

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*Table 1.* Implant status by self-reported physician diagnosis of 3 health outcomes. Values are expressed as the number of women and odds ratios.

| Implant Status | FM Yes | FM No | FM OR (95% CI)‡ | Raynaud's Yes | Raynaud's No | Raynaud's OR (95% CI) | Other CTD* Yes | Other CTD* No | Other CTD* OR (95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| Extracapsular | 18 | 55 | 1.88 (0.83–4.29) | 6 | 67 | 1.84 (0.45–7.94) | 9 | 64 | 3.66 (0.96–16.80) |
| Intracapsular | 13§ | 150 | 0.50 (0.21–1.17) | 3 | 160 | 0.39 (0.059–2.04) | 6 | 157 | 0.99 (0.23–4.91) |
| Intact | 16 | 92 | 1† | 5 | 103 | 1 | 4 | 104 | 1 |
| Any rupture | 31 | 205 | 0.87 (0.44–1.79) | 9 | 227 | 0.82 (0.24–3.18) | 15 | 221 | 1.76 (0.54–7.47) |
| Intact | 16 | 92 | | 5 | 103 | | 4 | 104 | |
| Extracapsular | 18 | 55 | **2.73 (1.32–5.49)** | 6 | 67 | 2.94 (0.81–10.01) | 9 | 64 | **3.67 (1.26–10.47)** |
| Intracapsular and intact | 29 | 242 | | 8 | 263 | | 10 | 261 | |

FM: fibromyalgia; CTD: connective tissue disease.

* Dermatomyositis, polymyositis, Hashimoto's thyroiditis, mixed connective tissue disease, pulmonary fibrosis, eosinophilic fasciitis, polymyalgia.

† Reference group in OR calculations.

‡ 95% CI for the OR are by exact methods[3].

§ Derived from Brown, *et al* Table 4: 236 (No. of women with ruptured implants) × 0.131 (proportion of women with ruptured implants who self-reported a physician diagnosis of FM) = 31 women with ruptured implants self-reporting physician diagnosed FM. 73 (No. of women with extracapsular silicone) × 0.247 (proportion of women with extracapsular silicone who self-reported a physician diagnosis of FM) = 18 women with extracapsular silicone who self-reported a physician diagnosis of FM. The number of women with apparently intracapsular rupture self-reporting a physician diagnosis of FM is 31 – 18 = 13. Other table sample sizes are similarly calculated. Values in bold face are statistically significant.

ture versus intact plus intracapsular rupture) is 2.73 and is statistically significant. However, this is an epidemiologically inappropriate comparison (i.e., by the combining of intact implants with intracapsular rupture) given the authors' own data that show substantial differences in the OR for FM across the 3 implant status categories. By combining the intracapsular rupture and intact implant groups, Brown, *et al* decreased the FM frequency from 14.8% (in the intact-only group) to 10.7% (in the combined group). As a consequence, the difference in FM frequency between the extracapsular rupture group (FM frequency = 24.7%) and the intact/intracapsular rupture group widened beyond that which would have been found if only the intact group was used for the comparison. Combining the implant status categories this way caused the OR to increase and produce a perception of FM risk that the data did not support.

For Raynaud's phenomenon, a parallel analysis of Brown, *et al*'s data similarly shows (like FM) no evidence of an association for extracapsular rupture (Table 1). For the "other connective tissue disease" category, I found a borderline statistically significant association (OR = 3.67) for extracapsular ruptured devices compared to intact implants. According to the authors this category comprised 7 different self-reported physician-diagnosed conditions: dermatomyositis, polymyositis, Hashimoto's thyroiditis, mixed connective tissue disease, pulmonary fibrosis, eosinophilic fasciitis, and polymyalgia. Data for 9 women with extracapsular rupture were spread out over these 7 self-reported diseases, resulting in no clear disease pattern. I find it difficult to interpret the findings for this nonspecific category. I agree with the authors: "It is not possible to determine whether any of these disorders predominated. Our category of other CTD is artificial and therefore those results are difficult to interpret."

In summary, for Brown, *et al*'s data, I argue that it is biologically and clinically more relevant and epidemiologically more appropriate to categorize (and analyze) implant status into 3 categories: intact, intracapsular rupture, and extracapsular rupture. When I analyzed Brown, *et al*'s data this way, it became clear that no association was evident between extracapsular rupture (in fact, for ruptured devices in general) and FM. If the authors believe that intact implants and implants with intracapsular rupture can be plausibly collapsed in the analysis, I respectfully ask them to explain their rationale, especially in light of their own data. Based on 2 of the authors' written comments about the lack of information on breast implant rupture and disease[2], it seems sensible to me they would want to explore and provide information about the association of health conditions across both types of implant ruptures. If the data are analyzed as I maintain is more appropriate, then women with breast implants can be reassured that ruptured devices have not been found to be associated with FM in this study.

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*Dr. Bowlin is an employee of Dow Corning Corporation.*

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## Drs. Brown and Pennello reply

*To the Editor:*

We appreciate the opportunity to further discuss our results[1].

Dr. Ehrlich voices concern that women with silicone gel breast implants differ in personality traits and characteristics from other women. However, because our study only included women with silicone breast implants, that should not be an issue. Second, he believes that trial lawyers may have influenced women's response to our questionnaire. If the women in this study misreported diagnoses of connective tissue disease or symptoms, for any reason, then that would tend to dilute any association of these outcomes with implant rupture because the women did not know their implant status prior to undergoing magnetic resonance examination. His third point is that fibromyalgia (FM) may be a catch-all and that women with this diagnosis are simply more apt than other women to report, presumably minor, com-

plaints. Despite this opinion, others agree on a scheme for diagnosing this syndrome and it is widely, albeit not universally, recognized[1]. Others express opinions similar to Dr. Ehrlich's and question the value of a diagnosis that relies on reporting subjective symptoms[2]. This is a debate not unique to our findings. Dr. Ehrlich, presumably, would find fault with any study in which FM was diagnosed.

Dr. Ehrlich suggests that this study is an attempt to justify US Food and Drug Administration (FDA) restrictions on silicone gel breast implants. The FDA's restrictions of breast implants were due to the manufacturer's failure to prove that their device was safe and effective. This is a basic requirement for any implanted medical device. It should also be remembered that connective tissue disease was not the sole concern, but that local complications such as implant rupture and capsular contracture were considered important[3]. The FDA opinion on this issue was reiterated by the Institute of Medicine in their assessment, *Safety of Silicone Breast Implants*, when they stated that "Reoperations and local and perioperative complications are frequent enough to be a cause for concern..."[5].

Dr. Bowlin argues for comparing women with extracapsular silicone to women with intact implants only, as opposed to our comparison of women with extracapsular silicone to all other participants. When the analysis is performed his way, the association with FM is not significant.

Our comparison is biologically and clinically relevant because if extracapsular silicone was the sole cause of FM, then ruptures without extracapsular silicone could be combined with intact implants, particularly since there was no association with rupture when compared to all others. When all 3 categories are compared simultaneously (intact, ruptured, and extracapsular), then there are significant differences among these categories (Fisher-Freeman-Halton exact p value = 0.003). Further, Dr. Bowlin's comparison of extracapsular silicone with intact implants has less power to detect a significant difference than our comparison. Dr. Bowlin reports an odds ratio of 1.88. While not statistically significant, it is still highly suggestive of an association between FM and extracapsular silicone.

A genuine shortcoming of this study was that we were unable to compare women with implants to a comparable group of women without implants. This means that we still do not know whether women with implant rupture are more likely than women without implants to report FM or connective tissue disease. Further study will be required to assess this and obviously an improved study design would include a controlled clinical evaluation of all women in the study.

Our findings indicate that there is an association between extracapsular silicone gel and FM. This does not prove a causal association. In particular, we do not know if the diagnosis of FM came before or after the extracapsular rupture of implants. However, it is suggestive and since this is the first study in which implant status was known for all women in the study, followup studies with a clinical component will be important in clarifying this issue.

S. LORI BROWN, PhD, MPH, GENE PENNELLO, PhD, Office of Surveillance and Biometrics, Food and Drug Administration, Rockville, MD, USA.

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## Fibromyalgia: Can One Distinguish It from Simulation?

*To the Editor:*

The article by Khostanteen, *et al*[1] would have major implications in "industrial" and insurance policy/litigation, if there were not major methodology flaws. Premise assumptions and experimental design, however, preclude the article's sweeping conclusion[1].

The question of whether fibromyalgia (FM) can be faked is quite pertinent. Can an individual study or be coached as to how to respond during examination? Perhaps that depends upon the examination — and choice of control points.

What is the role of control points? Campbell, *et al*[2] found that control points were nontender in patients with FM. While Khostanteen, *et al*[1] note that they have published their disagreement, perhaps an issue is specification of the control points. One could question that the control points chosen in their study[1] (forehead, mid-ulna, hypothenar, lateral gastrocnemius) were too physically distant from FM trigger/tender points to be clinically useful. Yes, forehead tenderness might raise questions of secondary gain, and tenderness in the mid-ulna region might raise questions of general body tenderness, low pain threshold or interpreting touch sensations as pain. However, is that really the issue for assessing fakery or exaggeration?

I would suggest that a much better control point is one adjacent to a FM trigger point. Examining the trapezius ridge or rhomboid trigger points and adjacent scapula provides unequivocal evidence[3], in my experience. The points are too close for patients to discriminate. As for pain reporting on examining those points, I have not seen a single patient with FM who has tenderness also in the adjacent scapula. Those individuals with tenderness on scapula pressure also have a general body tenderness, something I classify (my own preconceived notion) separately from FM. Thus, I would suggest that control points do matter — if appropriate ones are chosen, ones for which patient's perception do not allow such "2 point discrimination."

The technique of pain assessment may also provide discrimination. It has been my approach to ask at the onset of examination for the patient to identify any pain produced during that examination. Thus, general or inappropriate tenderness can clearly be recognized — and distinguished from FM. Delaying the question to when specific trigger points are examined may miss that important information.

The arbitrary selection of at least 4 trigger points provides a more uniform group of patients with FM. However, presence of trigger points could be interpreted as a patient with FM, who simply doesn't have enough body regions affected to be entered into controlled studies. That, however, does not qualify them as controls. Would it not be more appropriate that controls be individuals without any trigger points. One certainly would not use as controls in a lupus study individuals who fulfill 3 criteria for lupus. Why then should we for FM?

One further critique must be considered. The control group was recruited from "posted notices in the hospital."[1] Relevance to the general population of controls derived from medical facilities is not established.

Subleties are often of great importance in rheumatologic diagnosis[3]. The term "trigger points" has been used throughout this discussion. Some might distinguish trigger points and tender points, requiring a referred pattern of pain for use of the former term. It would be of great interest to examine patient pain responses, to assess whether the pain is felt at the site of pressure or whether it occurs in anticipated referral patterns. Clarification of specificity for FM of physical examination findings is indeed an important research subject.

Concern must be expressed that those with an agenda will attempt to turn the article by Khostanteen, *et al*[1] into case law. However, the case has not been made. There is still no evidence that FM can be faked — as long as appropriate control points are assessed.

BRUCE M. ROTHSCHILD, MD. Northeastern Ohio Universities College of Medicine, Youngstown, OH 44512, USA.

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## Dr. Khostanteen replies

*To the Editor:*

Dr. Rothschild in his letter raises some very important issues. Control points need more exact definition and the most appropriate would be those which remain clinically nontender in the region of referred pain. A number of studies had addressed this question; in our study the design was based on previous work[1]. Our experience was that control points become progressively more tender in relationship to the tenderness at the tender points comparing healthy controls to patients with fibromyalgia (FM) or myofascial pain.

As per the concern regarding the technique of pain assessment, the point is well taken. The volunteer group was given information regarding technique of examination of tender points and were already examined by the rheumatologist prior to enrollment into the study.

Another concern of Dr. Rothschild was choice of control group. The inclusion criteria were: no history of chronic pain, which would by the ACR criteria[2] exclude any FM and clinical findings less than 4 points, which was chosen arbitrarily from population studies[3].

As per the question of relevance of controls derived from medical facilities, this population provided a convenient sample of healthy individuals. From our study design the volunteers were randomized to the normal group versus the simulators.

We agree that consistency in the use of terminology is important in respect to tender point versus trigger point descriptions. In our study we use the term of tender points.

As stated in the Discussion this study was not to be meant as a test for malingering, but rather tested the sensitivity, specificity, and accuracy of the ACR criteria to distinguish patients with chronic FM from motivated simulators under the conditions of a clinical trial.

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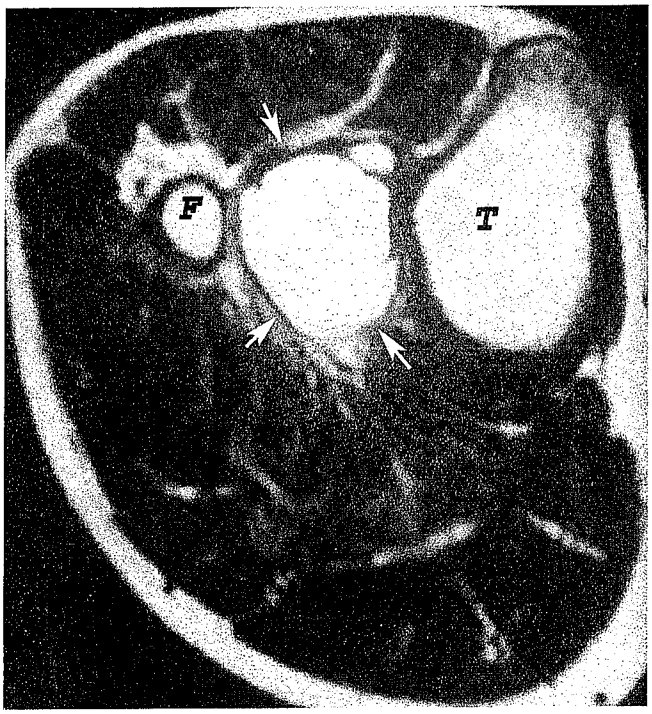
## Unusual Synovial Cyst of the Knee Treated with Fibrin Sealant

*To the Editor:*

We read with great interest the report by Jerome and McKendry[1], describing a case of synovial cyst of the proximal tibiofibular (PTF) joint. As noted by the authors, this condition is uncommon and no consensus exists on the most appropriate management, although surgical excision is recommended. We describe a case of synovial cyst arising from the PTF joint treated successfully by a fibrin sealant injection.

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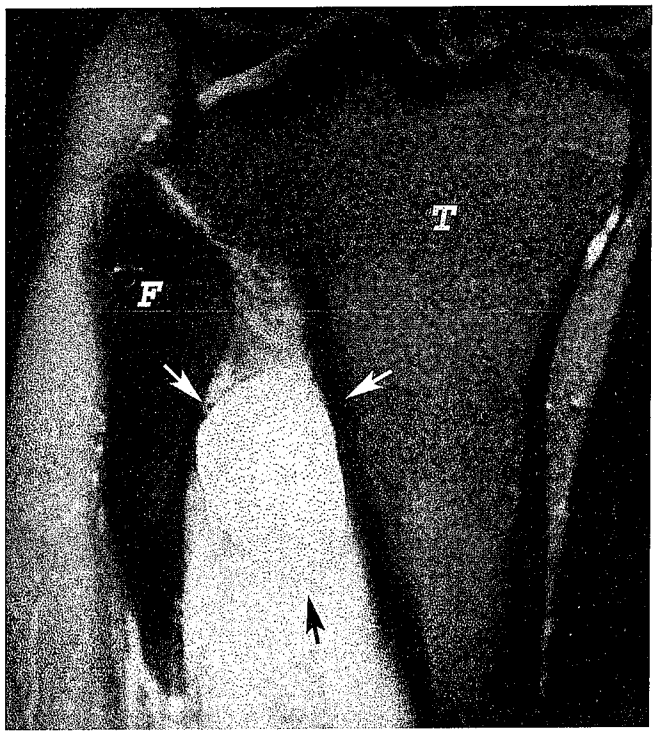


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*Figure 1.* Axial (a) and sagittal (b) T2 weighted MR images (2700/105) of right knee. A fluid collection with high signal intensity is seen (arrows) connecting with the proximal tibiofibular joint and extending craneocaudally in the muscle planes. T: tibia. F: fibula.

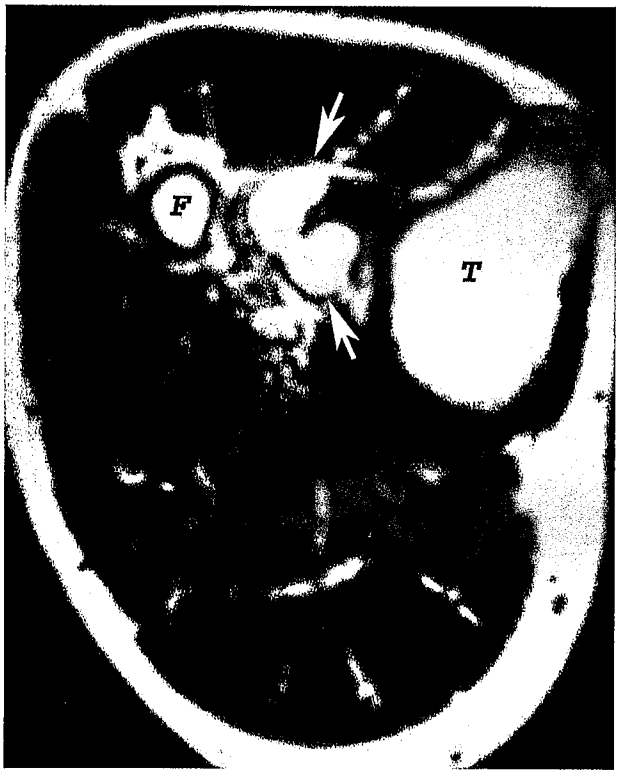


*Figure 2.* Axial T2 weighted (2700/105) MR image made 4 weeks after treatment by fibrin sealant injection method. T: tibia. F: fibula.

A 42-year-old man complained of a 2 month history of atraumatic lateral right knee pain that worsened with ambulation. Medical and surgical history was unremarkable. Examination revealed a focal tenderness around the anterolateral aspect of his right knee, without limitation of range of motion. Distal pulses were palpable, the sensation to light touch was intact distally, and motor function of the leg was normal. Right knee radiographs were normal. Axial and sagittal magnetic resonance imaging (MRI) showed a well encapsulated fluid collection with low signal intensity on T1 weighted and homogeneous high signal intensity on T2 weighted images (Figure 1 A, B), arising from the PTF joint and measuring 40 × 20 × 20 mm.

On the basis of fluid consistency and the location of the lesion a diagnosis of synovial cyst of PTF joint was made[2,3]. To avoid surgery, a nonoperative method was tried by injecting a fibrin sealant (Tissucol Kit, Immuno AG, Vienna, Austria) into the cyst with a fluoroscopic guide after needle aspiration of the contents. His pain resolved within a few days after the procedure. Followup MR study one month later (Figure 2) revealed that the cyst had decreased; the patient was asymptomatic and without relapse after 24 months.

Traditional nonoperative treatment of synovial cysts consists of mechanical rupture followed by applying pressure, aspirating the cyst followed by pressure, or aspirating with injection of a chemical irritant. Although this treatment often relieves symptoms, it is only temporarily effective because of cyst reinflation[4]. Fibrin sealant is a biodegradable surgical tissue adhesive used increasingly in many situations[5] and it would be clinically useful in wall-to-wall adhesion cystic lesions. Recently Shigeno, *et al*[6] assessed this substance in the management of cystic lesions of the soft tissue in which previous conservative treatment had failed, including a PTF cyst with multiple aspirations. In light of their successful results, in our patient we sought to inject fibrin sealant into the cyst to adhere to the cyst walls, as a more definitive therapy than aspiration alone. Given the complete resolution of one case after one injection, and the simplicity of the technique, we suggest this method before surgery of synovial cysts.

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## Drs. Jerome and McKendry reply

*To the Editor:*

The letter from Dr. Mifsut, *et al* on the treatment of proximal tibiofibular (PTF) joint cysts also highlights some diagnostic issues. It would appear that the PTF cyst in their patient was not superficial enough to be detected as a subcutaneous mass on physical examination, but rather was diagnosed by magnetic resonance imaging. How often is "knee" pain caused by an unsuspected, symptomatic PTF cyst? Could a PTF cyst of this size be reliably detected using less expensive and more readily available ultrasound imaging? The sustained improvement following intracyst fibrin sealant (Tissucol Kit) is impressive. We hope these authors, or others, will undertake a prospective trial comparing cyst aspiration to aspiration and injection of fibrin sealant to confirm that the excellent result in this patient is the rule rather than the exception.

DANA JEROME, MD; ROBERT J. McKENDRY, MD, FRCPC, The Ottawa Hospital, Ottawa, Ontario, Canada.

## Assessment of Prothrombotic Risk in Patients with Behçet's Disease Should Include Homocysteine Plasma Levels

*To the Editor:*

We read with great interest the paper by Toydemir, *et al* regarding the possible role of methylenetetrahydrofolate reductase (MTHFR) gene C677T, factor V (FV) gene G1691A (Leiden), and prothrombin gene G20210A polymorphisms in the genesis of thrombosis in patients with Behçet's disease (BD)[1]. The authors found no correlation between thrombosis and MTHFR gene C677T mutation in patients with BD, confirming reports that did not show any association between cardiovascular thromboembolic events and MTHFR 677TT genotype[2]. However, it is of interest that while factor V gene G1691A (Leiden) and prothrombin gene G20210A mutations are recognized as independent thrombotic risk factors, MTHFR 677TT genotype should be considered only as an indirect predisposing factor for thrombosis. Indeed, several reports showed that MTHFR 677TT genotype in association with low plasma folate levels is the major determinant for mild or moderate hyperhomocysteinemia, which is a well known risk factor for both arterial and venous thrombosis[3,4]. Plasma elevations of total-Hcy (tHcy) are typically caused either by genetic defects in the enzymes involved in Hcy metabolism or, more frequently, by nutritional deficiencies

in vitamin cofactors such as folic acid, vitamin B12 and vitamin B6[6]. A screening for thrombophilic conditions in patients with BD should include not only MTHFR genotyping but also homocysteine folate, and vitamin B12 plasma levels to exactly define the prothrombotic risk.

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## Drs. Toydemir, *et al* reply

*To the Editor:*

Our primary focus was to evaluate the possible role of 3 polymorphic mutations, alone or in combinations, in thrombogenesis in patients with Behçet's disease.

As we clearly pointed out in the Discussion, serum homocysteine levels may be affected by serum levels of folate, vitamins B6 and B12, cystathionine ß-synthetase and methionine synthetase, as well as MTHFR C677T mutation, which we examined in this work[1]. Our conclusion that MTHFR C677T mutation is not correlated with thrombogenesis does not preclude the association of these other thrombogenic factors, which, we concur, are worthy of study to expand on our findings.

We are pleased to see Danese and colleagues concur with our approach and we encourage others to extend our findings through similar studies.

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