Functional peptides

Osteoarthritis is becoming an ever increasing health care problem in both industrialized nations and the developing world. The cause of osteoarthritis is degradation of cartilage tissue in the joints, thus ensuing structural changes in adjacent bone, ligaments, the synovial capsule and the periarticular musculature, a pathophysiological process which eventually causes pain and restriction of motion. Osteoarthritis itself appears to be related to several factors. There is an ever increasing proportion of the population that is becoming overweight or obese and individuals living in Western societies increasingly adopt a sedentary lifestyle which both gives rise to and aggravates the symptoms of joint disease, thus reinforcing the vicious cycle of lack of physical exercise and obesity (1, 2). At the present time, there are about 20 million individuals living in the US who have been diagnosed with osteoarthritis. As the number of US citizens who are 50 years of age and older will double by the year of 2020, it is obvious that osteoarthritis will be an entity that both primary care physicians and orthopaedic doctors will increasingly be confronted with.

As other countries in the industrialized world are expected to experience similar demographic changes, we have to conclude that osteoarthritis will be the mushrooming epidemic of the future, representing a considerable burden for our health care systems.

THERAPEUTIC OPTIONS

The chief objective of treating subjects with osteoarthritis is to delay progression of the disease, which means that physicians usually, as a first line therapy, recommend physical exercise and weight loss to their patients. As patients with osteoarthritis are reluctant to adhere to physical exercise programs because of the pain they perceive, analgesic medication is the mainstay of pharmacological therapy for individuals with degenerative joint disease. Pain medication comprises non-steroidal anti-inflammatory drugs like ibuprofen, diclofenac and nabumeton, cyclo-oxygenase-2-inhibitors like rofecoxib or opioid analgesics like propoxyphone, codeine or oxycodon. One has to bear in mind that the drugs mentioned above merely constitute symptomatic treatment, providing relief of pain without affecting the pathological process of the underlying disease itself. Furthermore, non-steroidal anti-inflammatory drugs, unfortunately, are associated with the risk of gastrointestinal bleeding due to the genesis of ulcers in the stomach (3) and cyclooxygenase-2-inhibitors have been found to be associated with an increased risk of suffering a cardiac event (4).

Glucosamine is a chemical compound which – from the very beginning of being launched on the market more than 30 years ago – tried to establish itself as disease-modifying agent, thus reaching beyond the scope of symptomatic treatment. In some countries, glucosamine is classified as a drug, in others it is merchandized as a nutritional supplement. Glucosamine – chemically speaking - is one of the compounds of proteoglycans in cartilage tissue, which merely represent 25% of cartilage dry mass. Thus, from the experimental point of view, it is widely regarded as precursor for the synthesis of those particular macromolecules, allegedly reinforcing the morphological structure of articular cartilage.

From the perspective of clinical research, glucosamine – by some researchers - is considered as efficacious in the treatment of osteoarthritis, because in the medical literature there are two separate studies available showing that the ingestion of glucosamine is associated with radiological improvement of joint space narrowing in patients diagnosed with osteoarthritis (5, 6). Unfortunately, the research that has so far been carried out with glucosamine in the setting of osteoarthritis must be considered as incoherent, based on the fact that glucosamine studies were conducted with different types of glucosamine. Furthermore, both from the experimental and the clinical perspective, scientific results are inconsistent and inconclusive.

Glucosamine is considered to stimulate proteoglycan synthesis, however, it may be interesting to note that at the present time leading experts in the field of rheumatology in the US deny that the amount of glucosamine that reaches cartilage tissue is sufficient to stimulate the cartilage cells (7). There is an increasing number of glucosamine studies showing negative results (8) among which the most important study was the so-called GAIT study (Glucosamine Arthritis Intervention Trial) comprising 1583 individuals with osteoarthritis and demonstrating no difference between glucosamine and placebo (9). As more and more data are emerging, generally questioning the clinical usefulness of glucosamine for the indication of osteoarthritis, one has to bear in mind that the issue of toxicity associated with the intake of glucosamine has been neglected by both clinicians, patients and customers buying glucosamine products on an over-the-counter basis. A group of scientists in Boston (USA) was able to show that upon oral intake of glucosamine glucose tolerance in diabetic patients worsens, an effect which is probably mediated by interference with metabolic pathways in the liver, resulting in deterioration of insulin sensitivity (10).

A NEW CONCEPT – EXPERIMENTAL APPROACH

As neither pain medication nor glucosamine, although widely used, can adequately address the issues that need to be taken into consideration when providing treatment to patients with osteoarthritis, clinical researchers have been actively looking out for a new therapeutic principle that would embody a mode of action, which would provide experimental evidence on a molecular level, and that they could rely on based upon a large body of clinical data. In that context, FORTIGEL® – a special purified protein containing bioactive collagen peptides – is a new therapeutic approach for individuals with degenerative joint disease. FORTIGEL® is produced in a multi-step procedure by degradation of collagen of either porcine or bovine origin with an endo-enzymatic process in order to obtain specific bioactive collagen peptides (BCP).

As the degradation of collagen can be chemically defined as a process of hydrolysis, i.e. adding water to the specific enzymes that cleave collagen, FORTIGEL® is a special type of collagen hydrolysate.

Oesser et al. in an animal experiment were able to show that collagen peptides when ingested orally are absorbed across the mucosal barrier in a molecularly intact form (11). Interestingly, in another experiment involving mice that were administered radioactively labeled collagen peptides, the group demonstrated that 95% of the orally administered dose appeared in plasma after 12 hours, accounting for a high bioavailability. When chondrocytes that had been harvested from the shoulders of cattle and pigs were incubated with FORTIGEL®, Oesser was able...
to observe a dose-dependent increase in the synthesis of type-II-collagen and proteoglycans (12). See figures 1 and 2. Cartilage tissue is made up of cells, the so-called chondrocytes, that build up the extracellular matrix, consisting of type-II-collagen, i.e. fibrillar proteins, and proteoglycans, which represent macromolecules that form crosslinks between the collagen fibrils, thus stabilising the 3-dimensional architecture of cartilage tissue on a molecular level. Type-II-collagen constitutes 70% of the dry mass of cartilage, proteoglycans represent 25% and cartilage cells themselves together with a variety of other proteins like hyaluronic acid and other types of collagen like type-VI-collagen for instance make up the remaining 5% of dry weight. Consequently, the collagen peptides that FORTIGEL® consists of have an anabolic impact on 95% of dry cartilage mass. See figure 3. Apart from the in-vitro-experiments showing stimulation of bovine and porcine chondrocytes with bioactive collagen peptides, Oesser was capable to demonstrate that human cartilage cells are also stimulated by FORTIGEL®. In an experimental design, he incubated human cartilage cells that had previously been harvested from resected femur heads and confirmed the dose-response-relationship in human tissue.

CLINICAL RESULTS

Clinical research, regarding the beneficial effects of collagen hydrolysate, has been going on for the past three decades. In 1979, Krug (13) published data about 193 subjects who had been diagnosed with osteoarthritis in a variety of joints. In this open-label-study patients were given a daily dosage of collagen hydrolysate for a period ranging between 1 and 6 months. Krug was able to see that 75% of his patients reported improvement of symptoms. It was interesting to note that those patients who had been diagnosed with osteoarthritis of the lumbar part of the vertebral column became asymptomatic. In 1982, Goetz (14) recruited 60 individuals in whom a retropatellar form of osteoarthritis had been diagnosed. Collagen hydrolysate was administered to those patients for the duration of 3 months. During the study phase, findings like ability to climb up the stairs, soft-tissue-swellling, retropatellar rub and knee effusion were recorded. Goetz concluded from his study that after three months 52 subjects reported improvement of symptoms such as mobility and pain when climbing up the stairs. At the beginning of the study, out of the 60 patients that had been recruited, the physical finding of the retropatellar rub had been present in 58 subjects. After 1 month of administering collagen hydrolysate, that particular physical finding had disappeared in 47 out of those 58 individuals. In 1985, Oberschelp (15) published a study, comprising 154 subjects in whom the diagnosis of osteoarthritis of the hip, of the knee and of the lower spine had been established. Those 154 individuals were randomly assigned to three treatment groups. One group of patients were treated with physical therapy only, another group with physical therapy plus collagen hydrolysate and a third group with collagen hydrolysate only. Patients recruited for the study underwent treatment for three months. In order to assess the severity of symptoms during the baseline visit and at the end of the study phase, Oberschelp used a visual analogue scale. Thus, the changes of the severity of symptoms as numerically documented on the visual analogue scales and the comparison of the changes between the individual treatment groups were defined as endpoint of that clinical study. Interestingly, the results that Oberschelp obtained after evaluating the data revealed that the treatment of using collagen hydrolysate only was superior to the treatment of providing physical therapy only. At the end of the 1980’s, Adam (16) carried out a prospective, randomized, placebo-controlled, double-blind cross-over study by using the nutritional supplement collagen hydrolysate for the treatment of patients with degenerative joint disease of the knee or the hip. The results of that clinical trial revealed that 81% of individuals having been treated with collagen hydrolysate noticed improvement of symptoms whereas solely 23% of subjects taking the placebo had responded to treatment. Interestingly, the consumption of pain relievers diminished by 50% in individuals who had been assigned to the collagen hydrolysate group. From 1996 until 1998, Moskowitz (17) conducted a prospective randomized clinical trial by including 389 patients with knee osteoarthritis and assigning them to two treatment groups, i.e. 10 g of collagen hydrolysate a day versus placebo. Those 389 individuals participating in the trial were recruited in 20 medical centers, scattered across the US, Britain and the Federal Republic of Germany. Patients were given the nutritional supplement or the placebo for 24 weeks. The clinical endpoints of the study were pain, as measured according to the WOMAC score (Western Ontario Mac-Master Score), physical function and patient global assessment. When the data of the study were evaluated, Moskowitz was able to demonstrate statistically significant results in the German subgroup of patients (n = 112), whereas he failed to show statistically significant results in the US and the British patients. The reason for these contrasting results may be based on the fact that the drop-out-rate in the German subpopulation was extremely low, corresponding to 7%, while in the US and Britain it was unacceptably high, being equivalent to 42% and 37% respectively. Since most of the studies described above focused on subjective findings like pain, Rippe (18) decided to put into practice a rather different approach in clinical research regarding the nutritional supplement “collagen hydrolysate”. He selected objective parameters as clinical endpoints like isometric and isokinetic strength in order to verify changes of joint functioning that would be due to the ingestion of collagen hydrolysate.
Functional peptides

FORTIGEL® research has undoubtedly resulted in a clearer bioactive collagen peptides that FORTIGEL® consists of. This CONCLUSION hydrolysate can potentially improve their physical performance. The first study (19) to fulfill the criteria of a primary-prevention-effort was a clinical trial performed with young and healthy athletes who were active in varsity or club sports at Penn State University in University Park (Pennsylvania), USA. In that clinical trial, 147 athletes were recruited and randomized into two treatment groups, i.e. either consumption of 10 g of collagen hydrolysate a day or ingestion of a placebo for 24 weeks. The inclusion criterion that the athletes had to fulfill in order to participate in the study was activity-related joint pain. The diagnosis of osteoarthritis was considered an exclusion criterion. Joint function like pain or mobility was evaluated on a visual analogue scale during the study phase. Interestingly, as far as joint functioning was concerned, collagen hydrolysate was shown to be superior to the study phase. As far as joint functioning was concerned, collagen hydrolysate was shown to be superior to placebo.

Thus, Rippe carried out a prospective, randomized, placebo-controlled double-blind study by recruiting 250 patients suffering from a mild form of osteoarthritis of the knee. The patients were subdivided into two groups, one group of patients receiving 10 g of collagen hydrolysate and a control group obtaining a placebo. As far as those biomedical parameters like isokinetic and isometric strength were concerned, significant improvement could be noted in favor of collagen hydrolysate when the two groups of patients were compared after a study phase of 14 weeks had elapsed. All the studies mentioned above refer to the concept of a secondary-prevention-effort, which means that the individuals included in all those studies had already been diagnosed with degenerative joint disease before they started taking collagen hydrolysate.

The study showed improvement of joint-functioning in healthy subjects taking collagen hydrolysate, an aspect which clearly reflects a therapeutic effect from the perspective of primary prevention. The results of the study also suggested that athletes consuming collagen hydrolysate can potentially improve their physical performance.

CONCLUSION

All the studies, mentioned so far, have been performed with those bioactive collagen peptides that FORTIGEL® consists of. This aspect must be emphasized as there are various types of collagen hydrolysate available that in in-vitro-stimulation studies differ in their capacity to stimulate chondrocytes. The degree to which extent a particular type of collagen hydrolysate can currently stimulate or – in the worst case – fails to stimulate cartilage cells can be determined with specific methods offered by the Collagen Research Institute, which is situated in Kiel (Germany).

What we are able to conclude from the experimental and clinical findings described above is that there is a rapidly expanding knowledge about the effects that FORTIGEL® exerts on joint health. FORTIGEL® research has undoubtedly resulted in a clearer perception of pathophysiological processes that occur in the extracellular matrix of cartilage. Based on the experimental findings showing anabolic effects in cartilage tissue, the clinical application of FORTIGEL® has opened up new avenues to provide adequate treatment to individuals suffering from degenerative joint disease.

REFERENCES