



NATURE  
FORMULATES  
AMAZING  
THINGS

# METABOLIC ARTHRI BENEFITS™



SIMPLY FORMULATED  
**TO DELIVER MORE**

Joint health is one of those topics that doesn't often come up until a patient has experienced his or her own joint issues. When that happens, it can be difficult, too, to pin these issues to a direct cause.

For years, obesity has been implicated in joint dysfunction and discomfort for the undue pressure excess weight may place on the joints. But now, researchers have discovered that leptin, a peptide hormone and adipokine associated with obesity, may actually play an important role in the degradation of cartilage.<sup>1</sup> In fact, several links between adipokines like leptin and bone and joint health have been described.<sup>2</sup>

Knowing that both metabolic health and joint health are affected by certain cytokine activity, we can infer a connection. This paper will help to elucidate the connections between joint health and metabolic health, specific especially to C-reactive protein (CRP) and leptin, and help you discover the best way to provide the metabolic joint support your patients are looking for.\*

## **REVIEWING LEPTIN'S RELATIONSHIP WITH OBESITY AND JOINT HEALTH**

Leptin is a hormone secreted by adipocytes. This adipokine has varied and numerous effects on the body. It plays regulatory roles in immune system and reproductive system health, and is known for its effects on appetite. Leptin is not, it is important to note, an inherently "bad" hormone. But as is the case with any bodily substance or process (estrogen, metabolism, free radicals), balance is essential.

In normal-weight patients, leptin signals for the body to decrease food intake. But leptin resistance is a hallmark of obesity, as obese individuals are found to have increased levels of the hormone.

For many years, the mechanical aspects of obesity were blamed for joint health concerns – and that makes sense. It's obvious that there are mechanical aspects of obesity's association with osteoarthritis (for example), because our knees, hips and low back have a lot of work to do, including weight bearing. However, the existence of biochemical mechanisms behind joint health concerns are made obvious by the fact that non-weight bearing joints, like fingers, also display both pain and high leptin levels.

Given that we know leptin levels are high in the obese body and we know that fat tissue is complicit in joint health, we can look at whether or not leptin impacts cartilage degradation - and if so, how.<sup>3</sup> First, it's important to understand that the link between leptin levels and metabolism has been shown in various contexts; for example, researchers have found that synovial fluid (SF) leptin levels correlate significantly with both BMI and waist circumference.<sup>4</sup>

That correlation matters because we know that metabolic health can be affected by inflammation, that leptin correlates with metabolic parameters like waist circumference, and that leptin resistance is present with obesity. It stands to reason that a connection between leptin and inflammation may exist. In fact, studies have shown that leptin actually acts as a pro-inflammatory adipokine that upregulates proteolytic enzymes, working in synergy with other pro-inflammatory stimuli.<sup>5</sup>

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Leptin increases the production of cytokines such as TNF- $\alpha$ , IL-6 and IL-12, and can stimulate the production of interferon (IFN)- $\gamma$  and IL-2 in T lymphocytes.<sup>6,7</sup> Leptin may also induce Th1 phenotype development.<sup>8</sup>

It has also been identified as relevant to the immune system and to joint concerns, like rheumatoid arthritis, associated with immune function. It is posited that “leptin could be a member of the cytokine network managing the inflammatory immune response and host defense mechanisms.”<sup>9</sup>

This is where leptin’s connections with C-reactive protein come to light.

## **WHAT IS THE RELATIONSHIP BETWEEN CRP AND LEPTIN?**

We now know that several studies have brought clarity to leptin’s involvement in the pathogenesis and progression of serious joint health concerns. But how is CRP involved?

A protein found in the blood plasma, C-reactive protein is known to increase in response to the secretion of interleukin-6 by macrophages and T cells. It is also synthesized by the liver in response to factors released by macrophages and adipocytes, such as leptin. CRP also plays an important role in innate immunity.

Researchers have described how chronically elevated CRP positively correlates with both adiposity and leptin levels. Now, evidence suggests that circulating CRP may actually contribute to leptin resistance through impairment of leptin signaling.<sup>10</sup>

So we see that the levels of leptin and CRP circulating in the body are linked, not just through leptin’s stimulation of hepatic and vascular CRP expression, but also through CRP’s own potential effects on leptin signaling.

To review: There is innate complexity in the relationship between plasma leptin and plasma CRP levels. Leptin is able to modulate CRP expression levels both indirectly and directly (through action on molecules like IL-6 and through vascular and hepatic production, respectively).<sup>11</sup> CRP may help to regulate the bioavailability of circulating leptin in an interaction that impairs leptin’s ability to bind to its receptor.<sup>12</sup>

## **WHY HEALTHY REGULATION OF CRP AND LEPTIN MATTERS**

While there are extensive data to point to a relationship between the cardiovascular system and leptin and CRP, we won’t dive into that now – though the relationship between metabolic and cardiovascular health is an important facet of the conversation.<sup>13</sup> Here, though, we will focus on joint health: knowing the relationship between CRP and leptin, we can examine the impact of just one of these factors and assess how their interplay is likely to impact the process of cartilage degradation.

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Researchers have found that leptin stimulates some of the key mediating agents in cartilage degradation, such as the aforementioned interleukins. Further, the primary proteinases involved in the process of cartilage turnover include metalloproteinases – of which leptin is a known modulator.<sup>14</sup> In fact, in “Leptin produced by joint white adipose tissue induces cartilage degradation via upregulation and activation of matrix metalloproteinases,” researchers have clearly displayed the connection between leptin and cartilage degradation, concluding that:

“Leptin acts as a(n)...adipokine with a catabolic role on cartilage metabolism via the upregulation of proteolytic enzymes and acts synergistically with other...stimuli. This suggests that the infrapatellar fat pad and other WAT in arthritic joints are local producers of leptin, which may contribute to the inflammatory and degenerative processes in cartilage catabolism, providing a mechanistic link between obesity and osteoarthritis.”<sup>15</sup>

It is evident, then, that should we want to support both joint health and metabolic balance, addressing both leptin and CRP regulation is an intelligent choice.

## **HOW TO SUPPLEMENT FOR CONCOMITANT METABOLIC AND JOINT HEALTH CONCERNS**

Joint support aimed specifically at patients who also work to support healthy metabolic functions is a novel approach to musculoskeletal supplementation, but given the above information, one worth consideration.\* Metabolic Arthri Benefits™ is an industry first: it provides the highest level of joint support while taking into account the cross-linking mechanisms that extend to metabolic health.\* With two branded ingredients, Perluxan® and Oralvisc®, Metabolic Arthri™ offers support for both joint health and leptin levels.\*

OralVisc® acts using HA-Leptin (a hyaluronic acid preparation). The combination of glycosaminoglycans (GAGs) in HA-Leptin has demonstrated both anti-adipogenic and pro-chondrogenic effects in in vitro studies. In animal studies, obese rats treated with Oralvisc® showed a higher fat loss, reduction in leptin levels and greater insulin sensitivity.<sup>16</sup> Further, this preparation has been studied in humans for its relationship to pain experienced by obese, knee osteoarthritis patients. The results showed that Oralvisc® supports normal leptin levels in the synovial fluid, as well as normal joint function.\*<sup>17</sup>

The study outlined the application of Oralvisc in a patient base with concurrent obesity and structural changes in the knee joints. This was a double-blind, randomized, placebo-controlled study of 40 subjects over a period of 3 months. Visual analog scale, Western Ontario McMaster pain, and WOMAC function scores were recorded. Serum and synovial fluid were measured by enzyme-linked immunosorbent assays for cytokines, bradykinin, and leptin. Both serum and synovial fluid samples showed significant decreases for a majority of cytokines, leptin and bradykinin in the oral hyaluronic acid preparation group. Heavy water analyses revealed a significant decrease in hyaluronic acid turnover in the synovial fluid of the treatment group.<sup>18</sup>

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In 2013 51 symptomatic knee osteoarthritis (OA) patients were recruited sequentially at the time of an outpatient visit for OA documented by either MRI or radiograph. Subjects were between the ages of 50-75 years, had knee effusion, and marked their own pain visual analog scores (VAS) >50mm on a 10 cm line. There was a significant decrease between the initial and final serum and synovial fluid leptin levels in the Oralvisc® group ( $p>0.05$ ) as measured by immunoassay. There was also a significance decrease in the Oralvisc® serum and synovial final leptin levels as compared to placebo. There was no significance in the relationship of BMI or metabolic syndrome scores to initial or 12 week Oralvisc® usage to leptin levels. However, the Oralvisc® group lost an average of 0.55 kilograms compared to a 0.75 kilogram weight gain in the placebo group over the 12 wks. These data were as yet unpublished, but were presented to attendees at the ORS 2013 Annual Meeting.

In the past, scientists and clinicians believed HA only worked through supporting synovial fluid thickness. However, we now know that it can be incorporated into cartilage to support chondrocyte metabolism stimulation and cartilage reparation mechanisms.\* The vitamin C in Oralvisc® also supports both energy metabolism and healthy cartilage function.\*

Perlucan® is a well-known joint comfort and function support supplement.\* The formula includes a proprietary hops resin extract, standardized to contain high concentrations of alpha acids that have been clinically demonstrated to offer rapid support. Extensive research on the properties and abilities of Perlucan® has shown that it supports normal expression of the COX-2 enzyme and only moderate inhibition of the COX-1 enzyme, indicating it may be ideal for patients concerned about GI distress.<sup>19,20</sup>

Another demonstration of the impact that Perlucan can have on joint health was from a A double-blind, placebo-controlled randomized trial that evaluated the effects of 14 days of Perlucan oral supplementation.<sup>21†</sup> “Thirty-six subjects completed a questionnaire to evaluate joint comfort levels at baseline. The time to perform a 20-meter walk on a flat surface was also recorded. Study participants were then assigned to take either Perlucan or a placebo. On day 15, the time to perform a 20-meter walk on a flat surface was again measured and improvements in joint function were assessed. Results indicated Perlucan intake provided fast-acting relief; significant improvement over placebo could be measured only two hours after ingestion of the first dose.\* Perlucan significantly improved parameters of joint comfort, including relief while in bed, sitting, lying, and walking on a flat surface all of which are hugely impacted in patients in need of joint support.”<sup>22</sup>

Armed with the research concerning leptin, joint health and metabolic health, you and your patients can design the best supplement regimen to support their needs. Metabolic Arthri Benefits™ can help.

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# SUPPLEMENT FACTS

Serving Size 1 Capsule  
Servings Per Container 30

Amount Per Serving	% Daily Value	
Proprietary Hops Extract (cones) (Humulus lupulus L.)†	500 mg	*
ORALVISC® (proprietary, naturally occurring source of glycosaminoglycans (GAGs))	80 mg	*
*Daily Value not established.		

†The Perluxan® trademark is used with permission.  
Other ingredients: hypromellose (capsule), microcrystalline cellulose,  
vegetarian leucine.



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