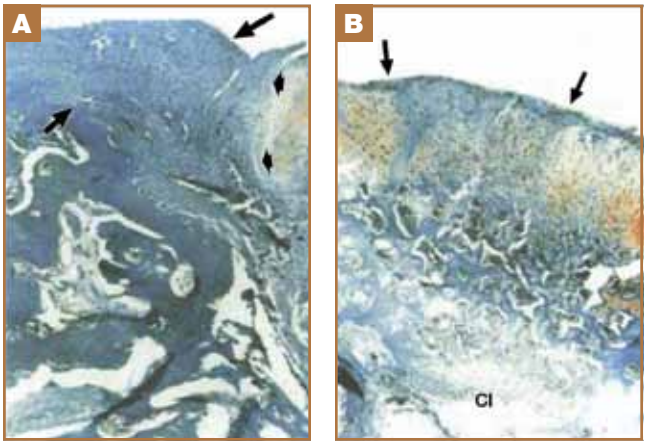


Figure 6. Photomicrograph of repair of 1.2-mm osteochondral defect in unstimulated animal sacrificed at 8 weeks (safranin O). (A) Short arrows indicate right margin of wound; long arrows indicate extrusion-like appearance of fibrous tissue forming pannus over articular cartilage. (B) Similar section from animal stimulated for 40 hours. Arrows indicate margin of defects. Note extensive remodeling in subchondral bone beneath defect site and presence of cartilage islands stained with safranin O (Cartilage Islands).

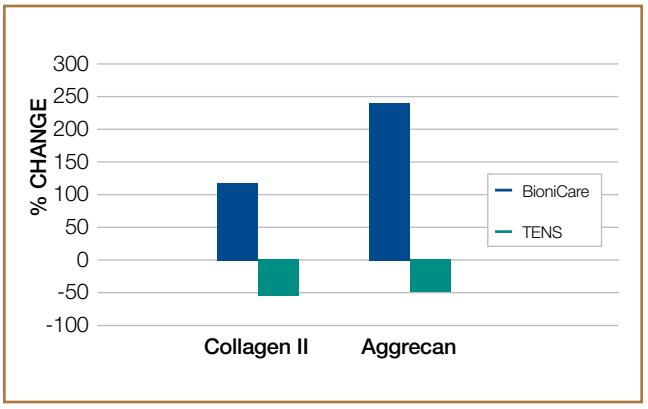


Figure 7. Increased matrix macromolecule production in human chondrocytes with BioniCare stimulator versus decreased production with transcutaneous electrical nerve stimulation (TENS).

was favored on all 7 outcome parameters (**Table IV**). A mean of 40% of combined-treatment patients (range, 35%-51%) and a mean of 32% of stimulator-only patients (range, 28%-39%) obtained substantial clinical improvement, at least 50%, on all 7 outcome parameters after 12 months (P = .005).

We expected that there would be an additive treatment benefit of combining stimulator and brace and that it would last until the full benefit of stimulator use was obtained, after 6 to 9 months. We were surprised to find some synergistic action between stimulator and brace, as the advantage of the combination treatment (vs stimulator-only treatment) continued throughout the study and was apparent even after 1 year of treatment (**Figures 3-5**). Unlike most medications used to treat knee OA, the stimulator exhibited no ceiling effect for the duration of the study (the longer patients used the device, the larger its effects). Thus, the benefits of stimulator treatment increased in dose–response fashion throughout the study.

## Discussion

In 1990, Lippiello and colleagues[13,21] studied the BioniCare pulsed electrical stimulator in the treatment of osteochondral defects in rabbits. Full-thickness cartilage bore defects (1.2 and 3.2 mm in diameter, 6 mm deep) and lacerative saw defects (1 mm wide, 3 mm deep, 1 cm in length) were created. The stimulator-treated cartilage defects healed with hyaline-like cartilage material and without any pannus formation; the placebo-device–treated control knees demonstrated material resembling fibrocartilage with no safranin O staining, and inflammatory pannus formation (**Figure 6**). Subsequently, Lippiello and colleagues[13,21] demonstrated that, when human chondrocytes are exposed to the stimulator signal for 2 hours, type II collagen is up-regulated by 118% and aggrecan by 241%. In the same system, when human chondrocytes are treated with a transcutaneous electrical nerve stimulation (TENS) device, the chondrocytes are damaged; type II collagen decreases by 54% and aggrecan by 50% (**Figure 7**). Although the histologic changes in articular cartilage related to BioniCare treatment have not been studied in human knee OA, the implications of these studies for treating OA in humans is compelling.

Successful preclinical trials were followed by a prospective, double-blind, placebo-controlled, randomized multicenter trial in 78 patients who had derived inadequate benefit from NSAID and/or analgesic therapy.[22] Patients remained on stable background therapy. There was significant improvement in patients treated with the active stimulator versus the placebo device in the entire intent-to-treat population for all 3 primary outcome measures: physician global assessment (P = .02), function (P = .04), and pain and associated symptoms (P = .04). Improvements in 2 secondary outcome parameters, morning stiffness and range of motion, were also significantly larger for the stimulator group than for the placebo group (P<.05 for both). The study was independently analyzed by the US Food and Drug Administration, which in 1997 cleared the BioniCare device for "use as adjunctive therapy for the treatment of knee OA for the improvement of pain and associated symptoms of knee OA and for overall improvement of the knee as assessed by the physicians global evaluation."[22]

Later, a confirmatory, 3-month, double-blind, placebo-controlled, randomized study of BioniCare treatment was conducted on 58 patients who had moderate to severe knee OA and insufficient benefits from conventional therapy.[23] All patients had Kellgren-Lawrence stage 3 or 4 radiographic changes. As in the first study, best medical therapy was maintained the month before and then throughout the study, rather than being withdrawn. Significant improvement was found in the entire intent-to-treat population for patient global assessment (P = .03), patient pain on a 100-mm visual analog scale (P = .03), WOMAC (Westren Ontario and McMaster Universities) stiffness (P = .03), WOMAC function (P = .01), and

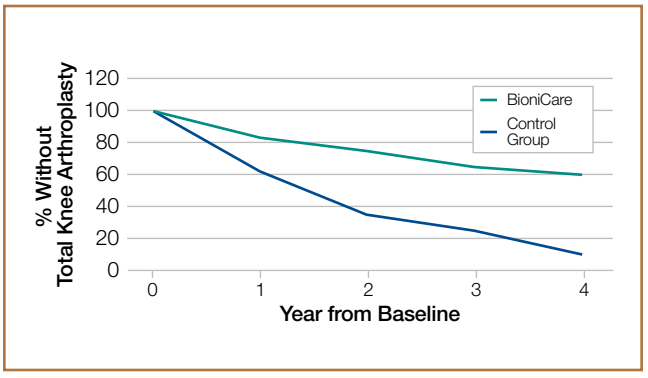


Figure 8. Percentage of 103 patients who were treated with BioniCare stimulator for 11 months (vs 42 matched controls) and who deferred total knee arthroplasty by year.

total WOMAC (P = .01).

Mont and colleagues[24] led a 4-year, prospective, open-label, multicenter study of 157 candidates for total knee arthroplasty (TKA) and compared them with 102 historical controls matched on clinical and radiographic severity. After a mean of 11 months of treatment, 60% of stimulator-treatment patients, versus 35% of patients given best therapy without stimulator treatment, deferred TKA surgery for at least 4 years. In patients with severe disease (Kellgren-Lawrence stage 4), 62% of those treated with the BioniCare device, versus 7% of those in the matched control group, deferred surgery for at least 4 years (**Figure 8**).

The present study clearly demonstrated that stimulator treatment alone or in combination with an unloading brace provided statistically significant and clinically relevant benefits on all 7 outcome parameters used (P<.001). It also clearly demonstrated that stimulator-and-brace treatment was superior to stimulator-only treatment. For all observation points (1, 3, 6, and 12 months) and all 7 outcome parameters, significant clinical benefit (≥20%) was obtained by a higher percentage of combined-treatment patients than stimulator-only patients (72% vs 63%; P<.001); likewise, substantial clinical benefit (≥50%) was obtained by a higher percentage of combined-treatment patients than stimulator-only patients (40% vs 32%; P = .005). This was also evident from the fact that there were more than twice (18.3% vs 7.5%) as many treatment failures in the stimulator-only group than in the combined-treatment group. This is an indication of increased adherence and increased efficacy with the combination treatment.

A weakness of this investigation is that one study ended in 2005 and the other began in 2010. We think the gap is compensated for by the large number of patients treated in each group, and by the groups' comparable demographics, rheumatologists and orthopedic surgeons, and disease severity, as evidenced by the outcome measures being equivalent at baseline. Moreover, no new treatment modality was introduced between studies, and corticosteroid injections and viscosupplementation were specifically prohibited from both. Tamperproof timers demonstrated comparable treatment duration with respect to the stimulator in both groups.

Both the magnitude of differences and the synergistic effect would indicate that there is a real treatment difference in combining the stimulator with the unloading brace. We have 3 hypotheses. First, the unloading brace may decrease the friction and the subsequent wear of the cartilage with weight-bearing. Second, placing the electrodes inside the brace maintains proper positioning throughout the treatment period. Third, stimulator treatment provides a capacitively coupled exogenous electrical signal similar to the endogenous signal of weight-bearing. When stimulator treatment is used alone, it is delivered with a night wrap while the patient is sleeping, and there is no concomitant endogenous signal created. When stimulator and brace are combined, the exogenous signal combines with the endogenous signal of weight-bearing, and the effect is somehow synergistic.

Whatever the mechanism, the long-term clinical studies of stimulator treatment have shown reductions in pain and associated symptoms, improved function, overall improvement in OA knees, and substantial deferral of TKA for at least 4 years. In the present study, stimulator–brace combination treatment clearly produced substantial improvement much more rapidly than stimulator-only treatment did. Thus, patients remained on the device long enough to achieve overall knee improvement. It is thought that rapid and increased improvement with stimulator–brace combination treatment should improve adherence and increase the ability to defer TKA surgery.

"... the long-term clinical studies of stimulator treatment have shown reductions in pain and associated symptoms, improved function, overall improvement in OA knees, and substantial deferral of TKA for at least 4 years."

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