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New Options for Treating Osteoarthritis of the Knee

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Overview

Osteoarthritis of the knee (knee OA) affects more than 20 million people in North America. This disease inflicts a growing burden of morbidity, health care costs, and lost productivity on affected patients and society. It accounts for a considerable portion of the $185.5 billion in expenditures attributed to OA in 2009.[1] Medical treatments and less invasive surgical approaches for knee OA are variably effective, and total knee arthroplasty (TKA) is generally reserved for the most severely affected. The care gap between more conservative treatments on the one hand and TKA on the other leaves many patients with unresolved pain and loss of function for long periods. (See page 4.)

The purpose of this paper is to inform physicians about two effective, but underprescribed nonoperative treatment modalities that offer additional long-term benefits for patients with moderate to severe knee OA. Unloading braces provide rapid pain relief and improve joint stability, while BioniCare® pulsed electrical stimulation (PES) provides more gradual, but sustained overall improvement in knee OA, and is cleared by the US Food and Drug Administration (FDA) for this indication. BioniCare treatment also allows many patients to reduce or discontinue nonsteroidal anti-inflammatory agents (NSAIDs) and analgesics, and to defer or avoid TKA surgery. In addition, the safety of bracing and PES are more favorable than both NSAIDs and TKA, and their costs are lower over time in comparison to these and other treatments. (See pages 4 and 13.)

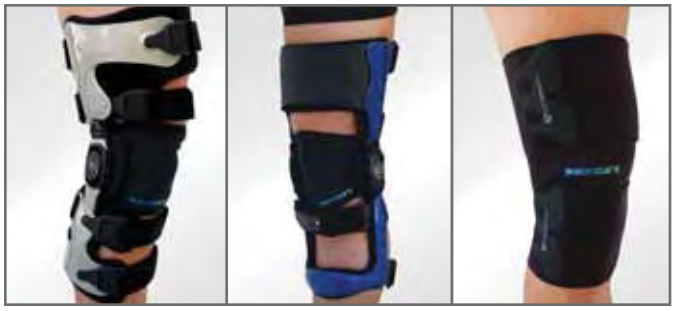

FIG. 1A: BioniCare® Oactive (Single Upright)

FIG. 1B: BioniCare® Eagle (Double Upright)

FIG. 1C: BioniCare® Night-Wrap (BioniCare® Alone)

VQ BioniCare OActive braces (**Fig. 1A and 1B**) provide the complimentary advantages of both bracing and PES by imbedding the BioniCare device within a lightweight unloading brace. Recent registry data suggest more rapid improvement from the VQ BioniCare + brace (**Fig. 1A and 1B**) than that reported previously for BioniCare treatment alone (**Fig. 1C**) (see page 7.), and the initial effect size in this group of patients with moderate to severe knee OA exceeds that reported for NSAIDs or injectable visco-supplements, and is in the range of that provided by TKA (**Fig. 2**).

Decades of scientific inquiry support the hypothesis that

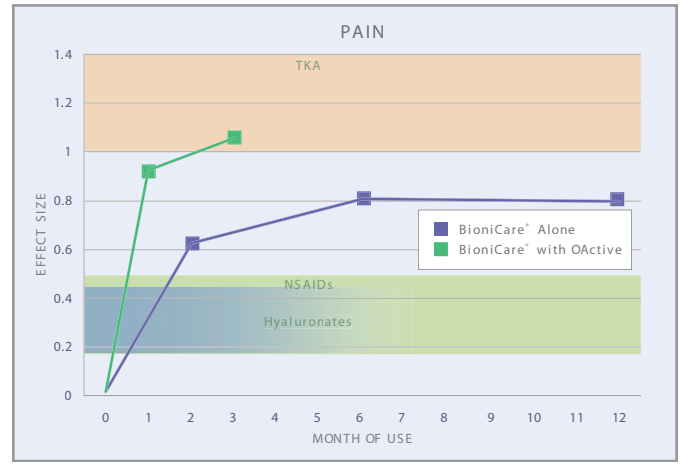

FIG. 2: Effect Size for Pain Relief. BioniCare® OActive Versus BioniCare® Alone Versus NSAIDs Versus Hyaluronates Versus TKA

electrical signals produced in cartilage matrix by mechanical compression and fluid streaming regulate chondrocyte genes, increasing either collagen and proteoglycan synthesis or metalloproteinase-mediated matrix breakdown (**Fig. 3**). (See page 9.) In osteoarthritic chondrocytes, synthesis of matrix macromolecules is decreased, while that of decreasing metalloproteinases and other inflammatory cytokines are increased. The principle behind using PES in knee OA is similar to well-established PES treatment for stimulating bone matrix synthesis by osteocytes to heal fracture nonunions.[2] Experiments using cartilage explants and intact animal models have shown further that PES signals with specific electrophysiological properties modulate chondrocyte functioning, and that effective exogenous signals are similar to those measured in intact cartilage during experimental loading.

The BioniCare device is engineered to deliver a similar optimal signal to the joint tissues. Its benefits depend on both the signal generated and, in particular, the method of delivering this signal, and on the high performance, special, proprietary electrodes that couple this signal to the joint tissues. These critical factors explain the superior results

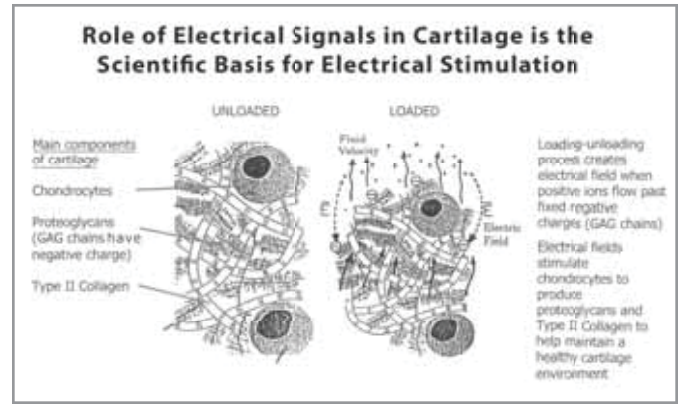

FIG. 3: Genesis of Endogenous Electrical Signal in Cartilage

of BioniCare compared to other PES devices and transcutaneous electrical nerve stimulators (TENS), and why negative results reported with other devices should not be generalized to the BioniCare PES treatment. (See page 10.)

The VQ BioniCare OActive braces offer high value for knee OA care, especially in the Medicare population where knee OA is common. (See page 13.) The benefits of bracing and PES reduce the use of other medical treatments, reduce patients' morbidities across the lifetime of the disease, and defer or eliminate the need for TKA. (See page 5.) TKA costs, excluding those for revisions and complications, were already estimated at $9.8 billion in the United States in 2002, and the growing older population will continue to escalate this burden. In 2005, Milliman Global estimated potential Medicare savings of $400 million per year from TKA deferral alone in patients with moderate to severe knee OA treated with BioniCare, and the savings anticipated from reduced NSAID use and complications would be greater still. (See page 13.)

The slow time for adoption of BioniCare PES treatment is similar to delays for many other effective new treatments, taking an average of 17 years as documented by the Institute of Medicine in 2001.[3] This is true in particular for innovations based on new principles that produce the greatest changes from established patterns of care. The authors encourage our colleagues to better understand the importance of electrical signaling in mesenchymal tissues, including cartilage, and how the VQ BioniCare OActive brace exploits this knowledge to achieve superior therapeutic benefits. ■

Background

More than 20 million people in North America have knee osteoarthritis (knee OA).[4] The greater prevalence of obesity and the aging population are increasing the numbers of affected persons and those disabled by this affliction. Consequently, knee OA is an increasing economic burden to the health care system and the United States economy. For example, total knee arthroplasty (TKA) is one of the most common orthopedic procedures performed in the United States with 542,000 hospital discharges for all ages in 2006, and 328,000 for those age 65 years and older.[5] The 2003 National Institutes of Health (NIH) Consensus Statement on Total Knee Replacement estimated that the mean cost for a TKA was $35,000 in the United States and the cost has clearly increased since that time.[6]

Osteoarthritis is primarily a degenerative disorder that results from excessive catabolism and inadequate repair of the articular cartilage matrix of movable joints.[7,8] Healthy articular cartilage is capable of withstanding the high and variable loading that accompanies normal movement, allowing optimal joint function with minimal wear and tear. This unique capacity depends on a highly organized matrix of proteoglycans, highly electrically charged molecules that make up the bulk of cartilage. The proteoglycans are enmeshed within and constrained by a dense network of collagen fibers. Homeostatic maintenance of articular cartilage depends on normal metabolic functioning of chondrocytes and their synthesis of these matrix macromolecules.

Articular cartilage degeneration in osteoarthritis begins with disruption of the intricate architecture of the matrix that leads to a loss of tissue resiliency. Proinflammatory and inflammatory cytokines are elevated in osteoarthritic cartilage, and play a pivotal role in the degenerative process by activating proteases that degrade the matrix and disrupt chondrocyte functions. One of the primary proinflammatory cytokines is IL-1, which, in turn, induces multiple inflammatory cytokines including PGE-2, reactive oxygen species, nitric oxide, and matrix metalloproteinases (MMPs). Several of the MMPs are collagenases that break down the Type II collagen. In the advanced stages of OA, cartilage becomes severely eroded, joint architecture is altered, and denuded bones rub against each other causing deformity, pain, and disability.

Conventional nonoperative treatments for knee OA have changed only slightly over the past 40 years, including education, weight loss, exercise, bracing, analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular glucocorticoids, and more recently intra-articular viscosupplements.[9] Two of the three COX-II inhibitors have been withdrawn because of adverse effects, and both knee lavage and arthroscopic debridement have been largely abandoned unless there is concomitant intra-articular ligament or meniscal damage.[10]

Any additional treatments that will provide long-term benefit for knee OA, short of TKA, must either stimulate chondrocytes to produce more matrix macromolecules—proteoglycans and Type 2 collagen—and/or decrease the proinflammatory and inflammatory cytokines that degrade cartilage. Candidate patients for such therapies will include not only those whose disease has not progressed to a severe stage, but also the many who are too young, too old or frail, too heavy, too sick with medical comorbidities, or who are unwilling to undergo TKA. ■

Clinical Effectiveness of BioniCare® and Unloading Brace Treatments

In this section, we will review the research that has demonstrated the effectiveness of BioniCare pulsed electrical stimulation (PES). In addition, new clinical registry data are presented on page 7 that demonstrate that combining BioniCare PES and unloading braces provides the complimentary therapeutic advantages of both, as well as a more effective and efficient delivery system for the BioniCare PES treatment.

BioniCare Treatment Alone

Controlled Trials

Two short-term double blind, randomized, multicenter clinical trials comparing the BioniCare device to a placebo device provided level 1 evidence for its effectiveness. The first was a 1-month trial that enrolled 78 patients who had derived inadequate benefit from NSAIDs and/or analgesic therapy.[11] Patients were not required to flare and, in fact, remained on stable background therapy. The primary outcome measures were those agreed upon with the FDA at the time of the study: Physician Global Assessment, patient assessment of pain and associated symptoms, and patient assessment of function in the treated knee.

Significant improvement with the BioniCare active device as compared to placebo device was demonstrated in the entire intent-to-treat population for the three primary outcomes measures: Physician Global Assessment (P=0.02), function (P=0.04), and pain and associated symptoms in the treated knee (P=0.04). Improvements in two of six secondary outcomes, morning stiffness and range of motion, were also significantly greater for the BioniCare device versus the placebo device group (P values <0.05 for both). Improvement was more significant for all measures in those time-compliant patients who used the device for 6 or more hours a day, as prescribed in the protocol—30/38 active device patients and 22/33 placebo device patients.

This study was used to obtain FDA clearance for the BioniCare device in 1997 for "use as adjunctive therapy in reducing the level of pain and symptom associated with osteoarthritis of the knee and for the overall improvement of the knee as assessed by the Physician Global Assessment." The improvement after only 1 month of treatment suggests that reduction of proinflammatory and inflammatory cytokines is at least in part responsible for the early benefits observed.

A second 3-month, double blind, placebo device controlled, randomized study of the BioniCare device was performed on 58 similar patients with moderate to severe knee OA.[12] All subjects had Kellgren's Grade 3 or 4 x-ray changes in the treated knee and had experienced insufficient benefits from conventional therapy. Best medical therapy was continued for the month before and throughout the study, rather than being withdrawn.

Significant improvement was demonstrated in the entire intent-to-treat population for the following primary outcomes measures: Patient Global Assessment (P=0.03), patient pain 100 mm Visual Analog Scale (VAS) (P=0.03), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) stiffness (P=0.03), WOMAC function (P=0.01), and total WOMAC (P=0.01). Only WOMAC pain did not reach significance (P=0.11).

A 20% improvement is used by the American College of Rheumatology as an indication of minimum clinical improvement. Even more relevant is the calculation of Minimal Clinically Important Improvement (MCII), which provides a more easily understood indicator of clinical effectiveness than does statistical significance, and unlike the latter, it is not highly dependent on sample size.[13,14] In this regard, this 3-month Garland trial reported that the percentage of patients who improved by 50% or greater in each of the primary outcome measures were two to seven times more frequent with the BioniCare device than with the placebo device (**Fig. 4**). Furthermore, the magnitude of the differences measured between the BioniCare device and the placebo device provide clear evidence of statistical significance and clinical effectiveness in even smaller study populations.

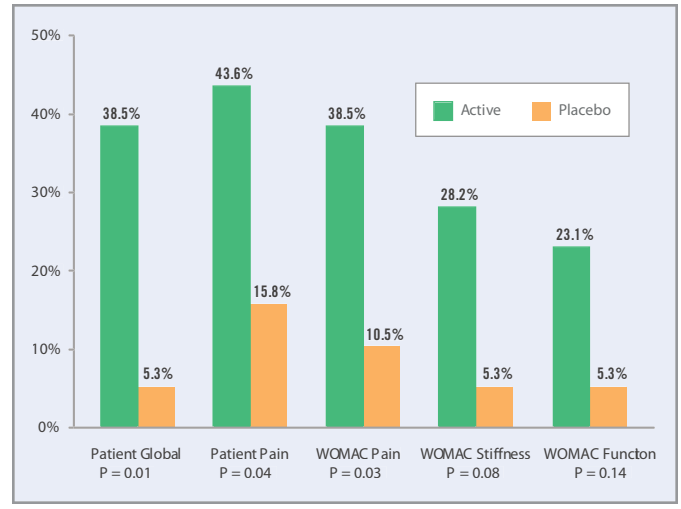

FIG. 4: Substantial (>50%) Improvement in Active BioniCare® Versus Placebo Device in Primary Outcome Measures.

Other Clinical Studies

Two additional longer-term clinical studies were then conducted to determine changes in the disease state and safety of the BioniCare device. Drs Michael Mont and David Hungerford, professors in the Department of Orthopedic Surgery at Johns Hopkins, performed a prospective, 4-year, open label, multicenter study in 157 patients who

were designated by an orthopedic surgeon or rheumatologist as TKA candidates—54 with moderate and 103 with severe OA.[15] After a mean of 11 months of BioniCare treatment, 60% of these subjects deferred TKA surgery for 4 or more years, whereas only 35% of similar patients in the Johns Hopkins knee OA historically matched control group had done so (**Fig. 5**).[16] Among the 103 patients with severe disease, 62% of those treated with BioniCare deferred surgery for 4 or more years as compared to only 7% in the matched control group (**Fig. 6**).

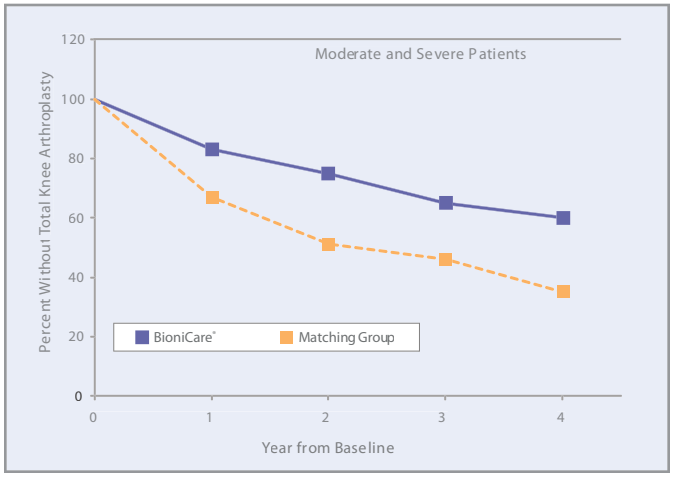

FIG. 5: Percent of Patients Who Deferred TKA by Year for All 157 BioniCare® Treated Patients Compared to 102 Matched Controls

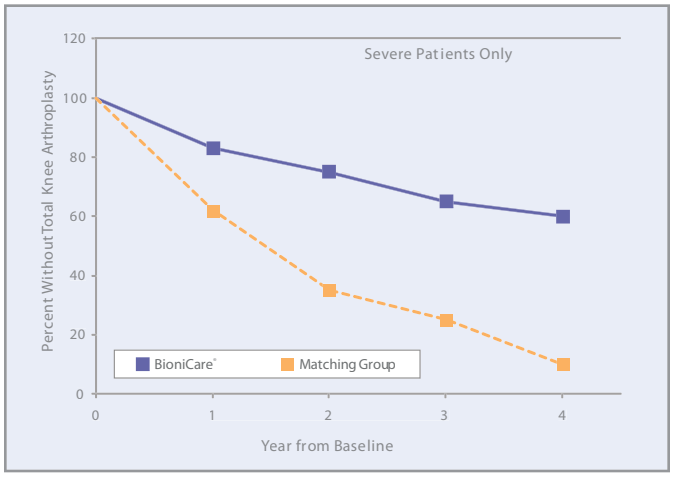

FIG. 6: Percentage of Patients Who Deferred TKA by Year for 103 Severe BioniCare® Treated Patients Versus 42 Matched Controls

Farr and coauthors also reported a long-term cohort trial of 288 knee OA subjects treated with the BioniCare device.[17] These subjects were evaluated at 57 orthopedic and rheumatology practices in the United States from September 2003 to July 2005. These patients reported significant relief of pain and improvement in function in excess of those reported for NSAIDs and hyaluronans within the first 750 hours of therapy; however, even better results were seen in patients who used the device for more than 1,750 hours. A significant dose-response relationship was found between efficacy and hours of use, and the effect size of their treatment was in the range of that reported for TKA. In addition, NSAID use decreased by 50% or more in 45% of patients, and 18% were able to discontinue NSAIDs entirely.

The scientific community, pharmaceutical companies, and regulatory agencies have become focused on developing drugs that might influence the natural history of OA by preventing, retarding, or reversing cartilage breakdown, so-called disease-modifying OA drugs. Expert opinion has suggested that studies of potential OA disease-modifying treatments should include primary outcomes measures that reflect impact on the natural history of the disease.[18] In particular, at OMERACT 7, candidacy for total joint replacement (TJR) was proposed as a "hard" outcome measure.[19] The deferral of TKA in the Mont study and the achievement of effect size comparable to TKA in the Farr study suggested that BioniCare treatment can be looked at as a disease-modifying OA treatment.

Unloading Brace Treatment Alone

The general purpose of a brace is to decrease pain and improve function. Knee OA often affects the medial compartment more than the lateral, and patients with medial compartment OA often have a varus alignment such that the mechanical axis and loadbearing pass through the medial compartment. At times, the opposite is true, and the lateral compartment is more affected. In either case, malalignment increases the risk for progression of knee OA and predicts decline in physical function.[20] Both valgisation and varisation braces are available for unloading the medial and lateral compartment, respectively.

A 12-month multicenter randomized controlled trial was performed by Brouwer et al in 2006 to study the additive effect of an unloading brace with conservative treatment of unicompartmental knee OA.[21] They included 16 patients in the intervention group (brace and standard conservative treatment) and 57 patients in the control group (standard conservative treatment alone). The VAS pain and knee function scores were not significantly different, but the walking distance was significantly longer in the brace group at 3 months, 12 months, and overall (P=0.03, P=0.04, and P=0.02, respectively). Effect sizes at the three assessment points ranged from 0.2 to 0.4.

Kirkley et al performed a prospective, parallel-group, randomized clinical trial comparing a custom-made valgus-producing functional knee (unloading) brace, a neoprene sleeve, and medical treatment only (control group) in knee OA subjects with varus deformity.[22] A significant improvement in the disease-specific quality-of-life (P=0.001) and in function ($P \leq 0.001$) were documented in both the neoprene-sleeve group and the unloading brace group compared to the control group. A significant difference between the unloading brace group and the neoprene-sleeve group in pain after both the 6-minute walking test

(P=0.021) and the 30-second stair-climbing test (P=0.016) were also reported, as was a strong trend toward a significant difference between the unloading brace group and the neoprene-sleeve group with regard to the change in the WOMAC aggregate (P=0.062) and WOMAC physical function scores (P=0.081). The results suggested that patients with knee OA and a varus deformity may benefit from an unloading brace added to standard medical treatments.

In patients with knee OA with both medial and lateral involvement in whom there is no single compartment to unload, a neutral brace may also improve proprioception and stability.[23] ■

Registry Data for the VQ BioniCare® OActive Brace That Delivers BioniCare® PES Therapy Within a VQ OActive Unloading Brace

The previously summarized studies demonstrated that long-term treatment with the BioniCare device approaches the effectiveness of TKA, and allows many patients to defer surgery for at least several years. However, it was also clear that 6 to 9 months of BioniCare treatment are required to achieve full benefit. In contrast, unloading braces provide early benefits, but are less likely to be tolerated on an indefinite basis.[21]

The VQ BioniCare OActive brace was developed to combine the BioniCare PES system and the OActive unloading brace developed by VQ OrthoCare in order to realize the complimentary benefits of both modalities, and to facilitate daytime application of BioniCare therapy.

The Device (see Fig. 1 on page 3): VQ OrthoCare now manufactures the OActive unloading brace and the BioniCare device. The OActive unloading brace is a single upright lateral unloading brace worn laterally that can be adjusted to push and unload the medial compartment or to pull and unload the lateral compartment. The lateral vertical component is important in patients who require bilateral bracing, since medial components would interfere with walking. For patients who require more stability, VQ OrthoCare has also combined the BioniCare device with a double upright unloading brace called the BioniCare Eagle. Obviously, gait is better if only one knee is in a double upright brace so only one brace is on the medial side of the knee.

The BioniCare device is a portable, battery-operated unit capable of delivering 0V to 12V at a frequency of 100 Hz. It is capable of delivering monophasic, spiked signal to the knee by way of proprietary skin electrodes (**Fig. 6**). The stimulator provides subthreshold pulsed electrical fields by noninvasive means. (Each patient self adjusts the voltage to a level just below perceptible voltage.) An embedded, tamper-proof timer records the number of hours of actual use.

The positioning of the proprietary BioniCare electrodes within the OActive unloading brace has been optimized by Finite Element Analysis to assure delivery of the signal at an optimal voltage to penetrate the periarticular tissues and stimulate the knee cartilage. The strength of the signal has to be sufficient to positively effect the chondrocytes, but not so strong as to damage them (**vide infra on page 11, Fig. 10**).

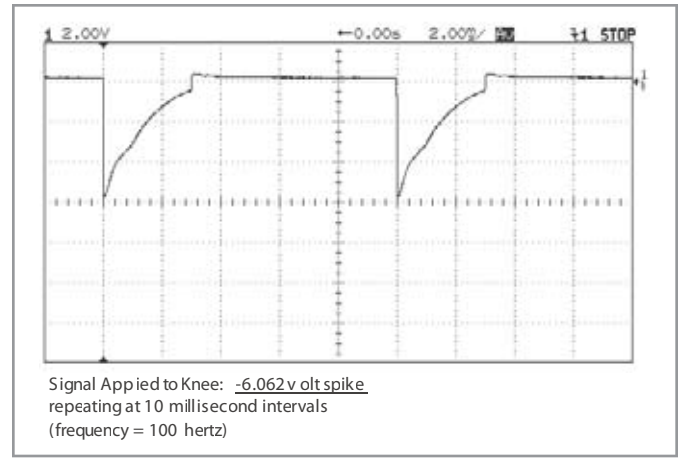

FIG. 7: BioniCare® Monophasic Negative Pulsed Signal

Registry Protocol: VQ OrthoCare established a clinical registry in January 2010 to evaluate the efficacy and safety of combining the BioniCare device and VQ OActive unloading brace in patients who had failed other nonsurgical options for knee OA. Sixteen orthopedic and rheumatology practices in the United States have been participating, and the study is ongoing. Advertising for patients was not done. All patients signed an informed consent that, together with the registry protocol, was approved by a central independent Institutional Review Board.

Inclusion criteria were age 18 years or older, the presence of OA in one or both knees, joint space narrowing and/or osteophyte formation on standing knee radiographs, and persistent pain. Exclusion criteria were pregnancy, nursing, presence of any implantable electronic device, or the presence of infectious or non-OA inflammatory arthritis. Although patients were allowed to continue concomitant NSAIDs and/or analgesics, all had responded inadequately to these medications before being enrolled.

Each study site conducted patient training on device use and supervised completion of the study forms. Patients were

trained during the baseline visit, and additional instructions were provided as needed during 1- and 3-month follow-up visits. For the data to be included, visits had to occur +/- 1 week from these intervals, and the subject had to use the device a minimum of 3 hours/day on average. At each visit, the patient questionnaire was administered, joint examination was performed, and records of treatment hours were collected from the device.

Interim Analysis: The 1-month (a mean of 167 hours) treatment results for the first 111 subjects and the 3-month results for 87 of these same subjects were analyzed in August 2011. Efficacy outcomes were measured using a five-point Likert scale (1=no symptoms; 5=very severe symptoms.) Outcome measures were the patient global assessment of disease activity in the study joint, assessment of pain and other symptoms, the patient's assessment of pain intensity in the past 48 hours, pain on walking on a flat surface, pain going up or down stairs, pain while sleeping, and the Physician Global Assessment.

When both knees were affected, the more symptomatic one was designated as the index joint to be followed. Statistical Analysis System (SAS) software version 9.1.3 was used. Univariate "screening" of associations between covariates and outcomes were done by simple statistical method-tests, chi-square, and log-rank tests. Selected covariates were examined in the Cox model. Patient baseline values served as controls for post-treatment values. Differences between baseline and final visit scores were compared using paired samples t-test.

A multivariate analysis examined the effects of age, gender, and number of hours of device usage on efficacy. Efficacy was expressed for each variable as the effect size. Effect sizes were previously defined by a 2003 European League Against Rheumatism (EULAR) task force as small from 0.2 – 0.5; moderate from 0.5 – 1.0; and large as greater than 1.0.[24] Effect sizes calculated from clinical trails of other OA treatments include 0.17 to 0.47 for hyaluronans, 0.2 to 0.5 for NSAID, and 1.0 to 1.8 for TKA.[25-28]

These patients were also compared to the 288 patients treated with the BioniCare alone in the Farr study summarized in Section 2.[17] Patients in both trials had experienced inadequate therapeutic responses to non-operative treatments often including activity modification, weight loss, physical therapy, NSAIDs, or analgesics. The same inclusion and exclusion criteria and outcome measures were used in both studies, and each patient served as his/her own control. Patients utilized from the Farr study were also required to average 3 hours or more of BioniCare treatment per day. The studies were conducted in private practice settings.

Results: Table I summarizes the effect sizes for seven

Efficacy Measure (Effect Size) for the VQ BioniCare® OActive Brace and the BioniCare® Device

Device	Duration of Use	Patient Global	Pain	48 Hour Pain	Pain Walking	Pain Stairs	Pain Sleeping	Physician Global
BioniCare® with	1 month	0.82	0.87	0.93	0.75	0.82	0.64	0.96
OActive brace – Registry Data	3 months	0.96	1.11	1.11	1.02	0.97	0.82	1.39
BioniCare® alone – Farr Study (Ref)	2 months	0.70	0.61	0.68	0.52	0.60	0.73	0.72
	6 months	0.78	0.79	0.86	0.66	0.84	0.78	0.96
	12 months	0.75	0.78	1.05	0.50	0.88	0.65	1.01

TABLE 1: The registry study population experienced greater efficacy by 3 months and a more rapid onset of effect from the VQ BioniCare® OActive brace than was shown previously in the 12-month Farr study for BioniCare® treatment alone,[17] or in the 1- to 3-month BioniCare® randomized, double-blind, placebo-controlled trials (REFs) (data not shown). Moderate to large effect sizes were documented for the VQ BioniCare® OActive brace by 3 months across all efficacy measure, equaling or exceeding the 1-year effect sizes in the Farr study for each measure (Fig. 8).

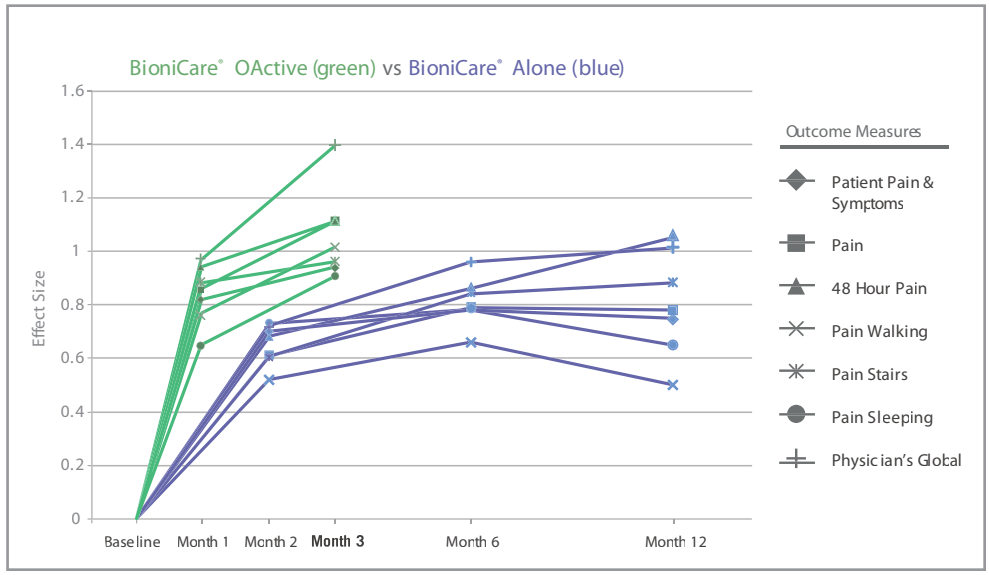

FIG. 8: Efficacy Over Time (All Outcome Measures)

standard measures of treatment effectiveness for knee OA from the current registry data for the VQ BioniCare OActive brace (Bracing + BioniCare) and the previously published Farr study for the BioniCare device (BioniCare alone).[17] Results include 1- and 3-month measurements from the registry for 111 and 87 patients respectively, and 2-, 6-, and 12-month measurements for 288 subjects from the Farr study. **Fig. 8** displays the individual effect size measures for the registry and Farr studies graphically.

Both BioniCare + brace and BioniCare alone provide moderate to large early and sustained benefits, but the BioniCare + brace device consistently produced equal or larger effect sizes, confirming the hypothesis that combining these two treatment modalities would provide a therapeutic advantage over BioniCare alone. Furthermore, the effect sizes for BioniCare + brace and BioniCare alone exceed those low to moderate effect sizes published previously for NSAIDs and hyaluronans, as shown graphically for pain in **Fig. 2**.

Conclusions: This interim analysis from a treatment registry demonstrates significantly higher effect sizes at 1 and 3 months for the VQ BioniCare OActive brace than for the BioniCare device alone at 2 and 12 months, respectively. In addition, both devices provide greater benefits than those previously reported for hyaluronates and NSAIDs. ■

The Scientific Rationale for BioniCare® Pulsed Electrical Stimulation Therapy

The specific characteristics of the BioniCare PES signal are based upon decades of scientific study that support the hypothesis that cartilage formation and repair are stimulated by intrinsic electrical signals generated in the matrix by mechanical compression.

In 1974, Baker et al first studied the in vivo effects of electronegative potentials on the healing of damaged hyaline cartilage.[29] Seventy percent of surgically created defects in rabbit femoral condyles healed with normal hyaline-like cartilage rather than fibrocartilage after stimulation with implanted electrodes.

- In 1978, Rodan et al showed that external, oscillating electric fields induced DNA synthesis in chick chondrocytes.[30]
- In 1988, Okihana et al reported that DC current enhanced both DNA and proteoglycan synthesis by rabbit chondrocytes, showing that electrical stimulation could up-regulate chondrocytes to both proliferate and to produce the materials that compose normal matrix.[31]
- That same year, Armstrong et al demonstrated that a specific capacitively coupled electric field increased glycosaminoglycan synthesis and chondrocyte cell proliferation in calf hyaline cartilage pellets.[32]
- In 1999, Mow et al and Grodzinsky et al confirmed the hypothesis that the charged proteoglycans of the extracellular matrix together with ionized interstitial fluid act as an electrical field signal transducer when cartilage was deformed in simulated weight-bearing.[33,34]
- In 2002, Schmidt-Rohlfing reported that mechanical stimulation and cartilage deformation induced an electrical current in ex vivo porcine knee explants.[35]
- In 2008, Brighton and his colleagues subjected human osteoarthritic articular cartilage explants to specifically

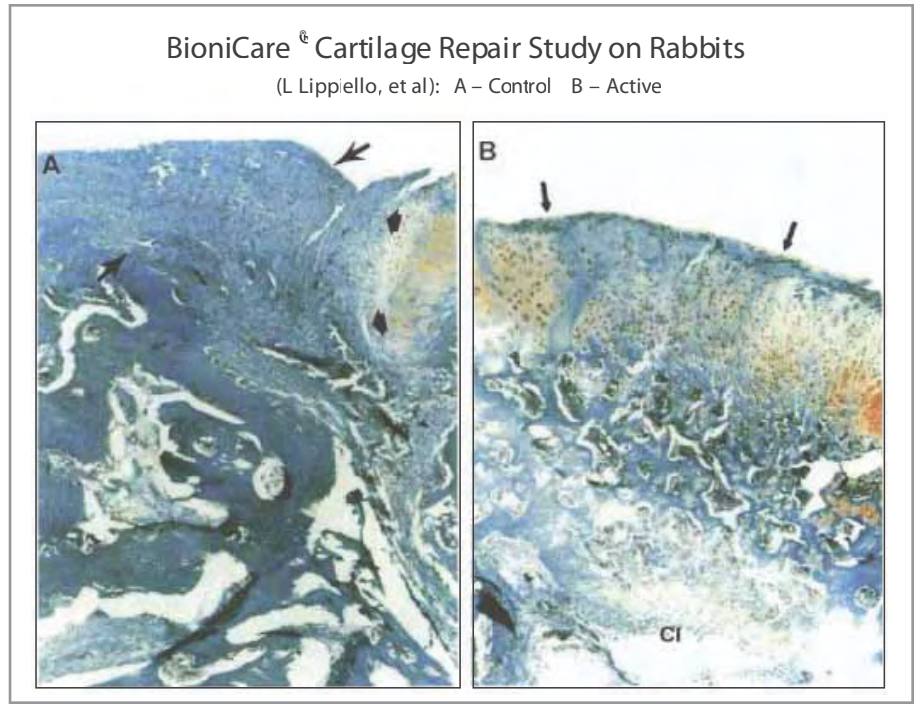

FIG. 9: Photomicrograph of 1.2 mm osteochondral defect stained with Safranin O. Repair in unstimulated animal sacrificed at 8 weeks. Short arrows indicate the right margin of the wound; long arrows mark the extrusion-like appearance of fibrous tissue forming a pannus over articular cartilage. (B) Similar section taken from animal stimulated for 40 h. Arrows indicate margin of defects. Note the extensive remodeling activity in subchondral bone beneath the defect site as well as the presence of cartilage islands stained with Safranin O (CI).

described electric fields and showed both increased production of mRNAs for aggrecan and Type II collagen and decreased MMP mRNA levels.[36]

- In 1990, Lipiello et al studied healing of articular cartilage lesions in rabbit lateral femoral condyles in response to an externally applied BioniCare PES device.[37] They created both full-thickness bore defects, 1.2 and 3.2 mm in diameter and 6 mm deep, and lacerative defects 1 mm wide, 3 mm deep, and 1 cm in length. The BioniCare-treated cartilage defects healed with hyaline-like cartilage material and no pannus was formed, while the placebo device control knees showed material resembling fibrocartilage with no Safranin O staining, and mild to severe pannus formation (**Fig. 9**). This study was the first to show healing of cartilage defects with hyaline cartilage with an externally generated signal (BioniCare) delivered by specifically placed, highly conductive electrodes.

Lippiello has shown further that if human chondrocytes are exposed to the BioniCare signal for 2 hours, Type II collagen is up-regulated by 118% and the most common proteoglycan, aggrecan, is up-regulated by 241%.[38] (**See Fig. 10.**)

Comments: The implications of these research studies for treating OA in humans are compelling. Cartilage repair in OA is compromised in part by loss of large, electrically charged proteoglycan molecules, reducing the magnitude of endogenous electrical fields produced during weight-bearing activities. BioniCare provides a capacitively coupled exogenous electrical signal similar to this endogenous signal and produces progressive clinical benefit during months of treatment. The histologic changes in articular cartilage related to BioniCare treatment have not been studied in human knee OA, so its mechanisms of action can only be inferred at this time, although the long-term clinical studies have demonstrated reduction in pain and associated symptoms and overall improvement of the osteoarthritic knee. ■

Critical Differences Between BioniCare®, TENS, and Other Electrical Stimulation Devices

BioniCare Versus TENS in Osteoarthritis

In broad terms, a transcutaneous electrical nerve stimulator (TENS) is any device that delivers electricity across the intact skin to activate underlying nerves. In current health care terminology, however, TENS refers to treatment by a "standard TENS device." Standard TENS devices are distinguished by their output characteristics: biphasic, repetitive, pulsed currents with a pulse duration between 50 µs and 1000 µs, and pulse frequencies between 1 and 250 pulses per second (PPS).[39] The purpose of TENS is to activate different selective populations of nerve fibers in order to produce desired physiological outcomes.

Increasingly, other nonstandard TENS-like electrical devices are being marketed to health care professionals for pain relief. These include interferential current therapy, microcurrent electrical therapy, high-voltage pulsed (galvanic) currents, TENS-pens, transcranial electrical stimulation and Limoge currents, Codetron, transcutaneous spinal electroanalgesia, action potential stimulation, and H-wave therapy. There is limited experimental evidence available for most TENS-like devices.[40] Thus, further discussion in this paper will relate to "standard TENS devices" only.

The BioniCare device is substantially different from TENS. Similarities end with both employing electrical fields to produce a benefit for the patient. Otherwise their clinical benefits, time to onset of effects, and the persistence of their efficacy are markedly distinct. Moreover, their theoretical and experimental rationales evolved independently, the physical characteristics of their electrical pulses are different, they share no biological commonalities in their mechanisms of action, the placement and the conductive characteristics of their electrodes differ, their target tissues are disparate, and their mechanisms of action are different.[40]

The FDA has classified the BioniCare device as a Transcutaneous Electrical Stimulator for Arthritis (TESA), with a product code of NYN. Transcutaneous Electrical Nerve Stimulator (TENS) Devices have a different FDA product code of GZJ. The BioniCare signal is applied at "sub-threshold" levels, ie, at signal strengths that the patient cannot detect. This permits long-term application times and double blind placebo device controlled studies. TENS signals are applied at strengths that cause paresthesias, a tingling at the application site. In fact, Long et al demonstrated that when TENS is applied at a subthreshold level, it loses its analgesic effects and is no better than placebo treatment.[41]

With low frequency TENS, analgesia usually occurs within 30 minutes but disappears 1-3 hours after cessation of therapy. Effectiveness wanes with increased usage, tolerance develops as seen with narcotic usage, and analgesia is absent in individuals tolerant to narcotics. With high frequency TENS, the analgesia disappears immediately upon discontinuation of treating. Published data indicate further that 70% of TENS users quit the device within 1 month, and that fewer than 10% of chronic pain patients use it for as long as 1 year.[42]

In contrast, with BioniCare, the onset of analgesia is delayed for greater than 1 week, but the duration of effect is often sustained for weeks to years after cessation of therapy. Effectiveness increases with time of use. Narcotics do not alter its potency, and published data have shown a mean time of use in a long-term trial of 11 months.[15]

The proposed mechanisms of action of BioniCare and TENS are different. The BioniCare device generates an exogenous time-varying electrical field that combines with the naturally occurring endogeous time-varying electrical fields that are mechanically induced in cartilage, impacting the chondrocytes, subchondral bone, and cytokine generation within the treated joint. (**See page 9.**)

TENS stimulates nerves, but has no demonstrated beneficial effect on cartilage, bone, or other connective tissues. Some authors have lumped all Pulsed Electrical Stimulation (PES) into the same basket; however, different devices produce different electrical signals as well as different biological effects. Specifically, studies have shown that the type of electrical current produced by some stimulators may harm and/or damage cartilage in a joint.[38,43]

BioniCare and TENS also have differing biochemical effects in stimulated tissues. As indicated on page 10, Lippiello has shown that if human chondrocytes are exposed to the BioniCare signal for 2 hours in vitro, Type II collagen is up-regulated by 118% and the most common proteoglycan, aggrecan, is up-regulated by 241%.[38] If these cells are treated with TENS, the chondrocytes are damaged, while the type II collagen is decreased by 54% and aggrecan by 50% (**Fig. 10**).

Data provided by one TENS device manufacturer shows

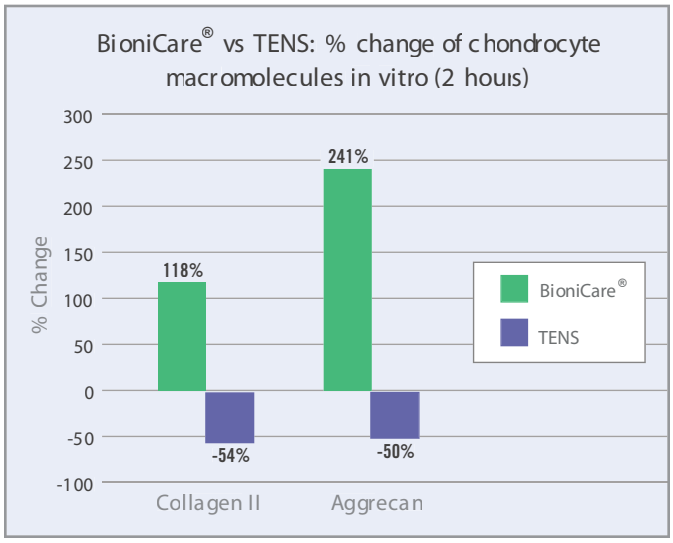

FIG. 10: Increased Matrix Macromolecule Production With BioniCare® Versus Decreased Production With TENS

further that one of its device's numerous signals—"composed of a 10 millisecond burst of asymmetric rectangular pulses, 200/28 microseconds in width, repeated at 15 Hz"—increases tissue nitric oxide levels.[43] It is well recognized that nitric oxide provokes serious inflammatory effects in arthritic cartilage and results in chondrocyte dedifferentiation and/or apoptosis (programmed cell death).[44] Clinical studies have demonstrated further that increasing nitric oxide has deleterious effects on cartilage, and that it may play a role in the "progression of cartilage degradation in osteoarthritis." For this reason, it has been proposed that "inhibition of nitric oxide production could be a desirable future therapeutic strategy" for osteoarthritis.[44-46] These findings raise safety, efficacy, and public health concerns about using TENS and similar electrical devices to treat osteoarthritis without supporting clinical trials.

In addition, devices that only relieve pain could have long-term deleterious effects on joints, regardless of the underlying disease process. A Charcot-like joint, which does not feel pain, has accelerated joint destruction and a shortened time to total joint replacement. Charcot-like joints are not only produced by syphilis and diabetes with peripheral neuropathy, but are iatrogenically induced in athletes. It is well known by sports medicine physicians that the injection into joints of Xylocaine-type products and corticosteroids, with the resumption of abusive activity, results in accelerated joint destruction. Prolonged use of narcotics or TENS devices could also produce a Charcot-like joint.

In 2010, the updated Osteoarthritis Research Society International (OARSI) recommendations were published for managing hip and knee osteoarthritis.[9] Electromagnetic therapy was not recommended in the OARSI guidelines despite evidence from an older 2002 Cochrane review that it might be associated with relatively large improvements in pain.

BioniCare Versus Other Pulsed Electrical Stimulators for Treating Knee OA

Any PES device developed to treat osteoarthritis must be validated in clinical trials before it can be considered to be safe and effective. How the signal is generated, how effectively the electrodes couple it to the skin surface and joint anatomy, how it is modified in transit through the periarticular tissues, whether it retains sufficient strength to affect the articular cartilage and bone, and whether the device can be worn comfortably are all critical factors. When others have tried to duplicate the electrical parameters and method of application of BioniCare, they have been unable to duplicate each and every one of these important parameters required for success.[47]

Clinicians need to avoid using devices that lack evidence for clinical efficacy, and at the same time not use negative results obtained for one PES device to judge others. As an example, a recently published study by Fary et al used a device, system, and method of application that they represented as similar to BioniCare.[47] A carefully designed clinical trial was performed, but no benefit was demonstrated for their active device. After engineering and testing a device developed to the specifications published by the authors, it is clearly improbable that such a device could have delivered effective BioniCare treatment. Requests to the authors to provide further technical details have not been answered. (The details of this analysis are included on page 12.) ■

The device used by Fary et al[47] is different from the BioniCare device in a number of critical ways. The exact waveform used by Fary was not disclosed, however, the signal is described as a "pulsed, asymmetrically biphasic, exponentially decreasing waveform with a frequency of 100Hz and pulse width of 4mS." It is also unclear if the pulse width measurement provided is measured at 50% of the amplitude (industry norm) or at some other point, or if it produced a net DC charge. Some additional information about the waveform can be inferred, however, from the device description as a TENS device that had been modified. Since this device was used on patients, only minor changes to the waveform would be allowed or questions of safety would need to be addressed in a 510(k) or other regulatory documentation.

Based on the above descriptions and assumptions, a commonly available TENS stimulator was modified to determine what waveforms were reasonably possible. The circuit was modified and the waveforms evaluated using a 500 Ohm resistive load (industry standard for waveform measurement). With this modified TENS device it was determined that waveforms as described above could be achieved by making simple modifications to either the primary or the secondary side of the stimulators output transformer. Waveforms created in this manner provide the appearance of a BioniCare type waveform when measured with a resistive load (**Fig.** 11). However, since these waveforms were generated using a TENS device having a transformer coupled output, the actual signal delivered to the patient is substantially different than the BioniCare signal. When a human load is attached to such a system, the waveform is radically altered and no longer bears any resemblance to what is delivered with the BioniCare device (**Fig.** 12). Clearly, trying to duplicate the BioniCare constant wave shape signal with a TENS unit is difficult and most likely impossible without significant modification to the TENS device. As discussed above, to achieve this would have meant more than using a modified TENS circuit and instead would dictate a radical redesign. The BioniCare device produces a waveform that does not change in any material fashion whether connected to a 500 Ohm load or connected to a human body load.

The excessive pulse width of the device used in the Fary et al study would also have a very material effect on the level of signal perceived by the patient.[47] Operating at six times the pulse width of a BioniCare signal would yield roughly six times more sensory response. If the patients adjusted to subsensory signal strength, the delivered voltage would be roughly one sixth that of a BioniCare signal. Combined with the radically different waveform seen by the human body, it is highly likely that this study used a waveform that cannot be compared to the

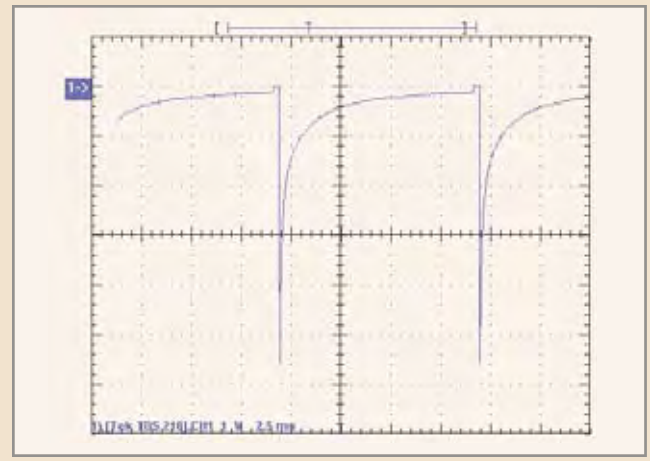

FIG. 11: 500 Ohm Resistive Load

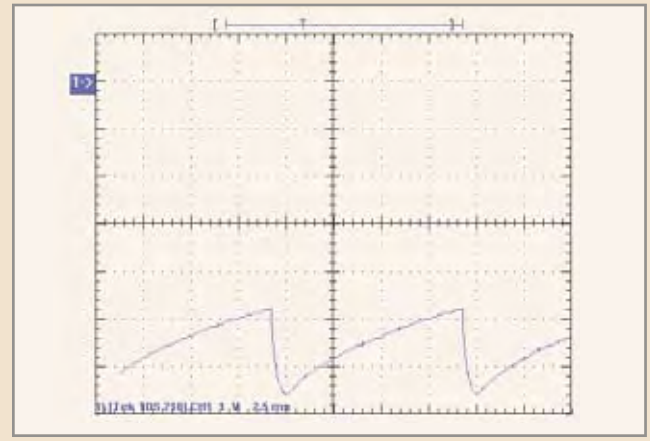

FIG. 12: Patient as Resistive Load

BioniCare waveform at all, and certainly cannot be compared in terms of efficacy. Thus, it is not surprising that the PES used in the study by Fary et al does not demonstrate effectiveness in any of the outcome measures they utilized. Moreover, one cannot draw a valid conclusion regarding treatment effect for the patient VAS pain outcome from the Fary et al study because of the high placebo response. The investigators in the Fary et al study acknowledge this problem and note that some of the patient characteristics in their study have previously been demonstrated to contribute to a high placebo response. Fary et al state that it is the subthreshold administration of the PES that equates their signal administration to that of BioniCare. With respect to a TENS device, Dr Donlin Long demonstrated that in 150 patients treated at The Johns Hopkins Pain Treatment Program, subthreshold or subsensory TENS was no better than placebo.[41] This is precisely what Fary et al have confirmed. The Fary et al study does prove that the device they utilized is not effective in treating OA. However, the conclusion that their study in any way reflects on the effectiveness of the BioniCare device is flawed. The two devices are too different to compare. ■

Health Care Value and Economic Implications of the VQ BioniCare® OActive Brace

Assessing value in health care: Michael Porter recently defined the value in health care in this way: Value = the outcomes across the total episode of care, including measurable benefits and risks / the aggregate costs of care.[48] Any care that improves long-term outcomes and safety increases value, whereas unnecessary care or higher than necessary costs reduce value.

In the case of chronic diseases including OA, the episode of care covers years to decades from the onset of symptoms to the life-long maintenance of a TKA, and includes multiple modalities used to reduce patients' symptoms and improve their function. The duration of benefit is also critical to assessing value since short-term benefits are of minimal value in chronic diseases. Finally, the costs of adverse events must be factored into the denominator.

Value of NSAIDs, visco-supplements, TKA surgery, and the VQ BioniCare OActive brace: Currently prescribed nonsurgical treatments for knee OA do not provide high value for the disease population in that outcomes for many patients are inadequate, and costs multiply over time. NSAIDs and injectable visco-supplements have low effect sizes, often provide only short-term relief, and over time generate a burden of adverse effects and costs. The outcomes of TKA are generally excellent and sustained, but many patients are not candidates, and complications, durability, and costs compromise the value of this modality.

The high value of the VQ BioniCare OActive brace differentiates it from other noninvasive treatments for knee OA. Unloading braces by themselves are effective and safe, but are seldom tolerated over the long term. However, the VQ customized unloading brace is well tolerated for months at least, and not only provides early relief of symptoms and joint stability, but also supports the application of BioniCare PES device. The high value of BioniCare PES is derived from its cumulative impacts on therapeutic effect size, its sustained benefit after 3 to 12 months of time compliant use, its safety, its reasonable cost over the disease episode, and TKA deferrals. Moreover, the device can be reapplied with similar benefits should symptoms recur.

Potential savings from TKA deferral: In 2003, the costs of hospitalizations for total knee replacements in the United States were estimated at $12.8 billion.[49] In 2005, Milliman Global produced an actuarial analysis of cost savings for Medicare patients who would defer TKR through treatment with the BioniCare device that documented potential net savings of approximately $400 million per year over a 4-year period.[50] They estimated that 1.7% of the Medicare population would meet the criteria for inclusion in the target population, namely Medicare beneficiaries with moderate to severe osteoarthritis of the knee who have received a recommendation for total knee replacement from one or more orthopedic surgeons.

As large as the savings projected were in the Milliman study, they were clearly underestimated for these reasons at least:

- Milliman based their cost projections on 2002 data and costs for TKA and related rehabilitation. These have clearly increased over the past 9 years.
- Projected savings from TKA deferral in that analysis only considered surgery costs. They did not include the savings from reduced drug usage or the adverse effects of drugs and TKA.

Since the Milliman report, the study by Farr et al reported that 18% of BioniCare patients discontinued all pain/arthritis medications as a result of successful BioniCare treatment, and another 25% reduced their use of these drugs by 50% or more.[17] This would reduce both medication costs and those of medication-related side effects. A 1998 Stanford-based study reported 107,000 hospitalizations and 16,500 deaths per year from gastrointestinal complications of NSAIDs.[51] The estimated cost was $5 billion per year for these complications, mostly in elderly (Medicare) patients. The drug reductions and discontinuations from BioniCare treatment would generate over $1 billion of savings to the health care system, even though the other major complication of these drugs, kidney disorders, including renal failure, although well recognized, were also omitted in this report.

The adverse effects associated with unilateral primary TKA were studied in 124,986 Medicare beneficiaries from 2000.[52] The complications observed during the 90 days following surgery included mortality (0.7%), readmission (0.9%), pulmonary embolism (0.8%), wound infection (0.4%), pneumonia (1.4%), and myocardial infarction (0.8%). In that same year, 11,726 Medicare beneficiaries underwent revision total knee replacement. There were even more complications observed during the 90 days following revisions: mortality (1.1%), readmission (4.7%), pulmonary embolism (0.5%), wound infection (1.8%), pneumonia (1.4%), and myocardial infarction (1.0%).[52] ■

Conclusion

It is clear that by combining the BioniCare device with the OActive unloading brace, patients receive substantial improvement much more quickly. Thus, patients are more likely to stay on the device for sufficient time to achieve "overall improvement of the knee." Indeed the dramatic and rapid improvement should result in greater compliance and a greater ability to defer total knee replacement surgery. ■

Registry Sites

Theresa Lawrence Ford, MD, Shaili Deveshwar. MD,
Craig M. Mines, MD, Mitchell B. Sheinkop, MD,
Joy Schechtman, DO, John R. Principe, MD,
Chadwick Prodromas, MD, David Mandel, MD, C.V. Mehta, MD,
Bhavesh Gandhi, MD, Jorge Minor, MD, Brian McKinley, MD,
Todd Schwartz, MD, Swamy Venuturupalli, MD

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