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Letter to the Editor

To the Editor:

Minimally invasive, cost-effective, and efficacious methods for managing osteoarthritis are desirable and welcome. Such interventions may reduce the number of total joint replacements when the indications for surgery are primarily pain related. Consequently, radiofrequency joint denervation procedures are deemed attractive and appealing to physicians and patients alike. Scientific studies in this area are scarce, and any publication in a high-impact journal is influential. Thus, the publication of Choi et al. [1] has become a seminal article that not only inspired physicians to implement the method, but also induced industry to develop teaching programs and invest in this emerging market. In fact, this rapid commercialization and adoption of this new procedure focused my attention on this article published almost 3 years ago. Notwithstanding the soundness of the methods, I cannot help but express several concerns that arose after reviewing this article in depth.

The authors claimed that the "articular branches around the knee joint are known as *genicular nerves.*" However, in the quoted original manuscripts [3–5], the words *genicular nerve* appeared only once, as described below. The most extensive anatomical investigation on a large number of cadavers was done by Horner and Dellon [4]. To summarize their findings, the innervation of the joint capsule is described as follows. The anterior part of the joint capsule is innervated by the terminal ending of the infrapatellar branch of the saphenous nerve. The medial retinacular nerve contributes to innervation of the medial aspect of the joint capsule and the medial collateral ligament. The lateral joint innervation is supplied by the inferior lateral articular nerve (a branch of the common peroneal nerve), which lies very near the joint line, and the second, recurrent branch, which takes off distally to the fibular head. The superior lateral genicular (here the word *genicular*) nerve has its origin from the sciatic nerve 8–10 cm proximal to the joint line, and courses toward the superolateral aspect of the capsule. A terminal branch of the nerve to the vastus medialis innervates the anterior capsule. Posterior articular branches of the tibial nerve were found to range from 1 to 5 in number originating 10 to 25 cm above the joint line.

Two other publications [3,5] did not include the term "*genicular*" at all. Therefore, based on the previously published anatomical studies, the name *genicular nerve* is a misnomer. There are multiple articular branches of nerves that follow Hilton's Law (ie, a nerve that innervates a joint also tends to innervate the muscles that move the joint and the skin that covers the distal attachments of those muscles) [2]. Perhaps some nerve filaments do follow the *genicular arteries*. Whether or not they contribute to the sensory innervation of the knee joint has yet to be determined. In addition, the innervation of the osseous joint structures has not been investigated at all. Perhaps the bone marrow nerve matrix plays a role in transmitting poorly localized joint pain.

So why did Choi et al. [1] base their entire technique on nonexistent nerves? Why have others followed their call and promptly adopted the method in clinical practice? It is worrisome that a terminology and methodology are accepted without scientific support and can become so pervasive.

Also of concern is that 2 of the presented figures in the article by Choi et al. [1] do not accurately support the manuscript. First of all, the authors claimed that only patients with Kellgren-Lawrence grades 2-4 (moderate-severe radiological degree of osteoarthritis) were enrolled. However, Figure 2 shows a normal knee joint. Indeed, the cannulae are positioned proximal to the femur condyles and distal to the medial tibial condyle. However, other than mechanically or thermally damaging the genicular arteries, the radiofrequency lesions in these locations would not result in the joint denervation. Figure 5 shows very superficial dissection. Some subcutaneous vascular or nerve structures are vaguely visible in the adipose tissue at the medial aspect of the knee. If the authors had followed their own description of the anatomy, their dissection would have been performed in a deeper tissue plane. Furthermore, the insets do not match the main figure and the labeling is incorrect. The authors called a fat tissue fold "the adductor magnus," and a transected tendon or ligament was labeled "the *tibial* collateral ligament."

I will leave it to the readership to critically appraise the scientific quality of the Choi at al. article [1]. The idea of knee joint denervation as a long-term palliative procedure to alleviate chronic pain is appealing. However, rigorous anatomically sound research must precede any clinical trials and further commercialization of this procedure.

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Response to letter to the Editor

To the Editor:

We would like to thank Dr. Gofeld, who raised several concerns about our article [1]. We had previously received similar remarks on our paper. Maybe it is because radiofrequency (RF) neurotomy for knee osteoarthritis is a new procedure based on knee innervations by multiple articular branches. According to the anatomy textbook [2], several articular branches of the knee originate from the tibial and common peroneal nerves and accompany the superior medial, inferior medial, middle, superior lateral, and inferior lateral genicular arteries. The superior medial, superior lateral, and inferior medial arteries pass the medial and lateral condyle of the femur and the medial condyle of the tibia, respectively. Because RF neurotomy is based upon the identification of anatomic landmarks for nerve innervations, points of condyle can be targeted for RF neurotomy.

There have been a few reports in which articular branches of the knee joint are called the genicular nerves [3,4]. Furthermore, it is known that several articular branches pass close to the epicondyle, anatomic landmark of long bone. This was also confirmed by nerve sensory stimulation for RF neurotomy in our study. Nevertheless, several anatomic problems, such as variation and function of the articular branches, remain to be established. Clearly, additional studies are needed to confirm the pain innervation of knee osteoarthritis and the safety of RF neurotomy.

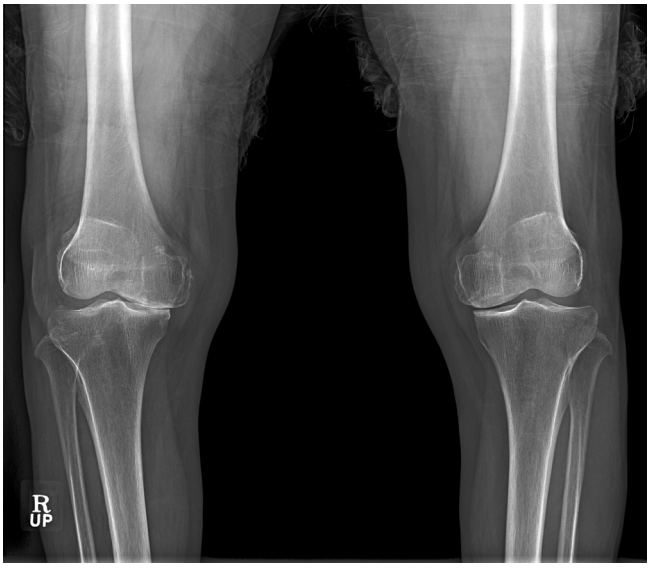

Fig. 1. The X-ray anteroposterior image of both knees in the standing position. The left knee joint shows a medial joint space narrowing with osteophytes (Kellgren-Lawrence grade 2). The right knee joint has more severe osteoarthritis than the left knee joint.

About Figure 2 in our article, this is the C-arm X-ray image for the left knee of a female subject in the supine position and with a pillow under the popliteal fossa. This image quality is so cloudy due to our old C-arm machine, and may be estimated as a normal joint. However, her left knee anteroposterior X-ray findings in a standing position (Fig. 1) showed a medial joint space narrowing with osteophytes (Kellgren-Lawrence grade 2).

We agree with Dr. Gofeld about his remark for Figure 5. We regret not providing sufficient detail in our explanation of Figure 5. In Figure 5, the left side of the picture is an image of the entire left knee with superficial dissection. The pictures on the right side of the figure are enlarged images of the left knee with deeper dissection. We selected the image of the left knee with superficial dissection because the deeper dissection image was not able to show exactly the muscles or ligaments that covered articular branches. Also, number 3 in picture A actually indicates the adipose tissue fold below the adductor magnus, not the muscle.

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Letter to the Editor

To the Editor

Genetic studies [3] have shown the important role that sodium channel $Na_v1.7$ (encoded by the SCN9A gene) has in human pain perception, and this protein has been targeted for the development of novel analgesics [2–5]. Several reported novel small-molecule $Na_v1.7$ inhibitor compounds are currently in clinical development. One of these compounds (PF-05089771) has been reported to demonstrate molecular selectivity for $Na_v1.7$ over certain other members of the voltage-gated sodium channel protein family [7,8].

We developed XEN402 as a potent state-dependent blocker of voltage-gated sodium channels, including nanomolar inhibition of $Na_v1.7$. In 2012 we published, in *PAIN®*, data from an exploratory trial studying the analgesic properties of XEN402 in patients with inherited erythromelalgia (IEM) [6]. Each of