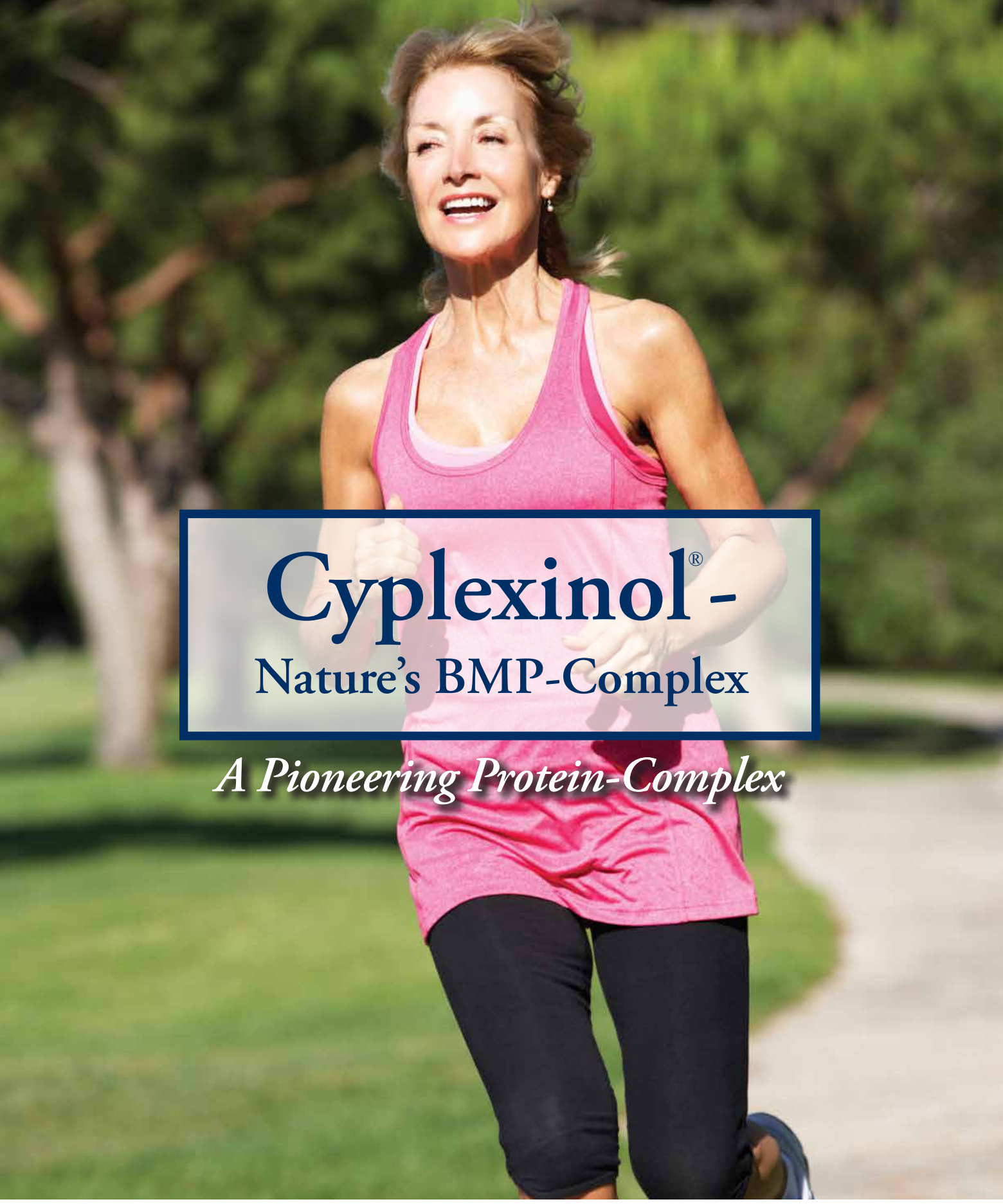

Cyplexinol®-
Nature's BMP-Complex

A Pioneering Protein-Complex

ZyCal Bioceuticals Healthcare Co.
Leaders in Natural Bio-Active Proteins

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Nature's BMP – Complex

Cyplexinol® - Nature's BMP-Complex

A Pioneering Protein-Complex

by Melissa Kvidahl

According to the National Osteoporosis Foundation, about 44 million Americans either have or at risk of osteoporosis, a systemic skeletal disease characterized by a loss of minerals and bone tissue, resulting in an increased risk of bone fracture. Additionally, 66 million Americans have some form of degenerative joint disease, of which one-third have osteoarthritis. Combined, these two conditions represent 110 million Americans, or one out of every two adults, suffering from a bone or joint problem. As the youngest of the 78 million Baby Boomers turns 50 years old this year, they reach a problematic milestone. Data shows about half of women and one-fourth of men over the age of 50 will eventually break a bone due to osteoporosis. Many will find it difficult to get around well into adulthood to do the things they enjoy and live a full and active life.

The good news is that consumers are looking to dietary supplements to help them achieve lasting vitality. In fact, according to Global Industry Analysts, the global bone and joint health market is expected to reach $9 billion by 2017. The troubling news is that many supplements on the market targeted for bone and joint health mask unpleasant symptoms but do nothing to solve the problem of degenerating tissue.

"In the bone space, you'll find calcium as well as vitamin and mineral blends. In the joint space, you'll find glucosamine, chondroitin, hyaluronic acid, and one or two others," said James J. Scaffidi, DNMc, BSc, chief executive officer and president of ZyCal Bioceuticals Healthcare Co., Inc. "But when it comes to bone health, minerals and calcium only stick to bone tissue—they don't regrow it. Similarly, many joint products may assist with aches and pains, and provide comfort by lubricating sore joints, but they aren't capable of growing new cartilage tissue."

But there is hope. The key appears to lie in bone morphogenetic proteins (BMPs), which naturally stimulate bone and cartilage tissue growth in the body by binding to and stimulating mesenchymal stem cells and activating their genetic expression. "These proteins have transcriptional abilities—or the ability to turn on other BMPs in the stem cell so that the stem cell differentiates," Scaffidi explained. "It turns a mesenchymal stem cell into an osteoblast which makes bone tissue or a chondrocyte which produces cartilage tissue."

This process of generating new tissue when proteins stimulate and transform stem cells is called osteoinduction, and the only oral supplement ingredient that contains these BMPs in their natural form is Cyplexinol.

Proven Results

Osteoinduction is a term coined in the 1960s by an orthopedic surgeon, Marshall Urist, M.D., while on a quest to discover how bones regenerate. Dr. Urist removed all of the mineral and cellular components in bone and was left with a new protein complex. When he mixed this protein complex with mesenchymal stem cells (MSCs), the stem cells were transformed, or morphed, into osteoblasts and chondrocytes, producing *de novo* bone and cartilage tissue. He called this protein complex "bone morphogenetic proteins" and the autoinduction of bone he named "osteoinduction." This process has been extensively studied and applied in medicine and healthcare ever since.

It was in the early 1990s that Dr. Urist's discovery was introduced into orthopedic surgery. "If you went skiing and broke your arm, for example, the surgeon would open the skin and apply the BMP-complex directly on the bone to stimulate new bone tissue growth. Similarly, the complex was used successfully for spinal fusion," Scaffidi said, "and became the gold standard for fusion."

"While direct application of the complex worked for fusion, we wondered how well a small, daily systemic form of the complex would work for bone and joint health," Scaffidi said. "We found we could extract this BMP-complex from an animal source, administer it systemically as a natural supplement and it will support bone and cartilage health—both through tissue growth and healthy signaling for people with inflammation." For the past 10 years, this ingredient has also enjoyed a reputation as the safe and effective oral supplement known as Cyplexinol® - Nature's BMP-Complex.

One recent study published in *Integrative Medicine: A Clinician's Journal* intended to demonstrate the clinical effects of Cyplexinol alongside glucosamine and chondroitin in healthy individuals with degenerative joint disease due to osteoarthritis (OA).[1] Researchers sought to examine the increase in joint flexibility and reduction in pain.

Researchers recruited 18 women and 10 men with a mean age of 61 years, and administered a combination of 150 mg/d Cyplexinol plus 1,500 mg/d glucosamine sulfate and 1,200 mg/d chondroitin sulfate. After four weeks, the research team noted a significant reduction in overall pain (54.7 percent) and frequency of pain (58.8 percent), per visual analog scale. Similarly, a significant reduction in pain and stiffness was reported during activity as participants moved affected joints.

Next, researchers studied Cyplexinol to measure its safety as well as its ability to relieve pain and stiffness in participants with moderate to severe OA.[2] This randomized, double blind, placebo-controlled study involved 87 participants aged 55 years and older with OA-related joint pain in the hip or knee. Participants were administered 150 mg/d Cyplexinol or placebo for 12 weeks. At the end of the study, the Cyplexinol group reported a significant decrease in pain and stiffness and an increase in quality of life, per the Western Ontario and McMaster Universities Arthritis Index (WOMAC), with results seen as fast as seven days. The researchers concluded Cyplexinol at 150 mg/d was statistically more effective than placebo in improving joint discomfort in a weight-bearing joint (hip or knee). They also concluded Cyplexinol was a natural and safe option for joint health.

"Cyplexinol is safe because we are replacing what is missing in the body," Scaffidi explained. In 2006, the *Journal of Arthritis Research and Therapy* published findings that two of the proteins in Cyplexinol (BMP-4 and BMP-5) are decreased or missing in the synovial fluid of people with osteo- and rheumatoid arthritis.[3] Cyplexinol represents a breakthrough in molecular nutrition because it is the first and only protein which can replace what the body is missing through a safe and natural complex.

Building upon these findings as they relate to OA, a 2013 case study sought to explore Cyplexinol's effect on bone health.[4] The subject was a 59-year-old female, who had been using calcium and vitamin D supplements but continued to progressively lose bone mass. For about four and a half years, she underwent bone scans, which showed a progressive loss of bone mineral density (BMD). After taking calcium and vitamin D3 for 53 months, a regimen of 200 mg Cyplexinol twice daily was added. This regimen continued for nearly three years, from March 2009 through January 2012.

Additional bone scans during supplementation revealed statistically significant increases in bone density. After the eighth month of Cyplexinol, the subject's DEXA score increased by 8 percent correlating with a cessation of the 53-month history of bone loss. After the thirty-fourth month of Cyplexinol, the subject's DEXA score increased by 51.5 percent in BMD. Further, at the onset of treatment, the L4 vertebrae t score (used to demonstrate the number of units that bone density is above or below average) was at -3.0, indicating diminished bone health. After 34 months of treatment, that same vertebra's t score improved to -0.9, indicating normal bone density.

It is well-documented that Cyplexinol stimulates bone growth, where needed, over time; however, Cyplexinol is also capable of easing inflammation and producing clinical results in the short term.

Interleukin-1 (IL-1) is a protein that is responsible for inflammation. Its activation pathway includes spurring NF-kb as well as matrix metalloproteinases (MMP), which degrade cartilage and exacerbate inflammation. "Cyplexinol works at the beginning of this inflammatory cascade," Scaffidi said. "As it works on those pathways, there is a rapid onset of joint effects that can take place in as quickly as seven days."

Indeed, in one study, the earliest effect experienced by participants was a decrease in pain after taking 150 mg/d of Cyplexinol for one week.[2]

An Organic Source

Cyplexinol is derived from a natural, certified USDA organic bovine source. ZyCal Bioceuticals Healthcare Co. starts with closed herd cows, which are isolated from other cows and tested to confirm that there are no contaminants. One of several requirements to become certified organic is a confirmation that the grass the cows graze upon has been pesticide-free for three years. At the company's cGMP facility in New Jersey, Cyplexinol is extracted via a proprietary cold process to maintain bioactivity. "That is a patented product and process," Scaffidi said. "Every lot we produce is triple-tested by three independent labs: one for basic chemistry to be sure it's pure and safe; the second lab tests for metals; the third lab tests the bioactivity of every lot to be sure the Cyplexinol is bioactive and osteoinductive."

The facility is certified GMP by the Natural Products Association with an "A" rating.

In the study, researchers stated pro-inflammatory cytokines such as tumor necrosis factor α (TNF-α), IL-1 and IL-6 are often detected around joints affected by diminished tissue and are believed to be one of the causes of chronic pain and inflammation. The acidic environment that develops as a result of pro-inflammatory cytokines, as well as proteolytic fragments that accumulate around the affected joint, lead to the activation of growth factors such as BMPs. Once activated, BMPs begin to down-regulate both basal and TNF-induced expression of cytokines such as IL-1 and IL-6. Therefore, researchers said, BMPs act upon inflammatory processes, and the rapid decrease in pain that was observed for participants who were administered 150 mg of Cyplexinol is attributable to its immunoprotective effect of the BMP moiety within the complex.

Improvements that were observed in relation to joint stiffness and quality of life may also be attributable to BMP activity (particularly BMP-7), researchers added, which has been shown to improve the amount and quality of cartilage while shortening the amount of time it takes for cartilage to normalize. Researchers found that BMP-7 (one of the proteins within Cyplexinol) strengthens cartilage by stimulating proteoglycan synthesis in human osteoarthritic chondrocytes. Furthermore, BMP-7 acts upon articular tissues by upregulating chondrocyte metabolism and increasing the survival of chondrocytes, which are cells that play a major role in the cartilage-repair process.

In the end, researchers concluded that enhanced chondrogenic activity mediated by BMP-7 results in an increase in cartilage, synovial membrane and surrounding tissue. Similarly, BMP-6 (a component of Cyplexinol) has a stimulating effect on chondrocytes that leads to an increase in proteoglycan synthesis, indicating that both BMP-6 and BMP-7 play a vital role in the maintenance of joint integrity.

And because Cyplexinol is a natural BMP-complex—researchers have discovered that there are receptors in the gut for these proteins, allowing for a safe and natural replacement of what our bodies have stopped producing.

Synergy Today and Looking to Tomorrow

In addition to Cyplexinol's remarkable ability to stimulate tissue growth while decreasing inflammation, it also works well to optimize the efficacy of other bone- and joint-friendly ingredients. "Cyplexinol does not replace calcium for bone or glucosamine/chondroitin for joints," Scaffidi said. "But if there is no bone tissue to which the calcium can adhere, it can't do its job. Cyplexinol works on a molecular level that other nutrients can't reach because it is the only ingredient which can turn on those stem cells to create new, healthy tissue."

Cyplexinol's ability to work synergistically is important. As noted earlier in the study published in *Arthritis Research & Therapy,* scientists agree that people with OA and RA are missing the bioactive proteins found in Cyplexinol in their joints. Regardless of the cause—whether it's environmental, nutritional, genetic, epigenetic, toxins or something else—the bioactive proteins necessary to activate the stem cells for regeneration are not produced in these individuals, leading to a breakdown in bone and joint health. Cyplexinol replaces these missing bioactive proteins and results in *de novo* bone and tissue growth.

Going forward, the future of Cyplexinol will include exploring new applications through research. "Applications for GI health, nerve function, muscle growth, post workout recovery and beauty from within are already supported in the literature," Scaffidi said.

*Zy*Cal Bioceuticals is already working on a sister ingredient to Cyplexinol called 2-Beta Coxatene™. "It contains a low-dose of Cyplexinol, combined with *Boswellia serrata,* its most active ingredient, enriched to 65-percent 3-O-acetyl-11-keto-beta-boswellic acid (AKBA)," Scaffidi said. "It's a proprietary blend with synergistic effects shown to produce clinical response in seven days as it pertains to joint health by acting on the seven pathways of inflammation. 2-Beta Coxatene™ will be an ideal product for retail brands, multi-level marketing companies and direct-response companies who are looking for a clinically tested ingredient, with rapid results which offer a costing profile more in line with those businesses," Scaffidi said.

"Cyplexinol is well-researched for bone and cartilage growth, and we remain focused on that application," he concluded. "But we are also beginning to branch out into new applications, partnerships, and research to determine where it can go in the future."

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