Collagen Hydrolysate and its Relationship to Joint Health

A Scientific Compendium

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Health Initiative

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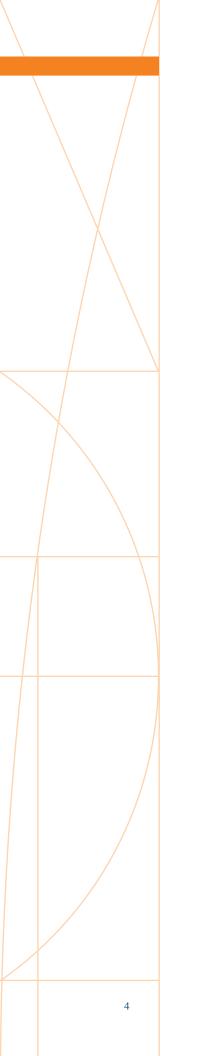 Rippe Lifestyle Institute, Massachusetts, USA

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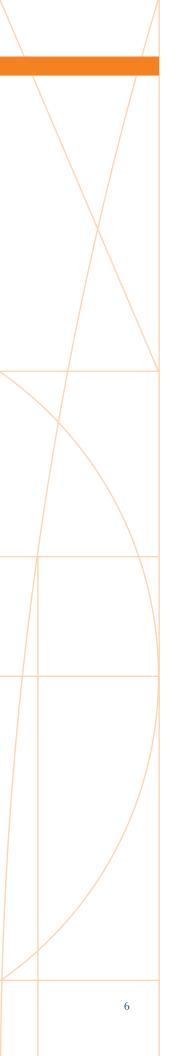 University of Kiel, Germany

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Content

Foreword

Roland Moskowitz, M.D.

Collagen is a vital component of structural matrix throughout almost all tissues and organs of the body [1]. It is particularly concentrated in skin, bone, tendons and cartilage where it plays a major role in the integrity of joint-related connective tissues. Studies reflect a relationship with collagen not only to normal healthy joint metabolism, but also to collagen-related alterations related to the aging process [2-4]. Increased formation of advanced glycation end-products (AGEs) leads to significantly accelerated collagen cross-linking with increased susceptibility of cartilage to degenerative change in response to mechanical and nutritional stimuli. Collagen alterations also play a role in osteoarthritis wherein alterations in collagen structure result from an imbalance in synthesis versus catabolism with resultant articular hyaline cartilage breakdown1. The importance of normal collagen structure is vividly seen in the severe generalized arthritis associated with collagen gene mutations [5; 6].

Studies support a role for dietary collagen hydrolysate in maintaining healthy joints by nutritional support mechanisms; proline may be a dietary indispensable amino acid [7]. Studies by Oesser *et al* [8] which demonstrated a preferential uptake of ^{14}C-labelled proline suggest nutritional advantages to the use of collagen hydrolysate as a source of structurally important amino acids. Studies indicating that preexisting collagen might be translocated and utilized to form "new" fibrous tissue would support a role for exogenously administered collagen hydrolysate which might be utilized in an undigested form [9]. Of particular interest are recent studies which demonstrated stimulation of type II collagen biosynthesis by collagen hydrolysate [10]. In these studies, bovine chondrocytes were exposed to culture media with and without collagen hydrolysate. Utilizing immunocytochemical methods, it was demonstrated that type II collagen synthesis was stimulated in the presence of the collagen hydrolysate. It is postulated that collagen hydrolysate would accordingly add to anabolic reparative responses.

Given the importance of collagen to joint-related connective tissues, and experimental data which support nutritional advantages to the use of collagen hydrolysate as a source of structurally important amino acids, clinical trials have been performed to assess the efficacy of collagen hydrolysate in the maintenance of normal articular structure, prevention of joint breakdown/dysfunction, and relief of symptoms related to joint degenerative change (osteoarthritis). A number of studies described in this Scientific Compendium report a salutary efficacy and a high safety profile associated with administration of collagen hydrolysate in osteoarthritis [11-16].

In a multi-national study, the effectiveness of pharmaceutical grade collagen hydrolysate (PCH) in decreasing osteoarthritis pain was evaluated in a randomized, double-blind placebo-controlled trial involving 389 patients randomized in twenty sites; six in the United States, three in the United Kingdom, and eleven in Germany [16]. Results revealed no statistically significant differences for the total study group (all sites) between treatments in the intent-to-treat (ITT)

analysis for the differences of the mean score for pain, physical function, or patient global assessment. There was, however, a meaningful statistically significant treatment advantage of PCH over placebo for pain and physical function, and a trend to significance in patient global assessment in the German sites. Explanations for these observed variations in response between the United States/United Kingdom and Germany may include differences in diagnosis and recruitment between sites; differences in principal investigators (rheumatologists in the United Sates/United Kingdom sites; orthopedists in the German sites); nutritional differences in the overall diet in these countries with respect to intake of collagen hydrolysate-containing products; differences in the drop-out rates; and differences in metabolic responses amongst various ethnic populations.
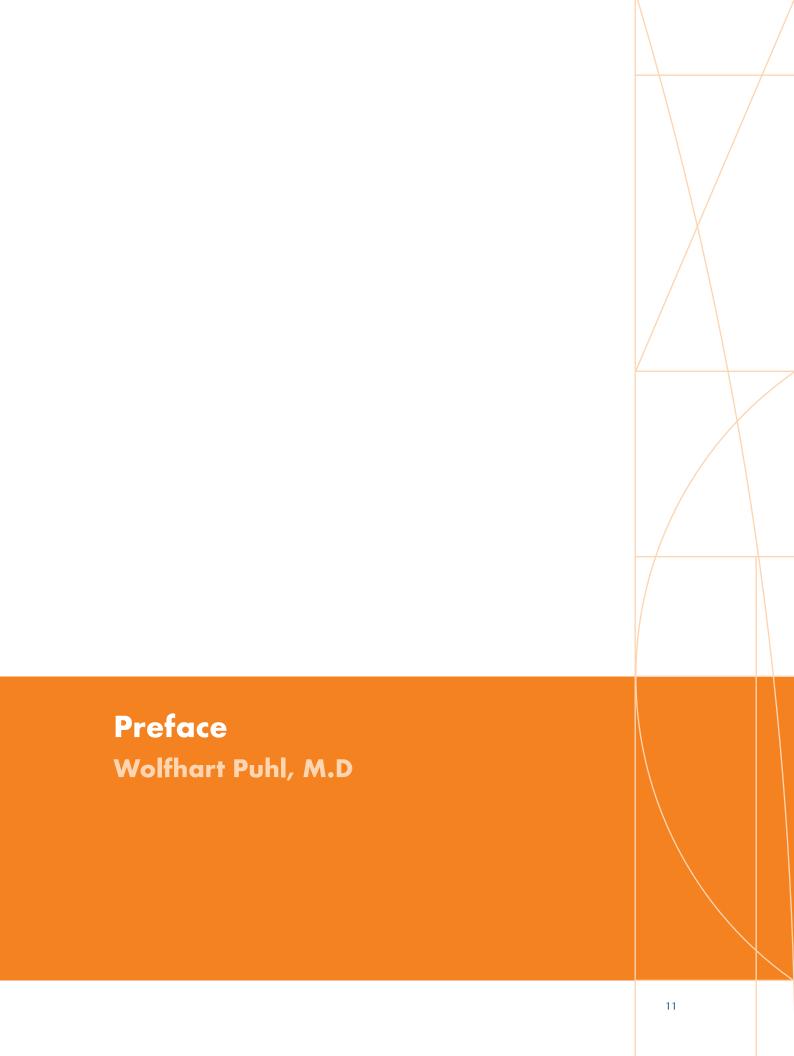
In summary, collagen, a vital component of normal extracellular matrix, is of particular importance in joint tissues where it is found in high abundance. Maintaining normal collagen integrity in bone, cartilage, tendons ligaments and joint capsular tissues is vital to maintaining joint homeostasis. The availability of collagen hydrolysate administered orally to provide amino acids important to collagen synthesis would support a role for collagen hydrolysate in general body nutrition. Demonstration that collagen hydrolysate stimulates chondrocyte collagen synthesis provides further biologic support for clinical observations of collagen hydrolysate efficacy. In addition to basic studies, which demonstrate an effect of collagen hydrolysate-related amino acids on tissue structure, clinical studies suggest beneficial responses with respect to symptomatic improvement in patients with osteoarthritis.

Collagen plays a significant role in normal joint architecture; an imbalance in synthesis and degradation due to relative deficiencies in nutrition may allow degradative catabolic processes to be overbalanced leading to joint degeneration. Collagen hydrolysate administration would be of potential merit for use in individuals at risk for development of joint degeneration. Such at-risk populations include older individuals; individuals who are overweight; individuals whose occupational or sports activities predispose to osteoarthritis; individuals with a past history of significant joint injury; and individuals with a family history suggesting a genetic predisposition to osteoarthritis [17]. The high safety profile of collagen hydrolysate would make it especially attractive as a nutritional supplement for use over many years in such individuals in the prophylaxis of joint degeneration, as well as an agent with potential for therapeutic benefit in the active treatment of osteoarthritis. Additional ongoing studies of its mechanisms of action on joint tissues, and clinical responses, will further define its role in the prophylaxis and treatment of degenerative joint disease.

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Preface

Wolfhart Puhl, M.D

Is it useful to collate knowledge about the syndrome of osteoarthritis?

Yes – and the more we go into this condition, its individual and economic importance, the chances for therapy and also unfortunately the problems of therapy, the more we will see the problem of osteoarthritis and also recognize opportunities in prevention and therapy.

What we so naturally refer to as "osteoarthritis", as if it were a single disease, will very soon have to be recognized as a group of diseases with different etiologies but which correspond greatly in their course and in particular in their final appearance.

When we speak of "secondary osteoarthritis", we mean those cases whose origin we can explain. When we talk about "primary osteoarthritis", we do not know the mechanisms by which it develops. Through research, this group is getting smaller, and perhaps it will disappear completely some day.

The word "arthrosis" used in the German-speaking countries communicates the information that this is a degenerative disease. In the Anglo-American regions, in contrast, the term used is "osteoarthritis". This designation makes it clear that while this joint condition is characterized fundamentally by degenerative changes in the joint cartilage, the pathological and thus naturally also the clinical picture is characterized episodically by inflammation.

This inflammation arises secondarily, to a certain extent as an epiphenomenon, because of the destructive process in the joint cartilage, and the destruction may also be due to this. The avascular joint cartilage cannot react with inflammation, it can only show the picture of degenerative changes. With its destruction, mediators are released which reach the joint capsule (synovium) through the joint fluid (synovial fluid) where they are able to induce inflammation (synovitis).

As the joint cartilage does not possess any nerves, early joint cartilage lesions are not associated with the early warning symptom of pain.

The synovitis which sometimes occurs in the early stage thus leads to an "osteoarthritis picture", often with the symptoms of capsule swelling, capsule pain and swelling of the joint due to effusion, although there is a primary degenerative joint disease.

Osteoarthritis often develops silently and insidiously, it is initially not a dramatic event for a person and does not threaten his life, or at least not directly. These are the reasons why it was for a long time overlooked that osteoarthritis has become a real large-scale disease, which can affect the fate of the individual affected and is an ever-increasing economic problem for the community.

Joint health is an essential requirement for mobility, and mobility is a requirement for our overall health, so immobility for example signifies a high risk for

the function of internal organs and organ systems. Furthermore, the immobile person will tend to become overweight, leading to further hazards and injuries.

In addition, immobility sets in train a disastrous series of interactions for the joint, as the joint cartilage, which we assume to be damaged when we are considering osteoarthritis, is an avascular tissue that receives its nourishment through diffusion and needs movement and intermittent pressure for optimum health. Immobility on its own can cause joint damage.

Our (German) health system databases are sparse but a few figures can show the importance that the syndrome of osteoarthritis holds for the individual and society: In America, one person in three complains of joint pains and 30-40% of Germans over the age of 50 years report that they have pain in the hip and/or knee. Often the complaints are so severe that only operative treatments can help. Thus (in Germany), about 250,000 patients underwent ambulant arthrscopy in 1999, and almost 300,000 further patients were treated as inpatients. With more severe symptoms, painfree walking can be made possible again by implantation of an artificial hip. More than 170,000 patients received an artificial hip replacement in 1999 while a further 70,000 had a knee replacement.

In the ambulant area, 700 million € were spent in Germany on the costs of medical treatment because of osteoarthritis and arthritis, and prescribed medications cost a further 500 million €. In hospitals, approximately 4.7 million days of hospital care cost 1700 million, with a further 1000 million € for inpatient rehabilitation.

The diseases under discussion rarely cause death but as chronic diseases they have substantial financial significance because of unfitness for work and early retirement. When the cost situation and economic importance of osteoarthritis are considered, along with the direct costs, the indirect costs in particular are of great significance. Projections for 1999 assume that 9 million working days will be lost because of osteoarthritis, and it is estimated that this will cost about 780 million €. A further 70,000 working years have been lost because of early retirements. The resulting costs for the community are estimated at 2200 million €.

When all direct and indirect costs are added up, a total of 7000 million € can be assumed, which is equivalent to about 0.5 % of gross national product.

When we look at the increasing number of cases of osteoarthritis requiring treatment on account of demographic shifts and if we identify individual suffering with loss of quality of life, it is inevitable that we should consider whether we can preserve necessary joint health or can influence the "normal" course of the disease to a certain extent.

It is certain that joint health is promoted and maintained by movement. The small child has to achieve mobility, the adult must use his mobility intelligently and the old person must maintain his mobility to ensure his overall health.

It is also certain that joint health can be promoted by correct nutrition.

An "exercised" life with the conscious use of exercise and relaxation, correct diet and consistent awareness of risk factors can be the basis of good physical mobility and the associated mental agility until an advanced age.

Along with addressing the question of a healthy diet when considering osteoarthritis, which must also look at metabolic diseases which cause or promote osteoarthritis, data which relate to diet have arisen in popular experience which is so to speak empirical. When considering this area of possible prevention, a diet high in gelatine or collagen hydrolysate is to the fore, which should contain the required amount of vitamins and minerals at the same time. Decades ago, research attempted to convert these experiences into clear scientific data, but failed because of method-related deficiencies. In the meantime, research in this area has progressed considerably and has shown that cartilage cells can be influenced by dietary choices. The result is the prospect of rational nutrition and increased supplementation with certain dietary components, so that prevention and early osteoarthritis therapy appear possible.

Chapter 1

Introduction to Osteoarthritis

Wolfgang Pförringer, M.D.

1.1 Definition

In general medical practice, in contrast to highly specialized hospitals, diseases that can be described as frequent and chronic and those that have an effect on well-being and performance, in short "banal", are of particular importance, even if they have little influence on mortality statistics. The loss of quality of life in patients is adequate motivation to provide as comprehensive a therapy as possible as well as targeted care. This is particularly true of osteoarthritis as the frequency of this condition makes it a focal point in any orthopedic practice.

The diagnosis osteoarthritis is not a specific entity but rather a collection of symptoms of various origins affecting different locations in different ways. All of the different forms, however, have one thing in common: they are a largely degenerative condition of non-infective origin affecting one or more joints. In the first instance osteoarthritis is a disease affecting joint cartilage; this is where the initial degenerative changes take place. It is only in the later course of the disease that the adjacent bone and periarticular structures are affected; these cause pain and restrict function.

Osteoarthritis is a degenerative joint disease characterized by progressive destruction of joint cartilage and associated structures such as bone, synovial and fibrous joint capsule and the periarticular musculature.
According to: Guidelines of the German Society for Orthopedics and orthopedic surgery (DGOOC) and the Professional Association of Orthopedic Physicians (Leitlinien der Deutschen Gesellschaft für Orthopädie und Traumatologie und des Berufsverbandes der Ärzte für Orthopädie) [1]

In particular, the numerous forms of arthritis in which the inflammatory changes are responsible for the pain and limited function of the joint or joints involved (rheumatoid arthritis) have to be distinguished. Furthermore, the arthropathies must be differentiated systematically; these comprise various joint diseases with different and heterogeneous inflammatory and non-inflammatory components and are mostly the result of metabolic, neuropathic or hematological disturbance. The correct diagnosis of osteoarthritis and differentiation from other joint diseases are not only of epidemiological statistical value, but represent the basis for targeted influencing of the progression of the disease and the relief of troublesome symptoms.

Cartilage damage always arises from a disparity between the ability on the part of joint cartilage to cope with stress and the actual stress applied.

On the one hand, structural deficits in the tissue (in spite of a low level of stress) can cause osteoarthritic changes; on the other, normal age-related cartilage can be damaged by excess stress.

There are two basic etiological forms of osteoarthritis:

■ Primary (idiopathic) osteoarthritis

The actual cause of this form is unknown. Genetic predisposition, tissue weakness, nutritional anomalies within the bradytrophic joint cartilage and other similar general factors have been considered; however, a clear trigger for primary osteoarthritis has not yet been identified.

■ Secondary osteoarthritis

This type is the consequence of previous damage or of another illness. Secondary osteoarthritis is thus characterized etiologically by its wide variety, which is of the greatest importance in approaches to prevention.
Possible causes extend from incorrectly applied stress due to congenital or acquired deformity of the skeletal system, non-physiological stress e.g. due to heavy manual work or high-performance sports and various types of trauma to the degenerative consequences of primary inflammatory processes.

The most important causes in practice are:
- **Overuse injuries** whether because of occupation or sports/hobbies.
- **Post-traumatic change** (e.g. incorrect axial position following fractures or injuries of cartilage, meniscus, ligament or capsule).
- Inflammatory, age-independent **joint disease** (e.g. chronic rheumatoid arthritis, septic arthritis, spondyloarthritis, gout and other types of crystalopathy)
- **Systemic, metabolic and endocrine disorders** (e.g. hemophilia, Wilson's disease, hemochromatosis, acromegaly, hyperparathyroidism) and indirectly as a result of diabetes mellitus (via polyneuropathy)
- **Neurological disease** (e.g. tabes dorsalis, syringomyelia etc)
- Joint disease during the **growth phase** (e.g. Perthes' disease, slipped femoral epiphysis, aseptic necrosis, osteochondrosis dissecans), including post-traumatic and post-infectious disorders of growth.
- **Congenital developmental disorders and joint deformities** (e.g. congenital dislocation of the hip, coxa vara / valga, club foot and other deformities of the foot, endochondral dysostosis, chondromatosis etc.)

Numerous other relatively rare causes can be included in the list, e.g. side-effects after corticosteroid injections.

1.2 Osteoarthritis: frequent symptoms in the elderly

Osteoarthritis is the result of chronic stress and is the most frequent pathological joint change observed in adults. It increases with age but also exists in younger people. The pain clinic *Am Arkauwald* (Bad Mergentheim, Germany) reports an incidence of osteoarthritis of 4 % in those aged 20, with women predominating. THEILER gives a figure of 9 % in those aged 20 and finds an incidence of about 17 % in 34-year olds. Thus, the asymptomatic early stages of arthritic changes are present during the second to third

decades of life in a few persons. Slight pathological change can, however, be observed in almost all joints in their fourth decade if these joints are stressed by overweight. Almost all seventy-year-olds have some form of osteoarthritic joint disease.

In the much-quoted and comprehensive United States Health Examination Survey (NHANES I) carried out during the period 1989 – 1994, osteoarthritis of the hands. 2.4 % of the men and 3.6 % of the women had osteoarthritis of the knee. These findings correlate extremely well with clinical findings (2 % of men and 3.6 % of women). Radiology showed that 4.3 % of men and 7.5 % of women between the ages of 55 and 64 had forms of osteoarthritis. In the age group over 65, radiology indicated that 8.7 % of men and 19.5 % of women had osteoarthritis. These investigations were performed using an ap-procedure and hence there was no additional stress placed on patients [3]. In the Framingham study gonarthritis occurred in a third of those over 63 subject-ed to x-ray.

PEARL *et al.* established that 10 % of those over 55 had degenerative knee joint disease in different stages of development; the investigators categorized one third of these cases as severe.

The frequencies differ from study to study and are dependent on the popula-tions and on the techniques used.

However, common elements of all the age-related studies are that osteoarthritis is one of the most frequent conditions of the elderly, that women dominate in the higher decades and that there are often differ-ences between diagnosis and the perception of symptoms.

Even clear-cut osteoarthritic changes e.g. in the knee joint can be tolerated over a long period of time without apparent symptoms. This is confirmed by studies that, in addition to establishing a radiological picture, compare the clinical symptoms and their courses (e.g. SCHOUTEN *et al.* [6]).

1.3 The risk of contracting the disease

There are certain factors that contribute to the formation of secondary degen-erative joint disease. Also, factors such as age and gender, in this case female, that cannot be influenced should be taken into account in assessing risk. However, according to the experts, there are no specifically defined risk groups which, on their own, and without the influence of external factors or pre-existent disease, represent an increased risk of osteoarthritis.

It is, however, a known fact that osteoarthritis of the knee and hands can occur with some frequency in families [2] and that certain genetically deter-mined conditions such as chondro-epiphysial dysplasia or hemochromato-

sis can lead to secondary osteoarthritis. **Risk factors,** apart from age and female sex (over 55) include, in particular:

- **Incorrect and excess strain on cartilage** as a result of occupational demands, performance sport or postural anomalies.
  It has been known for some time and has now been incorporated in occupational preventive health measures that working e.g. with a pneumatic hammer places stress on elbows and wrists that can lead to osteoarthritis. Recently, however, there has been increased evidence that regular lifting of heavy items and repeated bending over while load-bearing can lead to degenerative changes in the hips and knees. This was suggested as early as 1992 by CROFT [7] who found an increased incidence in agricultural workers who had been doing this work for 10 years.

- **Trauma**
  Power and contact sports with a high risk of injury (meniscus injuries, rupture of the cruciate ligament, repeated joint injury) increase the risk of severe degenerative joint disease of the joints involved. THEILER [2] (see above) refers to a threefold increase in the risk of osteoarthritis after severe joint trauma. The risk might in fact be much higher.

- **Overweight**
  There is some scientific conflict as to whether there is a linear etiological causal correlation between overweight and the frequency and severity of osteoarthritis. However, it is accepted that degenerative joint disease occurs much more frequently in obese persons. It is possible that the crucial risk factor is not just the increased mechanical stress brought about by overweight but also the metabolic disturbance associated with obesity that also has an effect on cartilage metabolism. This is also suggested by the fact that osteoarthritis of the fingers that cannot be explained by mechanical stress occurs more often in obesity.
  Overweight is, according to the Guidelines on osteoarthritis of the knee of the German Society for Orthopedics and Orthopedic Surgery (Leitlinie Gonarthrose der Deutschen Gesellschaft für Orthopädie und orthopädische Chirurgie), at least an influencing factor in the development of osteoarthritis even if the specific mechanisms have not yet been clarified. In practice, however, reduction of weight in obese patients clearly reduces the severity of symptoms (see WAHLE, chapter 4.4). In this context, obesity can be assessed as being a definite risk factor for the progress of the disease. The worldwide increase in obesity also implies that osteoarthritis will increasingly become a public health problem.

- **Skeletal deformity and joint malposition**
  Due to the uneven stress on joint cartilage e.g. in the case of genu varum or valgum, in acetabular dysplasia and other axial malpositions, stress and premature wear can occur in certain parts of the joint cartilage and hence lead to osteoarthritis ("pre-arthrotic deformity").

These conditions are of minor importance in general medicine and are generally cared for by orthopedic specialists. When deciding on possible surgical correction, the high risk of osteoarthritis should also be taken into account.

- **Inflammatory joint disease**
  Chronic rheumatic disease of the joints can lead to secondary osteoarthritis. Here also the actual causes have not yet been fully elucidated. Trophic disturbances and imbalance between cartilage formation and degradation are possible factors. Changes in the micro-conditions of the chondrocyte environment are regarded as the trigger (see topic 3.6).

- **Crystal arthropathy**
  In the case of gout, chondrocalcinosis or hydroxyapatite disease, there would also appear to be some connection with accelerated progression of osteoarthritic changes, and the risk increases with age.

- **Other metabolic or neurogenic disease**
  The causes of secondary osteoarthritis listed above also represent a risk of degenerative joint disease and should be treated consistently in the sense of secondary prevention.

- **Lack of exercise**
  It is not only over-stress of joint cartilage that represents a risk; lack of stimulating stress is also a risk factor. Only through stimulation and relaxation of the avascular joint cartilage can its nutrition from synovial fluid be guaranteed (see below).

It can be established generally that osteoarthritis is multifactorial. Certain triggers predominate but are not the sole cause. The main problem in all of these risk factors is that damaged joint cartilage is not fully regenerated with hyaline cartilage but with inferior fibrous cartilage.

1.4 Structure and function of cartilage tissue

Even if osteoarthritis is primarily an isolated cartilage injury and involves the entire joint secondarily, the joint cartilage is in fact the tissue that is the principal element once the disease is established and begins to progress. In order to understand the basic pathophysiological process, some of the special features of hyaline cartilage will be treated here.

Hyaline cartilage has neither blood nor lymph vessels and has no nerve fibers. It consists of 95 % water and extracellular matrix. Only 5 % consists of the chondrocytes. In spite of the constant cartilage restructuring (see below), the chondrocytes have a very long cell cycle, similar to that of the nerve cells of the CNS and muscles.

Cartilage tissue comprises chondrocytes and the dominating extracellular matrix that extends between the chondrocytes. The bradytrophic metabolism is

ensured by diffusion from its environment. Normal cartilage function, as mentioned above, depends on the constant change between pressure and the relief of pressure, between stress and relaxation. It is only by this pump action that adequate amounts of nutrient-rich fluid can reach the cartilage from its surroundings and the metabolic waste products can be eliminated during the compression phase.

Joint cartilage requires not uncritical protection but rational well-dosed stress – this physiological property of cartilage tissue is of practical relevance.

The extracellular matrix of joint cartilage consists of two classes of macromolecules, the proteoglycans and collagen. Both proteins are important for the specific function of cartilage.

The proteoglycans (e.g. aggrecan) ensure the compressive strength of the cartilage. The collagen fibrils (type II collagen) ensure the tensile and shear strength.

1.5 Metabolism and turnover

In spite of the lack of a blood supply, cartilage has an active metabolism with constant turnover. Lysosomal proteases (e.g. cathepsins) are limited in their activity to the intracellular and immediately adjacent pericellular areas; however, there are several matrix metallo-proteinases (stromelysin, collagenase, gelatinase) that, at neutral pH, can cleave all of the building blocks of the extracellular matrix. Chondrocytes and matrix proteinases work together in this process. Proenzymes are secreted from the chondrocytes; these are then activated as required in the matrix. Both the chondrocytes and the matrix structures are equally responsible for maintaining equilibrium between the anabolic and catabolic processes.

The activity of the matrix metalloproteinases becomes a functional cascade through the interaction of activating and inhibiting factors.

The cytokine interleukin II appears to play a key role. This cytokine, which is also produced by chondrocytes, activates the formation and secretion of matrix metalloproteinases on the one hand and on the other it releases tissue plasminogen activator. This in turn activates the plasminogen in the cartilage that is either produced by the chondrocytes or reaches it from the synovial fluid. Within this complex cascade, plasminogen in turn activates the metalloproteinases which promote the degradation of cartilage substance (the catabolic phase). In addition, interleukin II in lower concentration is believed to inhibit repair processes in the matrix by inhibiting the synthesis of proteoglycans.

Two inhibitors (TIMP and PAI-1) that inhibit both the metalloproteinases and the plasminogen activator control the rates of flow. If these are absent or

present in lower amounts, stromelysin and plasmin can enter the cartilage unhindered and bring about degradation of the cartilage.

Polypeptide mediators such as IGF-1 (insulin-like growth factor) or TGF-α (transforming growth factor-α) act as opponents to a certain extent. They generally exert an influence on matrix metabolism in healthy cartilage in the sense of anabolic repair processes. By inhibiting the interleukin receptors they can reduce degradation of the proteoglycans.

It can be assumed that other mediators are also involved in this complex interaction between anabolic and catabolic processes throughout the life of the joint cartilage.

The purpose of this overview is simply to inform the physician carrying out treatment of the complex regulatory systems involved and to explain that simple mono-causal therapeutic or preventive measures in osteoarthritis are doomed to failure for these pathophysiological reasons. It is necessary to know the processes that take place within the cartilage matrix if it is to be possible to use both stimulating and inhibitory factors against anabolic and catabolic processes both long term and without failure in a targeted fashion. This also holds for the exogenous administration of drugs such as glucocorticoids or certain building blocks such as collagen hydrolysate. By inhibiting and stimulating the anabolic and catabolic processes within cartilage tissue, a multidimensional cybernetic control system is created that is capable of adapting to various conditions and stresses.

Recent investigations by OESSER [8] have confirmed that the collagen fragments contained in collagen hydrolysate can themselves act as mediators within cartilage tissue where they stimulate the synthesis of new cartilage matrix (see chapter 3).

Stimulation
- IGFs (insulin growth factors)
- TGF-βs (transforming growth factors)
- PDGF (platelet-derived growth factor)
- EGF (epidermal growth factor)
- BMPs (bone morphogenetic proteins)
- CDMPs (cartilage-derived morphogenetic proteins)
- Growth hormones
- **Collagen hydrolysate**

Stimulation
- γ-Interferon
- TNF-α
- Prostaglandins
- Oxygen radicals

Chondrocyte

Matrix components (e.g. collagen, proteoglycans) ← **Anabolism**   **Catabolism** → Proteolytic enzymes (e.g. cathepsins, matrix metalloproteases)

- IL-1
- TNF-α
- IL-17
- FGFs (fibroblast growth factors)
- γ-Interferon
- LIF (leukemia inhibitory factor)
- Glucocorticoids
- Pro-collagen fragments

- TIMP (tissue inhibitor of metalloproteases)
- Plasminogen activator inhibitor
- Callicrein

Inhibition   **Inhibition**

Regulation of cartilage metabolism

1.6 Pathophysiological genesis of osteoarthritis

The hypothesis that osteoarthritis is a "disease caused by wear and tear" is without a doubt too mechanical, even if the extreme frequency with which the disease occurs in the elderly would suggest such a mechanism. A normal joint in a healthy body has an extremely low coefficient of friction when placed under stress, which makes it unlikely that such a joint would become progressively worn under these conditions. Together with the synovial fluid, the coefficient of friction is still about 15 times lower than that of two closely fitting ice cubes!

It is more likely that osteoarthritis develops due to primary changes in the collagen fibers combined with a reduction of the adherence between the fibers in question. These defects within the network of collagen fibers are associated with biochemical changes (matrix metalloproteases, plasmin, cathepsin) and are presumably irreversible. The catabolic processes predominate and cartilage matrix substance is lost gradually. The anabolic growth factors can slow down this process temporarily but cannot reverse it.

There has recently also been discussion on whether nitrogen monoxide (NO) plays a part in the lesion of the joint cartilage. It has been demonstrat-

ed that NO increases the activity of the matrix metalloproteases. Chondrocytes are the main source of NO synthesis; this is increased by the stimulus of shear forces on the cartilage. These phenomena, currently still being researched, might provide new possibilities for the prevention of osteoarthritis if selective NO inhibitors – as proven in animal studies – could reduce the extent of joint damage.

It is also apparent that chondrocytes are anything but passive in the development of osteoarthritic changes. They do not degenerate but become particularly active metabolically. They appear to be triggered. They produce an ever-increasing amount of DNA, RNA, collagen, proteoglycan and non-collagen protein. According to one hypothesis, this initially leads to a thickening of the joint cartilage but this is of inferior structure and poor function. This cartilage is less elastic and hence places a stress on the adjacent bone. The consequence is "wear and tear" under degrees of stress that normal hyaline cartilage would have tolerated without difficulty. Micro-fractures can occur; these in turn produce callus leading to the well-known osteochondrophytes. Thus osteoarthritis comes about via intermediate tissue thickening and reaction of the surrounding bone material.

Bearing in mind these active metabolic processes in the joint, it is incorrect from the pathophysiological aspect to designate osteoarthritis as a "degenerative" disease; actually, at the beginning of the disease there is increased synthesis activity on the part of proteoglycans and other structural proteins in the cartilage matrix, though these are of inferior functional quality.

Osteoarthritis therefore begins at a much earlier stage than when joint cartilage changes become evident.

This suggests that a causal or prophylactic therapy should be started earlier and that the metabolic processes in the chondrocytes must be taken into account.

1.7 Diagnosis of osteoarthritis

Diagnosis of osteoarthritis generally requires little effort, although the modern imaging and invasive techniques available can lead to a marathon diagnostic program. This can only be justified if other causes of pain are to be excluded or in the case of special expert opinions. Such exaggerated diagnostic procedures are unnecessary for the treatment of symptoms. There is no clear relationship between the severity of symptoms and the extent of morphological joint changes.

Osteoarthritis in practice is a clinical diagnosis!

In practice, a differentiation of the types of osteoarthritis can be helpful for therapy:

- Non-active osteoarthritis (neither pain nor functional disturbance)
- Painful, non-active osteoarthritis
- Active osteoarthritis with pain, inflammation and functional disturbance
- Decompensated osteoarthritis (involvement of periarticular structures and joint instability)

The most frequent symptom and the reason for consulting a physician is the **pain.** However, this is not an early symptom. As joint cartilage has no nerve fibers, the pain signals that periarticular structures are involved.

A **special medical history** initially serves to make the pain suffered by the patient more precise e.g.:

- How long has there been pain?
- Where is the pain located precisely?
- Where does it radiate to?
- When during the day does it appear? Is it morning pain?
- How long does the pain last?
- How intense is the pain?
- Is joint function affected?
- Can the joint be placed under stress (e.g. knee)?
- Is there also swelling of the joint?

Joint pain is generally described as a deep, dull, continuous type of pain restricted to a joint and its immediate environment. It occurs on movement but not at rest. Simultaneous pain in several joints is not normally caused by osteoarthritis.

In the case of early-stage osteoarthritis, brief initial pain is typical, normally occurring after intensive or abnormal stress on the joint. As the condition progresses, the pain becomes constant; this is intensified when stress is applied. Alternating periods of intensive and weak pain are typical. This increases with activity and stress and decreases at rest. Typical "morning stiffness" can last 15 – 30 minutes.

The American College of Rheumatology in 1986 produced a special classification for osteoarthritis of the hip, knee and wrist [9]. In practice, however, simplified criteria are quite adequate. Differentiation into early and late types of pain in the case of specific joints can be helpful but should not be regarded as dogma.

A diagnostic **early triad** consists of:

- Starting pain (morning stiffness, initial pain)
- Fatigue pain
- Stress pain

The **late triad** consists of:

- Constant pain
- Night pain
- Local muscle pain

As the disease progresses, mobility of the affected joint is restricted and there is increasing tenderness within the joint area. Synovitis can also occur as a complication and suggest rheumatic symptoms.

The second cardinal symptom of osteoarthritis is the **restriction of mobility** of the joint affected. However, this is normally only noticed by the patient when it leads to restrictions in daily routines.

The **examination** should begin with **palpation** of the affected joint. If the peri-articular structures are already involved, there will be some tenderness (peri-arthropathy) and there may be palpable thickening of the joint capsule, heat and a synovial effusion.

A **test of function** is also indispensable to establish limitation of movement in any direction. Rubbing, cracking or crunching joint noises can sometimes be heard. Often blocking of the entire joint movement and severe end-phase pain may occur on provocation. Muscle shortening further limits mobility. Depending on the location, there may be other findings, e.g. gait instability in the case with osteoarthritis of the hip and knee pain on moving the patella in osteoarthritis of the patello-femoral joint.

Radiological investigation is of little help in the early stages of osteoarthritis; however, it may be of help in excluding other causes of pain or to indicate uncharacteristic increased subchondral sclerosis in the more stressed parts of the joint as an early sign of possible osteoarthritis. On the x-ray (in two planes), typical changes only occur at an advanced stage and are normally character-ized by asymmetric and irregular narrowing of the articular cavity, cystic changes and increased radiological density in adjacent joint bone as well as the well-known periarticular osteophytes. These radiological findings are assessed quantitatively and qualitatively using various scales. In practice, the simplified four-stage KELLGEN scale has proven of value: I = doubtful change; II = slight; III = moderate; IV= severe. The PFÖRRINGER and STOLZ scale [10] classifies osteoarthritic changes of the ankle as grade 0 (no radiographic changes), grade 1 (initial osteoarthritis with some avulsion), grade 2 (mild osteoarthritis with avulsion at the base of the tibia and the malleoli and mild sclerosis), grade 3 (moderate osteoarthritis, the articular cavity being narrowed by half, obvious loss of the rounded roll of the talus, osteophytic bulging at the edge, pronounced subchondral sclerosis) and grade 4 (severe osteoarthritis with obvi-ous joint destruction, reduction or obliteration of the joint cavity, cyst formation and deformity).

In practice, it is important to realize that there is no linear correlation between the radiologic appearance and the severity of symptoms.

Severe changes may well be pain-free whilst x-ray findings that are hardly rec-ognizable may be extremely painful (e.g. in patello-femoral osteoarthritis).

A negative radiograph can therefore not exclude clinically suspected osteoarthritis.

In a targeted search using x-ray techniques, more than 90 % of those over 40 showed some degree of osteoarthritis; however, only 30 % of these had clinical symptoms [11].

Magnetic resonance imaging can undoubtedly extend the assessment of peri- and intra-articular structures but is only indicated in special cases and to exclude other diagnoses. In routine practice, the technique is of little relevance.

Ultrasonography can help in differentiating periarticular findings but is only of limited use in diagnosing early osteoarthritis.

There are no typical **laboratory findings** for osteoarthritis. Laboratory analyses, including the investigation of synovial fluid, are also of use only in differential diagnosis with specialists.

Invasive methods (e.g. **arthroscopy**) provide very good and reproducible results even in the early stages of osteoarthritis; however, for understandable reasons, they are not suitable for routine investigations.

Overall, with respect to the assessment of the diagnostic techniques currently available in medical practice, the history and clinical findings dominate, x-ray is for verification and documentation but, like other special methods, is used mainly for differential diagnosis and exclusion of other diseases that may require different therapies.

1.8 Therapy of osteoarthritis

There is no conservative causal therapy for pronounced osteoarthritis.

In secondary osteoarthritis, treatment of the underlying disease can slow down progress; however, the joint affected cannot be returned to its original state.

In treating a patient suffering from osteoarthritis it is advisable to inform the patient of the therapeutic goals right from the start (see also chapter 4.4). As it is not possible to eliminate any changes that have occurred, it would be wrong to arouse unrealistic hopes in the patient as the failure to fulfill these hopes can lead to a disturbance in the patient-physician relationship.

Therapeutic goals are:
• Reduction of pain
• Maintenance of (still present) mobility
• Reduction of disability
• Avoidance of periarticular complications
• Delaying progression

The therapeutic procedure cannot be schematized as this depends greatly on the individual's symptoms. Treatment is always an individual matter; it is complex and symptomatic and is based on a number of pillars.

In patients without constant symptoms, advice on a health-promoting lifestyle, suitable nutrition, weight loss if necessary, suitable physical exercise and analgesics if and when required are normally adequate.

■ Medication

Physical procedures and other supportive measures such as nutritional supplements represent first-line therapy in osteoarthritis. At present, there is no single drug that results in a reversal of osteoarthritic changes or permanent prevention or even demonstrable delay of progression. The occasionally postulated chondro-protective effect of a number of non-steroidal anti-inflammatory drugs has not been proven in controlled clinical studies [11].

Pain relief is thus the main goal of the medication of patients with osteoarthritis. **Non-steroidal anti-inflammatory and anti-rheumatic drugs** (NSAID = non-steroidal anti-inflammatory drugs) are suitable for pain relief and improving joint mobility; however, the effect cannot be described as outstanding. On average, 30 % pain relief and 15 % functional improvement are achieved. In controlled, double-blind studies on patients with symptomatic osteoarthritis of the knees, no significant differences were found between analgesic and anti-inflammatory doses of ibuprofen (2,400 mg/d) and low, only analgesic doses (1,200 mg ibuprofen per day) (cited in [11]). Dex-ibuprofen, a drug developed by separation of the enantiomers of ibuprofen has a quicker and more reliable effect, acting on lipoxygenase (LOX inhibitor) in addition to inhibiting cycloxygenase (see below). This should be the drug of choice for long-term medication.

Even in the case of a confirmed inflammatory reaction of the periarticular tissue, analgesics without an anti-inflammatory effect (paracetamol) proved to be just as effective in relieving pain as NSAIDs.

The risk of gastro-intestinal bleeding as a side effect of NSAIDs is much lower with the modern **cyclooxygenase-2 inhibitors** (COX-2 inhibitors) than with non-selective nonsteroidal anti-inflammatory drugs such as naproxen (CLASS study; VIGOR study). Thus, they should be preferred in the symptomatic treatment of osteoarthritic pain.

The systemic administration of **glucocorticoids** is not effective in osteoarthritis. Depot glucocorticoids, however, can have a pain-reducing effect over a number of weeks if given by intra- or periarticular injection. In animal experiments, however, it was shown that the glucocorticoids can attack joint cartilage. Intra-articular injections should thus be reserved for specialists and be given at most two to three times a year to the same joint.

The injection of **hyaluronic acid** into the joint also provides pain relief in osteoarthritis. Hyaluronic acid is a natural polysaccharide constituent of the proteoglycans and synovial fluid. Injected hyaluronic acid appears to improve the flow properties of synovial fluid, hence improving the gliding properties of the joint. Five injections at weekly intervals are recommended. They can provide relief from symptoms over a period of months. However, intra-articular injections should be administered by specialists because of the risk of infection.

Glucosamine sulfate is also a component of the proteoglycans. Exogenous administration is said to stimulate the build-up of cartilage matrix. However, for this to happen, adequate amounts of active chondrocytes must be available. Bearing this in mind, administration of glucosamine sulfate is meaningful only in the early stages of osteoarthritis. In Germany, glucosamine sulfate is only available in oral form and only approved for the treatment of osteoarthritis of the knee.

The substance **ademetionine,** which occurs naturally in the body, is involved in a number of metabolic processes that can help to prevent osteoarthritis. The reduction in histamine release or its inactivation inhibits pain-causing inflammation of the cartilage environment. Ademetionine increases proteoglycan and protein synthesis by the chondrocytes and is also believed to stabilize cartilage by inhibiting the influence of proteolytic enzymes. As ademetionine is converted to glutathione and as glutathione as an antioxidant inactivates free radicals, it is assumed that this represents protection of joints from further damage as well as further progress of the disease. In animal experiments, using rabbits with induced osteoarthritis, an increase in cartilage thickness and an increase in the number of chondrocytes was established after 12 weeks of treatment (expert conference of the German Association of General Practitioners, 1996) and the drug was therefore recommended as supportive treatment or as a prophylaxis against progression of the disease ("basic therapy") in patients with an increased risk of osteoarthritis.

In some cases, **muscle relaxants,** surprisingly, are able to relieve the pain of osteoarthritis; this is because they reduce muscle tension and hence the pressure on the joints in question.

The use of **topical anti-inflammatory drugs** in cases of joint pain is usually rejected, mainly because the diffusion distance from the skin to the joint in question is too long. However, there are indications that **Diclofenac** is quite effective in relieving pain due to inflammation in small joints that are near to the skin, e.g. finger joints, provided it is applied correctly and the local tissue concentration is adequate [16]. **Capsicaine patches** on the other hand, cause an artificial inflammatory reaction to produce hyperemia of the joint environment and can thus provide pain relief by enhancing blood flow. Topical drugs have no effect on the osteoarthritis itself.

Phytotherapeutics such as Devil's claw extract, nettles etc. are unjustly underestimated. Constituents of nettles inhibit the synthesis of interleukin-1-β and TNF-α. These pro-inflammatory cytokines are secreted in increased amounts into the synovial fluid of patients with osteoarthritis or other forms of arthritis. They exert an influence on the pain symptoms and on the progression of the joint changes. Their inhibition can provide adequate pain relief in mild forms of osteoarthritis.

Extracts of the root of the Devil's claw (*Hapagophytum procumbens*), a plant originally found in the savannahs of South West Africa, contains hapagosite and other iridoglycosides; these, apart from other properties, have an anti-inflammatory and analgesic effect. Clinical studies have now confirmed that, in daily doses of 480 mg, there was substantial relief of symptoms and practically no side-effects. In advanced stages of the disease, a combination of higher doses of Devil's claw extract with NSAID is possible and can lead to a reduction in the dose of the NSAID.

Extracts of willow, oak bark, golden rod, aspen bark, mistletoe etc. have also been used as therapeutic alternatives or as concomitant therapy in the relief of osteoarthritic pain, though the data obtained is not so favorable. In folk medicine, wrapping with cabbage leaves is recommended to provide natural relief from osteoarthritic pain.

In medicine, **leeches** are receiving attention again and not only in vein therapy. The enzymes hiruidine (an anti-coagulant) and egline (anti-inflammatory, analgesic) contained in the saliva of leeches are said to relieve pain and improve mobility.

Orthokine therapy
Orthokine therapy has been propagated in recent years as a special form of medication although scientific proof of its positive effect is still to be produced. In this case the body's own interleukin-1 receptor antagonist is utilized therapeutically. It is said to protect cartilage and reduce inflammatory reactions. The interleukin-1 antagonist is obtained from the blood of the patient (50 ml) and isolated in special laboratories. Six to ten injections are then given directly into the joint at weekly intervals. A precondition, however, is that there is still enough cartilage tissue. In the late stages of osteoarthritis this therapy approach is unsuccessful.
The procedure is not yet well known and there are no clinical studies.

In the case of **secondary osteoarthritis** medication also has the goal of eliminating the **original cause** of the disease (see above).

In spite of this relatively wide spectrum of symptomatic therapies, the fact remains that there is no causal medical therapy or reliable medical prophylaxis of osteoarthritis.

However, patients with painful joints should not be refused symptomatic treatment. The choice of drug or method should be based on individual experience and the patient's conditions.

■ Non-drug treatment

The biggest hindrance to **physiotherapy** is the mistaken view that the damaged cartilage has to be protected in order not to aggravate the damage. According to pathophysiological and practical experience, this is wrong. Of course, excess stress and incorrect stress should be avoided, e.g. by correcting errors of posture or monotonous movement routines. However, this does not mean that the joint in question has to be freed of all stress using apparatus. Only through targeted and well-dosed physical stress can the avascular cartilage (see above) be supplied with nutrients and any metabolic waste products be removed. A lack of stress thus hastens joint destruction.

Thus, physiotherapy is the most important partial aspect in the complex treatment of osteoarthritis.
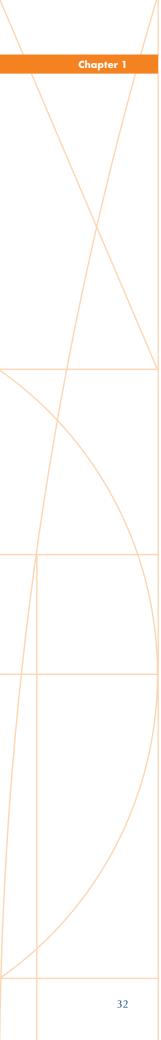
Within the scope of physiotherapy, function training, isometric, isotonic and isokinetic exercises, postural training and general strengthening exercises are recommended. Daily stretching exercises are very important if muscles, tendons and ligaments are to retain their power and if no further restrictions in mobility are to be caused. However, exercises should be moderate in nature so as to support the physiotherapy being applied. In addition, relaxation is also important (at least four to six hours a day) to ensure rehydration of the cartilage.

Physical therapy in osteoarthritis is completely accepted. The **application** of heat (showers, heat pads, warm compresses, heat lamps etc.) can often provide pain relief. However, many patients report better pain relief from the **application of cold.** The method producing the best effect should be the one of choice.

All physiotherapeutic and physical methods can be used in a medical practice:
• Ultrasound
• Massage
• Physiotherapy
• Electrotherapy
• Mineral mud packs
• Application of heat or cold

Particularly important supportive measures, if relevant, are **weight reduction** and change in lifestyle **(exercise!).**

The use of **orthopedic aids** (e.g. crutches etc.) should be decided depending on the individual situation.

Another important and promising method for stabilizing cartilage and stimulating metabolism is a change in **eating habits** (food adapted to the disease in question, not a diet), as shown by new data now available (see chapter 2). More detailed information on the value of **collagen-containing foodstuffs** or appropriate nutritional supplements is given in chapters 2 and 4.3 because of its practical importance.

■ Alternative methods of treatment

Patients suffering especially from chronic diseases with little chance of cure are often easy prey for untrustworthy profiteers offering dubious cures. On the other hand, supportive procedures can often have a positive influence on the conventional treatment of osteoarthritic pain and may help to bring about functional improvement. However, in all methods that have not been scientifically underpinned, it should be taken into account that some may well be successful in individual cases temporarily, which can usually be explained by the "placebo effect". The German Osteoarthritis Forum (Deutsches Arthrose-Forum; www.deutsches-arthrose-forum.de) cites the results of the Texan surgeon Bruce Moseley as an impressive example of the placebo effect. Moseley operated on ten patients suffering from osteoarthritis of the knee. In five of these, he opened up the knee as usual, flushed it out and smoothed the cartilage; in the other five, he only made an incision in the skin but went no further. All ten patients subsequently reported that there was a marked reduction in pain, including the placebo patients.

Homeopathy
Homeopathic preparations such as Duralell N, Miburell and combinations of these under the name Duralell Classic are used in the treatment of degenerative joint disease. However, there are no evidence-based studies, even if numerous positive reports (placebo?) have been written on their use.

Acupuncture
Of course, acupuncture can neither cure osteoarthritis nor can it slow down progression. However, pain relief is achieved in many cases. This applies especially to osteoarthritis of the knee. Caution is advisable in active osteoarthritis as periartricular inflammation cannot be cured by acupuncture. Currently, the health insurance companies in Germany are sponsoring comprehensive studies in order to be able to assess the value of acupuncture in osteoarthritis.

Copper armbands
The effect of this so-called alternative therapy is completely unproven.

Amber

Within the scope of the so-called "healing stone" application, amber is promoted as a treatment for osteoarthritis. However, there is no scientific proof that this method has any therapeutic effect.

Magnetic field therapy; pulsed signal therapy

Both methods expose the diseased joint to magnetic fields; this is intended to stimulate the cartilage metabolism to such an extent that full regeneration takes place. In treating fractures, magnetic field therapy appears in fact to produce more rapid healing. Success is also claimed in the relief of pain with a resulting improvement in well-being up to 70 %. As to whether cartilage regenerates better is still the subject of intense discussion. One study has shown that there was directed growth, increased cell density and increased cell growth in-vitro under the influence of modulating magnetic fields [12]. As a rule, the German health insurance companies do not reimburse the costs of these methods. The use of magnetic mats and high-tone therapy must be clearly differentiated from this form of treatment. Neither of these "therapies" has any scientific basis whatsoever and their efficacy has not been confirmed by serious studies.
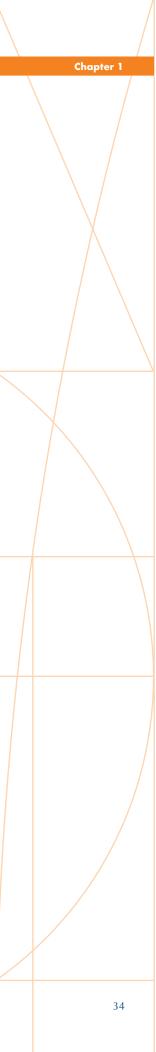
Radionuclide synoviorthesis

This method employs weak radioactive substances which are injected intra-articularly for the treatment of inflammation of synovia. The weak irradiation causes crusting of the superficial layers of the joint cartilage thus inhibiting the synovitis and its consequences. The effect does not set in immediately, but only after several weeks or months. It has not been confirmed that this has any effect on the progression of the osteoarthritis. As this treatment is restricted to special nuclear medicine departments, it is hardly of relevance for general practice.

Chirotherapy

Chirotherapy carried out by appropriately trained physicians has to be distinguished from that carried out by non-medical practitioners, even if both use largely identical manipulative techniques on the painful joint by "resetting" to relieve the loss of function. When skillfully used, the method is suitable for relieving pain and functional lesions caused by muscle spasm, for instance of the spine. However, it has no effect on the osteoarthritis itself.

Laser treatment

The use of low-energy lasers of wavelengths from 780 – 800 nm has proven useful in recent years in the relief of pain in osteoarthritis [13]. With a penetration depth of about 8 cm, the energy can be delivered, pain-free, to the cartilage tissue. Apparently, the increased supply of energy stimulates mitochondrial structures to excite cellular and tissue metabolism and to increase the production of new connective tissue by activating the chondrocytes. As a rule, 5-6 treatments are recommended. Combination with physiotherapy methods has proven successful.

■ Surgical treatment

Surgical intervention is the ultimate method for the treatment of osteoarthritic pain and loss of function that cannot be controlled by conservative methods.

In general, a distinction is made between joint retention methods and joint replacement methods. The decision on the most suitable method depends on the joint affected, the severity of symptoms and the overall condition of the patient. As the methods are the exclusive domain of specialists, only an overview of the various forms of treatment will be given here.

Joint-retaining methods

- **Arthroscopy** for flushing out the joint and subsequent smoothing of the cartilage
  In the case of damaged but not inflamed cartilage, a probe can be inserted into the joint, flakes of cartilage can be removed and the joint surface thus smoothed.
- **Abrasion arthroplasty**
  In osteoarthritis of the knee, the most superficial layer of the bone within the joint is milled off and removed through an arthroscopy. This stimulates repair mechanisms in the joint. New cartilage (fibrous cartilage) is gradually formed and, after a two-month protective period (crutches etc.) and a total healing period of 12 – 18 months, the artificially created defect is bridged over. The new fibrous cartilage cannot be stressed as much as the old, hyaline cartilage but it can remain pain free and functional for long periods of time. The method is relatively popular; however, well-controlled studies on efficacy have shown that permanent improvement is not possible.
- **Displacement osteotomy**
  In this method used on hip and knee joints, the joint axis is altered in such a way that incorrect stress is at least reduced. This can have an effect on the progression of the disease and relieve pain.
- **Arthrodesis**
  Ankylosis can be carried out on all joints and on the vertebral column. The fixed connection eliminates pain but at the expense of loss of function. The operation is suitable for the ankle, less for the knee and not at all for the hip.

Joint replacement is mainly:

- Total prosthesis
- Shell-type prosthesis to replace the joint surface

Artificial joint replacement has become routine; it can eliminate pain and essentially restore joint function.

Today, finger joints, the elbow, shoulder, hip, knee and ankle can be replaced.

Much has been achieved in the surgical area for those suffering from osteoarthritis. Thousands of patients are now pain-free and have essentially full function thanks to invasive therapy. New techniques are being tried out on a

worldwide basis. However, in spite of all the progress made, it must be emphasized that these operations always represent the last resort and that early therapy of osteoarthritic pain and prevention are the medical priorities.

1.9 Supportive therapies

Even after surgical correction of osteoarthritis, **a complex treatment regimen** is necessary; this should include physiotherapy and behavioral aspects. In 1991, ADAM *et al.* [14] published a randomized, double-blind study of 81 patients suffering from osteoarthritis who received various collagen products as a nutritional supplement in different study arms along with placebo (ovalbumin) for 16 months. It was shown that collagen hydrolysate resulted in a clear reduction of the pain score in over 80 % of the participants and there was a significant reduction in the use of analgesics (for details see chapter 4.1.).

The possibility of optimizing food intake (e.g. the administration of collagen hydrolysate with the amino acid building blocks for cartilage matrix) to assist in preserving cartilage, to facilitate repair processes and to relieve pain [15] opens up new routes for the combined therapy of severe osteoarthritis (see chapters 2 and 4.3).

1.10 Conclusion

The numerous therapeutic recommendations signal that there is no one valid method for all patients suffering from osteoarthritis. Practical experience shows that it is primarily the combined methods that are the most successful, especially those consistently involving the patient (exercise, nutrition, lifestyle), in achieving freedom from symptoms and a stagnation or at least delay in the progression of the disease.

Based on this, the medical practice requires all currently available knowledge for the prevention of osteoarthritis and for facilitating what is in fact a complex therapeutic program. This includes **optimized nutrition,** but of course this excludes neither conservative nor surgical methods of treatment.

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Chapter 2

The Significance of Nutrition in Medicine

Kristine Clark, Ph.D., R.D.

The Significance of Nutrition in Medicine

Nutrition has become one of the most important areas of medicine in the last five years. What foods a person eats will in large part determine whether they will become overweight, develop cardiovascular disease, diabetes, cancer, hypertension, osteoporosis, or any other of a number of health complications related to excess fat and total calories, excess saturated fat, inadequate fiber, or lack of any essential vitamin or mineral. Industrialized countries offer fast food options to accommodate fast-paced lifestyles, at escalating rates. As a result, obesity and diabetes have become epidemics in many industrialized countries. In the US 65 % of all adults are overweight or obese – 6 of 10 children are either overweight of obese (cf. table).

Prevalance of Overweigth and Obesity among US adults, age 20-74 years

	Overweight or obese BMI ≥ 25.0	Overweight BMI 25.0–29.9	Obese BMI ≥ 30.0
NHANES II 1976–80 (n=11,207)	47	32	15
NHANES III 1988–94 (n=14,468)	56	33	23
NHANES 1999 (n=1,446)	61	34	27
NHANES III 1999–2000 (n=4,115)	65	34	31

BMI = body mass index

*Age-adjusted by the direct method to the year 2000 U.S. Bureau of the Census estimates using the age groups 20-34, 35-44, 45-54, 55-64, and 65-74 years.

Food processing has allowed more food choices for consumers. However, many fast food restaurants offering highly processed foods "super size" them. Consumers wanting more for their money are vulnerable to overeating, eating quickly, and making food choices that feed into this rapidly growing health dilemma. Lastly, the media promotes fashion and beauty by undermining optimal nutrition. Animal based foods, particularly meat, have been discounted in terms of their nutritional value. In the processing of meat, many high quality nutrient dense components are removed such as important collagenous parts.

This means that, even though the protein contained in the foodstuffs in industrialized countries may well be more than adequate in quality, there is a certain deficit in terms of collagen content. From a nutritional standpoint, this type of processing may have a negative impact on health.

In those countries with a high proportion of "fast food" (e.g. USA) or with a preference for meat (South America, Central Europe), the proportion of collagenous material is much higher than in Mediterranean countries. Precise statistics on average ingestion of collagen in different regions do not exist, however good estimates are available.

For example, the German Dietary Association (Deutsche Gesellschaft für Ernährung (DGE)) mentions in its annual report for 2000 (see chapter 4.3) that the mean quantity of meat and sausage eaten per day is 180 g for men and 140 g for women [1]. It can be calculated that the amount of collagen involved is about 5 – 5.5 g per day.

Collagen in food has declined according to national studies on nutritional habits [2] due to young consumers preferring lean, boneless meats without connective tissue is a current trend. In addition, the promotion of lacto-vegetarianism as a healthy nutritional form, may create additional health problems. The discovery of BSE raised many concerns about the safety of the meat supply, and although extremely well contained and controlled, the food industry experienced a decline in the consumption of meat within the more well-educated populations. Consequently, collagen consumption also declined.

■ Healthy nutrition as a preventive method

Nutrition, as well as increasing physical activity, has become increasingly important in maintaining health and preventing disease. The 51st General Assembly of the World Health Organization (WHO) passed a resolution in May 2002 on a global strategy for nutrition, activity and health. In this particular case it was a response to the disastrous consequences of hunger in the developing countries, the largest single problem in preventive health. However, it also applies to the consequences of unbalanced, inadequate and general poor eating habits in the industrialized countries. Gro Harlem BRUNDTLAND, a previous General Director of WHO, once said: "…Nutrition is a cornerstone that affects and defines the health of all people, rich and poor. It paves the way for us to grow, develop, work, play, resist infection and aspire to realization of our fullest potential as individuals and societies. Conversely, malnutrition makes us all more vulnerable to disease and premature death." [3]

Within the realm of preventive health, degenerative joint disease (see chapter 1), has been getting significant attention. Joint disease impacts an individual´s level of physical activity, overall mobility, and quality of life. With escalating obesity and overweight, individuals need the highest degree of chondro-protection available while they begin to manage more activity and improved food choices. One way to optimize nutrition for prevention and treatment of joint disease might be by increasing the content of collagen or collagen hydrolysate in the diet. This particular trend corresponds to the growing worldwide orientation

towards effective prevention of disease coupled with a higher degree of responsibility on the part of the individual concerned.

■ Osteoarthritis diet?

There is no special "osteoarthritis diet" that could scientifically justify a claim. However, there are scientific recommendations for an optimal, chondro-protective diet. Laboratory studies have shown that joint cartilage metabolism can be specifically influenced by collagen hydrolysate.

The nutritional recommendations published by international and regional associations and patient organizations include nutrition information for osteoarthritis patients; however, these tend to be general; ranging from increased amounts of fiber to use of specific vitamins such as vitamins of the B, C or D group, minerals; such as iron, phosphor, zinc, chromium, copper, magnesium, manganese, osteo-active nutrient components such as calcium and fluorine and some of doubtful value such as greenlip mussels.

Nutritional supplements taken for joint discomfort are for example ginger, omega-3-fatty-acid, gamma-linoleic acid, glucosamine, chondroitin or collagen hydrolysate.

General osteoarthritis diets and their subsequent recommendations appear regularly in the lay press literature. However, apart from recommendations in favor of collagen-rich foods, they have no scientific basis. As in the case of the recommendations of American experts, the guidelines produced by the German Society for Orthopedics and Surgical Orthopedics (Deutsche Gesellschaft für Orthopädie und chirurgische Orthopädie (DGOOC)) as well as those produced by the Association of Orthopedic Physicians (Berufsverband der Ärzte für Orthopädie) play no major role, apart from the general recommendations that weight normalization is a worthwhile goal and hence diets favoring this are beneficial in osteoarthritis.

In industrialized countries – in contrast to most developing ones – the proportion of protein in normal diets is adequately high, often more than official, scientifically founded recommendations. The daily proportion of protein in adult diets is approximately 90 g on average for men and 80 g for women [2]. However, the values tend to vary enormously in individuals. The high proportion of protein, however, does not only have positive aspects; the down side is that too much protein can result in over-acidification of the organism. Complications include an increase in the potential acidification of the renal system due to metabolism of sulfur-containing amino acids. Such a high ingestion of protein can initiate osteoporosis. Collagen and collagen products such as collagen hydrolysate contain no sulphur-containing amino acids therefore have no influence on bone metabolism, especially from a catabolic standpoint.
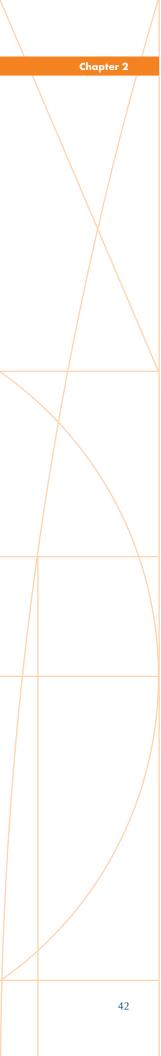
A more comprehensive approach should be considered on a worldwide basis with respect to the quality of protein in the diet.

■ Deficit of collagen characteristic amino acids

In spite of a general over-supply of animal and plant based protein, a deficit in the collagen characteristic amino acids proline and glycine may occur. A long-term administration of 10 g collagen hydrolysate per day may give rise to a continuous increase of proline and hydroxyproline in plasma, as demonstrated in clinical studies (see chapter 4.1). Under stress situations or in old age, an increase in the availability of amino acid building blocks could be of relevance and provide a measure of prevention for the cartilage matrix. The intensified incorporation of collagen building blocks via food has been clearly proven using radio-labeled isotopes [4].

In conclusion, an overall approach to prevent and support therapy of degenerative diseases has to include physical activity, a balanced diet, nutritional supplementation and, if necessary, adequate medication. Experimental and clinical data would appear to indicate that optimal nutrition involving additional collagen hydrolysate may support the complex therapy of osteoarthritis as well as providing preventive effects by influencing cartilage metabolism.

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Chapter 3

Collagen Hydrolysate and its Biological Value

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Collagen Hydrolysate and its Biological Value

Collagen is a protein of a special amino acid composition. It is the most frequently occurring protein in animal and man, and the most important functional building block of intercellular connective and supporting tissues, including cartilage. Its crucial function is due to its high elasticity. Three protein chains with a levo-rotating helix structure are twisted together to form a dextro-rotating super helix. In the meantime, 21 collagen types with differing numbers of α-chains in each triple helix have been differentiated; most of them are fibrillar. Apart from the fibrilous collagen type I (bone, collagenous connective tissue), type II (cartilage), type III (reticular fibers), type V (combined with types I and III) and type VI (combined with type II) there are non-fibrillar collagen forms such as type IV

Amino acid	Bovine hide collagen	Bovine hide gelatine (type B)	Calfskin gelatine (type B)	Bone gelatine (type B)	Pigskin gelatine (type A)
Alanine	10.3	11.1	11.1	11.3	10.7
Arginine*	8.2	9.1	5.7	9.0	9.1
Aspartic acid	7.0	6.6	6.7	6.7	6.7
Cystine	0.0	0.0	0.0	0.0	0.0
Glutamic acid	11.2	11.1	11.5	11.6	11.3
Glycine	26.6	27.2	27.5	27.2	26.4
Histidine*	0.7	0.7	0.8	0.7	1.0
Proline	14.4	16.3	16.5	15.5	16.2
Hydroxyproline	12.8	14.4	14.6	13.3	13.5
Hydroxylysine	1.2	1.1	1.1	0.8	1.0
Isoleucine*	1.9	1.7	1.8	1.6	1.4
Leucine*	3.7	3.4	3.4	3.5	3.3
Lysine*	4.0	4.7	4.6	4.4	4.1
Methionine*	1.0	0.8	0.7	0.6	0.9
Phenylalanine*	2.4	2.3	2.2	2.5	2.6
Serine	4.3	4.1	4.1	3.7	4.1
Threonine*	2.3	2.2	2.3	2.4	2.2
Tryptophane*	0.0	0.0	0.0	0.0	0.0
Tyrosine	1.0	0.3	0.2	0.2	0.6
Valine*	2.5	2.8	2.7	2.8	2.8
Total nitrogen	18.6	18.1	17.8	18.1	18.3
Total raw protein (N x 5.55)	103.2	100.5	98.8	100.5	101.6
Total raw protein (N x 5.25)	116.3	113.1	111.8	113.1	114.4

Amino acid composition of collagen and various types of gelatine [as % of the raw protein (N x 6.25), i.e. in g/16 g N] (after EASTOE und LEACH, 1977)
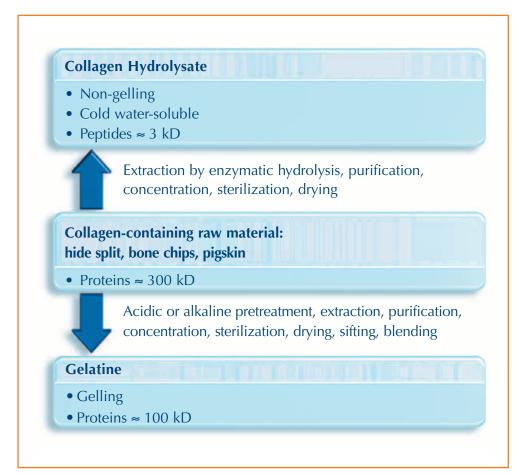*** essential amino acids**

(the lamina densa of basal membrane), type VI (pearl chain filaments in connective tissue and joint cartilage) or type X (pericellular and in the deeper layers of joint and epiphyseal cartilage) as well as other subtypes in skin, blood vessels and other membranes (e.g. types VII and VIII). Type IX can be established as a fibril-associated collagen type on the surface of type II fibrils in cartilage.

This diversity of the various collagen types demonstrates the functional versatility of the protein, but it is insignificant when it comes to producing gelatine and collagen hydrolysate, nor has it any impact on its biological value. In addition, the various types of animal raw material sources for gelatine do not differ significantly in amino acid composition of the respective gelatine and collagen hydrolysate.

■ What is collagen hydrolysate?

Collagen hydrolysate is produced by enzymatic hydrolysis of collagenous tissue (bone, hide and hide split from pigs and cows). So it is a mixture of different polypeptides of essentially identical amino acid composition. Gelatine in general comes from acidic or alkaline hydrolysis of collagenous animal material, which subsequently is extracted, purified, concentrated and

Collagen Hydrolysate

- Non-gelling
- Cold water-soluble
- Peptides ≈ 3 kD

Extraction by enzymatic hydrolysis, purification, concentration, sterilization, drying

Collagen-containing raw material: hide split, bone chips, pigskin

- Proteins ≈ 300 kD

Acidic or alkaline pretreatment, extraction, purification, concentration, sterilization, drying, sifting, blending
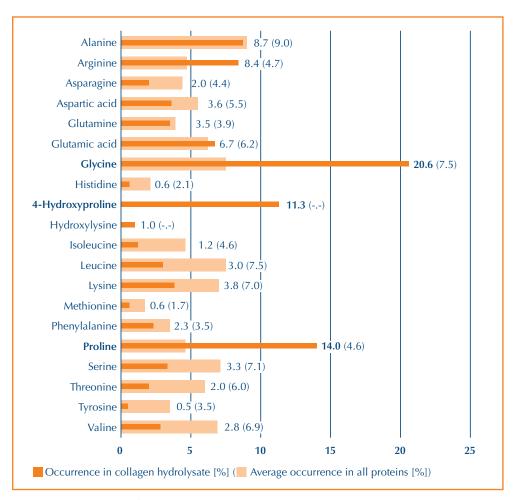
Gelatine

- Gelling
- Proteins ≈ 100 kD

Production of collagen hydrolysate and gelatine

sterilized. This substance is made up of proteins with a molecular weight of around 100 kDaltons and is characterized by its ability to gellate. Collagen hydrolysate is obtained using the same starting material, and the process also includes extraction, enzymatic hydrolysis, purification, concentration, sterilization and drying. But in contrast to gelatine, collagen hydrolysate does not gellate, it is soluble in cold water and is composed of proteins of a molecular weight of 3 (to 6) kDaltons. So ultimately, gelatine is hydrolyzed collagen and collagen hydrolysate is a variant with different physico-chemical properties but with the same amino acid composition in smaller, non-gellating molecules.

By comparing the concentration of the various amino acids in bone cartilage collagen with collagen hydrolysate made from calfskin, it becomes apparent that they are to a large extent identical. Native collagen and collagen hydrolysate differ in their amino acid composition from other natural proteins (see also chapter 3). So is arginine contained in collagen in a clearly higher proportion.

The biggest differences are in glycine and proline; in collagen hydrolysate, these are three times as high as in other proteins.

Alanine — 8.7 (9.0)
Arginine — 8.4 (4.7)
Asparagine — 2.0 (4.4)
Aspartic acid — 3.6 (5.5)
Glutamine — 3.5 (3.9)
Glutamic acid — 6.7 (6.2)
Glycine — **20.6** (7.5)
Histidine — 0.6 (2.1)
4-Hydroxyproline — **11.3** (-.-)
Hydroxylysine — 1.0 (-.-)
Isoleucine — 1.2 (4.6)
Leucine — 3.0 (7.5)
Lysine — 3.8 (7.0)
Methionine — 0.6 (1.7)
Phenylalanine — 2.3 (3.5)
Proline — **14.0** (4.6)
Serine — 3.3 (7.1)
Threonine — 2.0 (6.0)
Tyrosine — 0.5 (3.5)
Valine — 2.8 (6.9)

■ Occurrence in collagen hydrolysate [%] (■ Average occurrence in all proteins [%])

Amino acid spectrum of collagen hydrolysate (percent weight per weight)

However, it is not only the percentages but also the absolute amounts of amino acids in gelatine and other protein-rich food that are interesting and stand much in favor for collagen hydrolysate. Based on grams of amino acid per 100 grams of gelatine and food respectively, the following ratios have been established [1]:

Amino acid	Gelatine	Milk	Meat (Pork)	Potato	Bread (Wheat)
Alanine	9.27	0.12	1.53	0.11	0.24
Arginine	7.45	0.12	1.53	0.12	0.31
Aspartic acid	5.63	0.28	2.34	0.43	0.39
Cystine	-	-	0.31	-	0.2
Glutamic acid	9.58	0.75	3.9	0.46	3.15
Glycine	22.96	0.08	1.4	0.12	0.3
Histidine	0.61	0.09	0.99	0.04	0.18
Proline	13.04	0.35	1.21	0.11	0.96
Hydroxyproline	11.1	-	-		–
Hydroxylysine	1.2	-	-		-
Isoleucine	1.4	0.21	1.27	0.10	0.38
Leucine	2.74	0.35	1.92	0.14	0.59
Lysine	3.8	0.26	2.2	0.13	0.2
Methionine	0.76	0.08	0.72	0.03	0.13
Phenylalanine	1.98	0.17	0.98	0.10	0.42
Serine	3.5	0.19	1.1	0.10	0.39
Threonine	1.8	0.15	1.25	0.09	0.25
Tryptophan	-	0.05	0.31	0.03	0.08
Tyrosine	0.3	0.17	0.91	0.08	0.21
Valine	2.1	0.23	1.42	0.13	0.39

Amino acid content in different food (g amino acid per 100 g food; H. Scherz und F. Senser, Bundesministerium für Ernährung, Landwirtschaft und Forsten)

The table shows that the consumption of about 2.8 L of milk or 1.8 kg of potatoes would be required to take in the same amount of glycine that is contained in 10 g of gelatine or collagen hydrolysate. The proline content in 10 g of gelatine or collagen hydrolysate corresponds to 110 g of meat, 1.2 kg of potatoes or 140 g of bread.

This comparison confirms that collagen hydrolysate provides the required amounts of the most important amino acids for the cartilage metabolism much more effectively and more selectively than any other protein containing food.

■ Physiological value of collagen hydrolysate

An adequate supply of glycine and proline is essential to the stabilizing and regenerating processes of the cartilage metabolism. To synthesize a single picogram of collagen type II, over one billion glycine molecules and 620 million proline molecules are required. With protein-poor diet (age, chronic disease, one-sided diets), or after strenuous activity (high performance in sport, reconvalescence, growth), the alimentary supply of these amino acids particularly could well be inadequate. In consequence the anabolic phase of cartilage metabolism could be impaired. The synthesis performance of the chondrocytes would be deminished. Degradation processes would predominate (see chapter 1) reducing the thickness of the cartilage layer by way of "wear and tear".

In the meantime, the direct stimulation of collagen synthesis in chondrocytes by collagen hydrolysate has been proven scientifically (OESSER, S. *et al.* 2003: "Stimulation of type II collagen biosynthesis and secretion in bovine chondrocytes cultured with degraded collagen" [26]).

The causal nexus between the intake of collagen hydrolysate and the increased formation of collagenous cartilage matrix has been firmly established.

Claims that orally administered gelatine or collagen hydrolysate are not digested in the intestine and hence cannot be resorbed as a specifically configurated amino acid mixture have been refuted. Intestinal digestion and sequestration into the resorbed building blocks however is a precondition for a pharmacokinetic effect within the cartilage.

■ Biokinetics of collagen hydrolysate

Proof that gelatine or collagen hydrolysate is in fact hydrolized and resorbed in the intestinal tract has been presented by controlled studies on rats fed with gelatine. In comparison to the control group, the post-prandial concentrations of the amino acids proline, hydroxyproline and glycine in the portal vein of the animals fed by gelatine increased significantly [9]. In humans, the concentrations established in peripheral blood subsequent to the administration of 10 g of collagen hydrolysate showed identical findings [10]. In a single blind, randomized and placebo-controlled study on 60 male sports students between October 1990 and the end of March 1991, the amino acid concentrations in peripheral blood after a daily intake of 10 g of collagen for 4.5 months were determined six times. In relation to the control group the data for the amino acids glycine, proline and hydroxyproline in the verum group showed increased levels in a highly significant way. The concentrations of alanine, asparagine, glutamic acid and tryptophan were also higher. These findings confirm that gelatine or collagen hydrolysate is in fact digested in the intestine, and that the amino acid building blocks are resorbed in their collagen-specific form. The comparison with the

placebo group and their nutrition without enhancement in collagen-rich components confirms that the amino acid concentration corresponds to the food ingested. Usual food without additional collagen produces lower plasma levels of those amino acids with an affinity to collagen and hence also a lower supply at the sites of chondrocyte synthesis.

Apart from the resorption of special amino acids with an affinity to collagen, polypeptides originating from collagen hydrolysate are also resorbed in their original molecular weight distribution [11; 26]. Consequently collagen hydrolysate causes the stimulation of the chondrocyte metabolism and subsequently the new formation of collagen through its particular adequate amino acid configuration, and its native polypeptide structures as well.

OESSER [11] estimated roughly that approximately 90 % of the orally administered collagen hydrolysate would be resorbed within six hours from the gastro-intestinal tract. Just one hour after the oral administration 47% had been absorbed (as compared to isolated proline: 55%).

Investigations using radio-labeled collagen hydrolysate have shown that, within cartilage tissue, the enrichment is threefold.

Otherwise, in the whole organism except cartilage tissue radio-labeled collagen hydrolysate showed the same distribution and the same plasma level as proline. After 96 h, no radio-labeled substance could be detected in the plasma; in cartilage tissue, however, the period extends over 96 h. The degree of enrichment in cartilage tissue and the extended presence confirm the special affinity between cartilage and these protein building blocks, and suggest their anabolic effect. If there were only adhesive or temporary effects from the collagen building blocks, the significant enrichment effect and the extended period of presence could not be explained.

■ Selective cartilage effect of collagen hydrolysate

In the meantime, as already mentioned, the special affinity to cartilage and the stimulating effect on the synthesis of chondrocytes has been confirmed experimentally [11].

In cell cultures of chondrocytes collagen hydrolysate, dependent on the dose, enhanced both the metabolism and the synthesis of collagen type II.

The synthesis of cartilage-specific proteoglycans as components of the cartilage matrix (see chapter 1) was also increased significantly by administration of collagen hydrolysate [11]. The clearly measurable increases in concentration, especially of the collagen type II and the proteoglycans that occur in cartilage, confirm that **collagen hydrolysate has a specific metabolism-increasing and hence anabolic effect on chondrocytes and initiates the repair processes in cartilage.**

■ Tolerability

As collagen hydrolysate is a not a pharmaceutical drug but food, considerations on the possibility of toxicity are unfounded. But since collagen hydrolysate is a modified natural product, questions on its tolerability and possible side-effects have to be answered all the same. As should be the case with a substance that has been approved as a food additive and for medical applications, e.g. as an excipient in drugs, no side-effects are known. The US Federal Drug Administration (FDA), subsequent to conducting safety studies on collagen products (gelatine and collagen hydrolysate), allocated them to the highest possible safety category: **GRAS (Generally Recognized As Safe).** In a letter, dated December 21, 2001, the FDA formulated: "... In accordance with the provisions of § 170.35 the Commissioner proposed to affirm the GRAS status of gelatin as a direct food ingredient...". Thus, collagen hydrolysate products are categorized at the same level as the essential amino acids.

The tolerability of collagen hydrolysate has been assessed in a series of controlled comparative studies and subsequently found to be extremely good. In an earlier study, 580 rats were administered 1.5 g per day of collagen hydrolysate over a period of three weeks. No side-effects were observed [9]. MOSKOWITZ [12] in his much-cited international randomized patient study (see also chapter 4.1) established that of 389 patients who were treated over a period of 6 months with 10 g per day of collagen hydrolysate or placebo, only 12 (about 3%) dropped out due to side-effects (mild-to-medium meteorism and diahrrea). Of these 12 patients, 9 were from the placebo group and only 3 from the verum group that had received collagen hydrolysate.

TAKEDA has shown in animal studies that also in the cases of extreme oral dosing of gelatine products there were no alarming problems [13]. In studies on rats the LD_{50} doses were 10 g/kg, an amount that corresponds to some 700 g of collagen hydrolysate for the human body. The recorded effects on the rodents at 60% collagen in food were increases in the weights of liver and kidneys. This, however, is no special feature in the application of collagen. Weight increases of that sort also occur when other proteins are administered in above-average amounts and absorbed from the intestine.

As for all food components, native and modified, the problem of possible cancer-promotion is of high relevance in administrations over a longer period. It goes without saying that studies on this problem have been carried out with collagen hydrolysate [14]. The carcinogenic potential was assessed on five different strains of *Salmonella typhimurium,* an *E.coli* strain, and bone marrow cells taken from Chinese hamsters in the AMES test. The results confirmed that there is no indication of an increased mutagenicity or carcinogenicity by collagen hydrolysate. With respect to teratogenicity there were no disqieting hints or alarming signs, even if there are no studies on this specific aspect as yet. Considering the ubiquitous nature of collagen in strictly speaking all food of animal origin and the chronic exposure to daily routine food, such studies would appear to be irrelevant.

■ No allergy risk

As in all proteins there is in collagen and its derivatives a principal possibility of causing sensitizations and allergenic reactions. Individual intolerance reactions have in fact been observed when collagen was applied intravenously for volume replacement. An allergy test is recommended as well, if collagen is used for subcutaneous injections of wrinkles in cosmetic surgery. However, this only applies to invasive applications. On oral administration, no cases of allergy or massive gastro-intestinal over-sensitivity reactions have been reported as yet. In spite of its protein structure and frequent long-term exposure via numerous food-stuffs containing collagen, and in spite of the traceable penetration of low-molecular protein from the intestinal lumen into the blood (see above), orally administered collagen hydrolysate is apparently non-allergenic. Furthermore, no findings of non-allergenic incompatibility to food have ever been observed.

■ Interaction

In general, collagen hydrolysate is characterized by the highest degree of safety with respect to possible interactions with drugs, excipients or other food components; it is in fact subject to no limitations or restrictions as designated by the US Food and Drug Administration (FDA).

In case of the intravenous administration of collagen hydrolysate which is almost irrelevant, studies on animals have shown that the plasma fibronectin level may be affected, as published by NAGELSCHMIDT *et al.* [15]. In association with it wound healing was disturbed in the rats involved. The degree of risk involved in such an application, atypical in any case, is further reduced by the finding that there was no influence on the fibronectin level in plasma or on wound healing if a collagen solution (Haemaccel) with a lower molecular weight as that of gelatine was injected. Haemaccel has a molecular weight of approx. 40 kDaltons. The molecular weight of collagen hydrolysate, 2-6 kDaltons, is lower by a factor of ten; so that in the case of intravenous or parenteral subdermal application no risk results from the interaction with fibronectin is to be feared. Fibronectins are structural proteins in the extracellular matrix of connective tissue. They are constantly being formed by the fibroblasts and are components of the surfaces of normal connective tissue cells and their immediate environment. As a normal function, these structural and adhesion proteins bind to other macromolecules (not only collagen but also fibrinogen, fibrin, glycosamine glycane, actin, some types of bacteria, cell membranes etc.) and help e.g. fibroblasts to settle in wounds. No binding occurs with low-molecular substances, and thus no reduction of the fibronectin level by collagen hydrolysate.

■ Effects on chondrocyte metabolism

The resorption of amino acids from oral application of collagen hydrolysate has been verified as described above. The optimal supply of building blocks

for collagen with its distinctly higher concentrations of glycine, proline and hydroxyproline could already provide an explanation for the stimulation of chondrocytes and the enhancement of the synthesis of collagen type II, because the balanced substrate for the new formation of matrix can – in its specific distribution of components – only be found in collagen and not in other nutritional proteins. The hydroxyproline that is generated from proline and which is particularly important for the selective collagen synthesis can only be detected in considerable concentrations in collagen hydrolysate but not in any other food.

Apparently, the anabolic effect of orally administered collagen hydrolysate is not only due to the highly suitable substrate available. Gastro-enterologist VOLKHEIMER, during the 1960s, at the Charité in Berlin, carried out numerous resorption experiments to confirm what had already been observed by HIRSCH in 1906. Hirsch observed that macromolecules and even capsular elements from the intestine were able to be taken up in total by the organism by a process of persorption and subsequently detected in blood and urine (the Hirsch effect) [16; 17].

WARSHAW [18] as well as SEIFERT and SASS [19] also confirmed the transmural uptake of macromolecules from the intestine. Resorption of a proteolytic enzyme into the building blocks without cleavage has also been confirmed [20].

If in consequence collagen hydrolysate can be resorbed and enriched in the cartilage over a period of time, it is conceivable to think that the chondrocyte metabolism can be influenced directly by this hydrolyzed protein. This is of importance on principle in assessing the effect of collagen hydrolysate on cartilage metabolism and the potential prevention of cartilage degeneration.

Based on this, studies were carried out on primary cartilage cell cultures. Chondrocytes are responsible for the synthesis, organization, stability and maintenance of extracellular cartilage matrix and for maintaining an equilibrium between anabolic and catabolic restructuring as already mentioned in chapter 1. The essential matrix building blocks of cartilage are the proteoglycans and collagen. Collagen type II, characteristic for joint cartilage, through its 3-dimensional fibril network, provides the necessary firmness and the proteoglycans the elasticity of the cartilage tissue [21; 22]. It has also been confirmed in the meantime – in spite of many unanswered questions concerning the physiology of chondrocytes – that specific bioactive signals regulate the activity of the chondrocytes as well as the build-up and degradation processes [23]. This turnover on the part of cartilage matrix is also apparently subject to patho-physiological influences. In 1990, HARDINGHAM and BAYLISS [24] showed that in osteoarthritic joint processes the sensitivity of chondrocytes to various regulatory signals is decreased. This has an effect on the composition of the cartilage matrix. The authors postulated that the disparity between degenerative and regenerative and between anabolic and catabolic processes within cartilage tissue leads to a decrease in collagen type II. This primarily biochemical structural imbalance is

apparently responsible for the etio-pathogenic changes in joint cartilage that are generally designated as being degenerative and which are described in some detail in chapter 1. The thickness and the homogeneity of the joint cartilage are decreased; this in turn leads to a deterioration in mobility and possibly to joint pain. The typical clinical picture of (active) osteoarthritis then begins to develop.

This patho-physiological cascade leads to the consideration as to whether, through targeted influence on the chondrocyte metabolism, osteoarthritic changes in their early stages can be prevented and initial repair processes on cartilage supported. In such a case, the target structures would be the chondrocytes and not the cartilage matrix. Regulation of cartilage cell metabolism also influences the composition of the matrix. This can be achieved by stimulation of the chondrocyte metabolism but not only with anabolic dominance. The system is regulated in two ways. Cytokines and growth hormones can stimulate the biosynthesis of cartilage matrix molecules [25]. However, in contrast, the production of proteolytic enzymes such as collagenase and proteoglycanases can be stimulated [21; 22]; in this way the catabolic phase gains the upper hand.
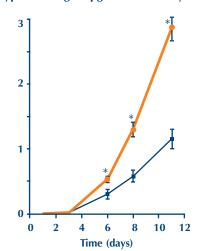
In practice the findings, here already pointed out extensively (see also chapter 1 for full details), that collagen fragments, especially collagen hydrolysate, exert an influence on the chondrocyte metabolism, and thus show an effect on the composition and function of the cartilage matrix. In order to make these practice-relevant findings more precise and to define the special functions more clearly, a study was carried out using primary bovine cartilage cell cultures to establish whether and to what extent various types of hydrolyzed collagen could stimulate chondrocytes and increase the synthesis of collagen and protyoglycans [26].

Denatured inactivated collagens (hydrolyzed collagen of type I, II and III and native collagen of types I and II) and, as a control, collagen-free hydrolyzed wheat protein of molecular weight of approx. 1.5 kDaltons were employed. ^{14}C-proline was added to the cultures and the cell-associated radioactivity after 2 days determined with a liquid scintillator. The target substances were collagen type II and proteoglycans, whose quantitative determination provided information on the stimulating potency of the various collagen products in comparison to the collagen-free wheat protein.

The results showed that the addition of 0.5 mg/ml collagen hydrolysate stimulated the cartilage cells to an increased output of collagen type II. After 11 days, the stimulated chondrocytes had produced more than double the amount of the untreated cells. Comparison of the various collagen additives showed that the hydrolyzed low-molecular collagen fragments increased the synthesis of collagen type II distinctly, and that the collagen-free wheat protein, in spite of its low molecular weight, and the native high-molecular collagen type I were not able to influence the synthesis of collagen type II in the chondrocyte culture.

This showed that the stimulation of collagen type II, the actual cartilage collagen, is a specific effect initiated by the low-molecular collagen hydrolysate.
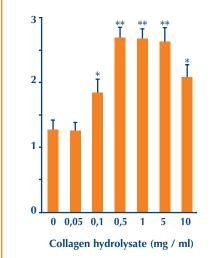
Type II collagen (µg/10⁶ chondrocytes)

Time course of type II collagen secretion into the supernatants of bovine chondrocytes cultured in basal medium (BM) or in medium supplemented with 0.5 mg/ml collagen hydrolysate (CH). Data represent mean ± SD of 4 chondrocyte preparations performed in triplicate.
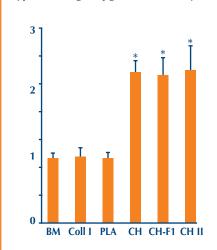
* p < 0.01 compared with untreated controls

Type II collagen (µg/10⁶ chondrocytes)

Collagen hydrolysate (mg / ml)

Type II collagen secretion measured in the supernatants of 11-day-old bovine chondrocyte cultures after treatment with collagen hydrolysate. Data represent mean ± SD of 6 chondrocyte preparations performed in duplicate.
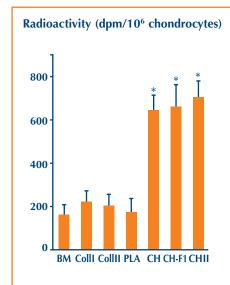
** p < 0.01 compared to treatment with 0.1 mg/ml CH

Type II collagen (µg/10⁶ chondrocytes)

Type II collagen biosynthesis measured in a bovine chondrocyte culture over 11 days after treatment with one of the following substances (0.5 mg/ml): native collagen type I (Coll I) collagen-free hydrolysate of wheat protein (PLA) collagen hydrolysate (CH) collagen hydrolysate fraction (CH-F1) and type II collagen hydrolysate (CH II). Cells in the group (BM) were cultured in basal medium. Data represent mean ± SD of 6 chondrocyte preparations performed in duplicate.

* p < 0.01 compared to untreated controls

Radioactivity (dpm/10^6 chondrocytes)

Stimulation of the collagen biosynthesis in 11-days-old bovine chondrocyte cultures, as measured by incorporation of [^{14}C]-proline (48 h incubation) after treatment with one of the following substances (0.5 mg/ml):
native collagen type I (Coll I),
native collagen type II (Coll II),
collagen-free hydrolysate of wheat protein (PLA),
collagen hydrolysate (CH),
collagen hydrolysate fraction (CH-F1)
and type II collagen hydrolysate (CH II). Cells in the control group (BM) were cultured in basal medium. Data represent mean ± SD for 6 experiments performed in duplicate.

* $p < 0.01$ compared to untreated controls

It is of interest to note that the proteoglycans were also produced in increased amounts subsequent to the addition of collagen hydrolysate; thus, both essential protein structures of the joint cartilage were made available for anabolic and repair processes.

This laboratory experiment showed, that through the addition of collagen hydrolysate two important building blocks necessary for the formation of new cartilage and the repair of existing cartilage, collagen type II and proteoglycans are formed in increased amounts by the chondrocytes.

It is also conceivable that, during normal cartilage stress, low-molecular collagen fragments are produced on and within the cartilage and that, thanks to the stimulating effect on chondrocyte activity, a self-healing process is initiated for minor cartilage damage controlled by a feedback mechanism. This would explain the repair effect of dosed stress on cartilage tissue as well as the catabolic effect during rest.

These data, however, are of even more importance for the practical consideration of using orally administered collagen hydrolysate to optimize the diet and in doing so to possibly slow down the progress of osteoarthritic degeneration and to provide true prevention.

The positive effect of collagen hydrolysate on the restoration of function and the relief of osteoarthritic pain has already been confirmed in a number of studies (see chapter 4.1).

From the data that are currently available we are able to conclude that it is useful to recommend collagen hydrolysate as a nutritional supplement.

The biosynthesis of collagen (and proteoglycan) by the chondrocytes is activated, hence preventing degenerative processes and even activating repair processes in the joint cartilage. In this way, early and effective protection from osteoarthritic degeneration is made possible at low cost.

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Chapter 4

Comments and Expert Opinions from a Clinical Point of View

4.1 Clinical Data on Collagen Hydrolysate

Milan Adam, M.D.

Clinical Data on Collagen Hydrolysate

Assessment of success resulting from traditional medicine and based on experience has little chance of being accepted by the expert committees in today's world of evidence-based medicine. However, such healing methods, that may be hundreds of years old, often provide the required trigger to take up such observed phenomena and to combine them with today's methodical possibilities. This also applies to the chondro-protective effects of collagen-rich nutrition. Not only the recipes established by Hildegard von Bingen in the Middle Ages referred to the healing effect of foodstuffs rich in connective tissue; even today, in several pharmacopoeias and as recommendations by orthopedic university academics such as BEUKER (personal communication) have given positive assessments. However, it is only the clinical and experimental studies that have provided confirmation of the observed positive effects brought about by collagen.

■ Clinical studies show: Collagen hydrolysate can relieve osteoarthritic pain

The first well-founded studies were carried out during the 1980s [1; 2; 3 etc.]. Already in 1991, we published data from our own randomized, double-blind study on 81 patients suffering from osteoarthritis [4]. Four therapeutic variations were tested using collagen hydrolysate and placebo (ovalbumin). Over a period of 16 months, subsequent to a wash-out phase of 2 months, 3 different collagen preparations and placebos were administered in different, double-blind sequence, to 52 volunteers. Evaluation of the results established that, in the verum groups receiving collagen hydrolysate, there was substantial pain relief compared with the control groups. There was a pronounced change in the pain score (>26%) of 42 (= 81%) in those treated with collagen hydrolysate whereas only 12 (23%) of the placebo group recorded such an improvement. The consumption of analgesics in the verum group was reduced by half. In a multi-center study on 359 patients suffering from gonarthritis, coxarthritis and rheumatoid arthritis, substantial pain relief was also achieved after administration of a mixture of L-cysteine and gelatine over a period of 6 months. In addition, the walking route, previously shortened due to pain, was lengthened [5; 6].

BEUKER et al. administered, over a period of 3 months, a daily dose of 10 g collagen hydrolysate or placebo added to the food of trained sports students (see also chapter 4.3) of average age 24.4 who had no disease of the joints [7]. All of the students carried out power training three times a week for a period of 1 hour. In an observation study carried out simultaneously and under the same conditions, 40 patients were treated in a sports medical practice. Apart from the subjective findings such as pain perception and mobility of the stressed joints subsequent to power training, the amino acid profiles in serum were determined (see below). A comparative evaluation with the placebo

group established that the effect of the analgesics administered was enhanced by the simultaneous administration of collagen hydrolysate.

Even the sole administration of collagen hydrolysate was superior to placebo and the combination of placebo and analgesics. In 81% of the collagen hydrolysate group there was a distinct improvement, although 19% indicated no improvement or even a worsening effect; thus, it can be assumed that there is an individual fluctuation range involved.

An elaborated, prospective, randomized, multi-center, double-blind study at 19 centers in the USA, UK and Germany involving 389 gonarthritis patients studied over a period of 24 months between 1996 and 1998 also established, with regional differences (see below), that there was a distinct relief in pain in the groups administered collagen hydrolysate [8].

■ Rippe *et al.* show: Collagen hydrolysate influences isokinetic power

The results of a double-blind, randomized, prospective and placebo-controlled study carried out by James Rippe and colleagues (Massachusetts, USA) on 190 patients with confirmed osteoarthritis of the knee are of high importance, too [9]. In this study carried out over a period of 14 months, collagen hydrolysate or placebo was administered and not just the usual parameters of pain, resilience to stress and mobility were measured but also the isometric and iso-kinetic leg power on extension and flexion (see chapter 4.2). In the verum group there was a significant increase in the isokinetic values between week 8 and week 14 whilst in the placebo group either no or just slight improvement was measured. The isometric differences were not significant; however, the trend was towards the verum group. These data are apparently much more sen-sitive than measurable differences in pain-free walking tests. They are of par-ticular relevance in sports medicine and could well open up new application areas for collagen hydrolysate.

All the studies quoted show the pain-relieving qualities of collagen hydrolysate in patients suffering from osteoarthritis; thus, independent of the preventive aspect of collagen administration, the analgesic-saving effect in therapy should be fully utilized.

■ Clinical studies demonstrate: Collagen hydrolysate can improve mobility and reduce the requirement for analgesics

BEUKER and ROSENFELD [7] in a 6-month placebo-controlled study on 100 elderly patients (average age 62) also established a distinct therapeutic effect. Half of the patients were given a daily dose of 10 g collagen hydrolysate with their food and the other half placebo. On completion of the study, the

verum group demonstrated distinctly improved mobility. In coxarthritis patients, improvement was achieved in the abduction/adduction (verum 5 degrees, placebo 1 degree), flexion/extension (verum 5.7 degrees, placebo 1 degree) and external/internal rotation (verum 3 degrees, placebo 0.5 degrees).

SEELIGMÜLLER et al. [5; 6] observed in his studies not only pain relief but a pronounced improvement in mobility of the diseased joints.

The already mentioned international multi-center study carried out by MOSKOWITZ also showed improvement in joint function of different extents in the verum group with primary gonarthritis (see below).

BEUKER and others (see above) have shown that the long-term administration of collagen hydrolysate in adequate dosages of 10 g per day can reduce the need for analgesics apart from relieving pain.

MOSKOWITZ [8] made the same observations. However, it was noticeable that the results obtained were different in different countries. In the 11 German centers the effects of the verum group were especially pronounced. Critical analysis of the study methods leads to the assumption that the cultural differences in the various regions, e.g. the degree of preparedness to take high dosages of analgesics, masked the effect of collagen hydrolysate.

GROMNICA-IHLE [10] in the German adapted version of "HARRISON's Principles of Internal Medicine" (15th edition; McGraw-Hill, 2001), emphasizes in particular in the chapter on osteoarthritis that there are differences between Europe and the USA in the concept of the use of analgesics. Whilst in the USA paracetamol is regarded as a first-line preparation, in Germany, non-steroidal anti-inflammatory drugs take preference, and, in recent years, has included coxibs.

■ There are no medical application restrictions on collagen hydrolysate

Collagen hydrolysate, a protein prepared by hydrolysis and which is contained in high proportions in foodstuffs of animal origin is highly tolerated and without side-effects. TAKEDA [11] already in 1982 in studies on rodents established that there was no participant amongst the 389 in whom serious side-effects resulting from the administration of collagen hydrolysate could be established and which could have resulted in a drop-out from the study. The extremely critical US agency, the Food and Drug Administration has, as mentioned in earlier chapters, allocated GRAS ("Generally Recognized As Safe") status to collagen hydrolysate. This assessment was also taken up by the German Federal Institute for Drugs and Medicinal Products and by the World Health Organization (WHO). None of the organizations has restricted its application in any way.

RIPPE (see above) in fact established side-effects in almost all members of the placebo group (headache, meteorism, diarrhea, cramp, excretion of blood, nausea etc.). These were higher than in the verum group (e.g. meteorism 7.8% in the placebo group, 2.3% in the collagen hydrolysate group, headache 3.9 versus 1.1). The same results were obtained in the international MOSKOWITZ study.

The allergenic potential of collagen hydrolysate is very low. It is in fact designated as being hypoallergenic and hence approved for use as a plasma expander. Hence, there is no reason to dispense with collagen hydrolysate in patients with allergies, even if, for safety reasons, a tolerance test should be carried out prior to use.

Interaction with other food / food ingredients or with medication is also unknown. Collagen hydrolysate is neither mutagenic nor teratogenic; it may thus be used in pregnancy.

■ Collagen is well digested and resorbed

Claims that collagen is hardly digested and only slightly resorbed during its passage through the intestinal tract have been refuted. It is not resistant to proteolytic enzymes and is resorbed to an extent of 85-95%. Its special amino acid composition with higher concentrations of glycine and proline, identical to the collagen structure of the cartilage matrix, makes it an ideal supplier of protein building blocks without even partial deficits (see chapter 3). In addition, those low-molecular proteins that are present in cartilage tissue and that apparently activate the chondrocytes [12] are resorbed.

■ Collagen hydrolysate has an effect on other collagen-rich vital tissues

In veterinary medicine, the highly significant improvement in the properties of hair and hooves brought about by collagen hydrolysate has been known for many years (e.g. MORGANTI [15]; BRODIE [16]). In human medicine also the positive influence of collagen on the growth of hair and nails has been observed.

WEH [17] has assumed that, apart from the anabolic effect of collagen hydrolysate on the matrix of the joint cartilage, other connective tissues such as ligaments, tendons and capsules benefit from substitution, hence contributing to the periarticular stability of ligaments and tendons.

Even if the prevention of osteoarthritis is the main goal of the physician in administering collagen hydrolysate, its supporting role in inflammatory joint disease (rheumatoid arthritis) has been demonstrated. As to whether and to what extent administration of collagen hydrolysate is meaningful in a number of skin conditions or in the prevention of degenerative skin changes (aged skin) will have to

be shown in further clinical research. However, from the point of view of the mechanisms involved, such an indication area would appear to be promising.

■ There is no health risk involved with collagen hydrolysate

The fear, sometimes expressed that, because of the bovine starting materials used in its manufacture, there is a risk of prions being transferred and hence a BSE risk not excluded, has been clearly refuted on a scientific basis. Firstly, the raw materials used originate from healthy animals that have been approved for human consumption by the veterinary authorities, i.e. they are subject to the stringent safety regulations of BSE prophylaxis. Secondly, as already described in the previous chapter, the production process involving several weeks of processing with hydrochloric acid and sodium hydroxide and sterilization at 140 °C is so aggressive that no vital organisms can survive.

■ Collagen hydrolysate causes no serious intolerance reactions

The exceptional compatibility of collagen hydrolysate that, as an original product is free from all preservatives or other additives, has already been referred to a number of times and the FDA designation of GRAS ("**G**enerally **R**ecognized **A**s **S**afe") emphasized – a category that is also applied to sugar, salt, vitamins etc.

This degree of harmlessness also applies to the fears of allergy sometimes expressed by participants in clinical studies. In the studies carried out to date involving a large number of controlled applications (see also chapter 3), no clinical or para-clinical indications of allergy were found. Also, there is no indication of the food incompatibility that sometimes occurs with other proteins as a result of intestinal enzyme defects. In the international study carried out by MOSKOWITZ [8] individual participants complained of slight flatulence and diarrhea and there may have been a connection to collagen hydrolysate even though this is anything but certain, especially as it was taken at placebo level.

■ Application recommendations

According to the data compiled in practice and as a result of studies, collagen hydrolysate might be effective and meaningful for:

- Prophylaxis of degenerative joint disease, especially for risk groups such as:
    - The elderly
    - Those whose families have suffered from joint disease
    - Adipose persons and those who are slightly overweight
    - Those involved in heavy manual work in their professions, sports or hobbies
    - Patients with existing orthopedic conditions (including secondary osteoarthritis) and false positioning of joints

- Those who are following false or extreme diets
- During growth phases
- Rehabilitation
- Intensive training
- Support during symptomatic treatment (relief of pain, reduction of functional restrictions, anti-inflammatory therapy) in:
  - Existing osteoarthritis, in particular coxarthritis, gonarthritis, poly-arthritis of the finger and vertebral joints)
  - Other degenerative diseases of the vertebral column (e.g. Scheuermann´s disease)
  - Chondropathy (e.g. chondropathy of the patella)
  - Growth disturbances
  - Consequences of trauma
  - Pain resulting from excess stress on joints
- Prevention of deficits of certain amino acids (glycine, proline) in chronic digestive disease and, generally, in the case of preferred, highly-processed (i.e. lacking adequate amounts of collagen) foods, in extreme, meatless diets and for general optimization of nutrition.
- Special indications such as subcutaneous application in cosmetic opera-tions (e.g. injection of wrinkles) or intravenously as hyopallergenic plasma expanders.

The excellent tolerability of collagen hydrolysate enables a wide range of ther-apeutic applications without narrow dosage limitations.

Clinical studies have shown that a daily dose of 10 g of collagen hydrolysate is effective. Administration should be at least over a period of 3 months [4]**.**

However, permanent application without intervals is also possible and even advisable (change in eating habits, health-promoting foodstuffs, stabilization of health, avoidance of risk).
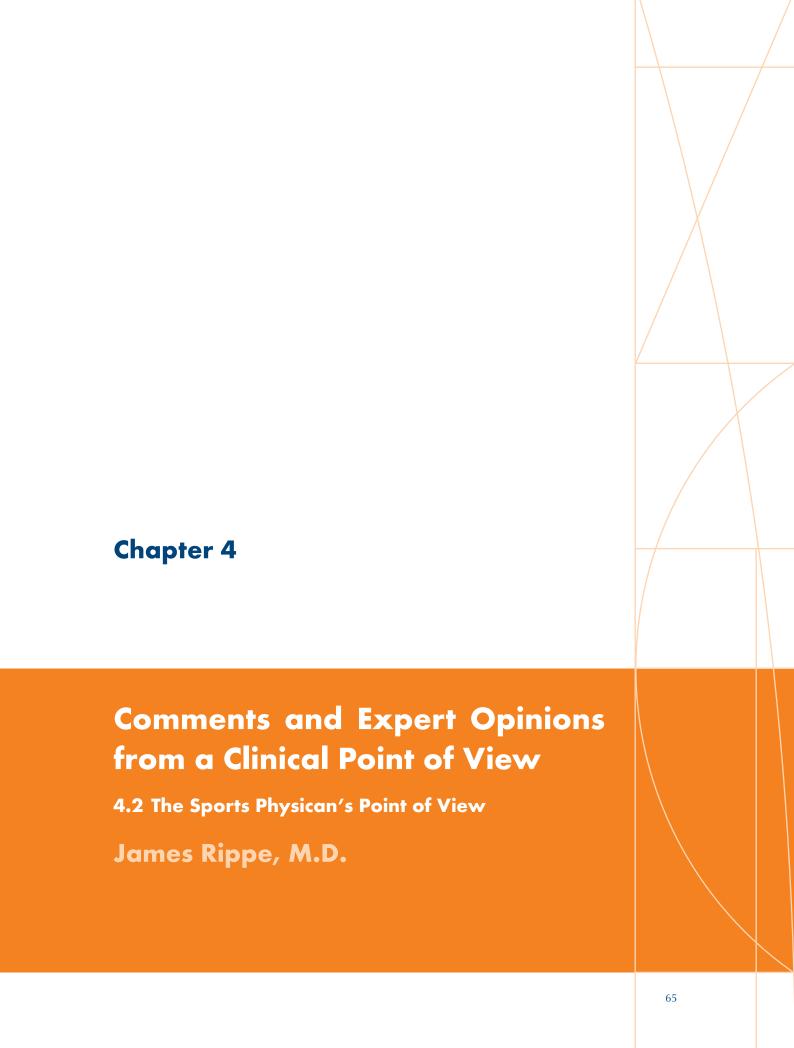
The possibilities of obtaining the recommended daily dosages are manifold as there is a comprehensive range of foodstuffs, nutritional supplements and beverages on the market containing collagen in relatively high concentrations. As some patients find it difficult to take pure, taste-neutral collagen hydrolysate on a permanent basis, their physicians, pharmacists and dietitians can recom-mend a number of ready-to-use products containing drinking or powdered gelatine and which are supplemented with appropriate flavors. Compliance is high in the case of recommended permanent administration thanks to the enjoyment effect involved. The range of products available extends from pow-ders for making drinks, capsules and beverages.

Patients interested in these products should consider asking their pharmacists or dietitians for more information that will enable them to find the most appro-priate product for their own special needs.

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Chapter 4

Comments and Expert Opinions from a Clinical Point of View

4.2 The Sports Physican's Point of View

James Rippe, M.D.

The Sports Physician's Point of View

The view that simply taking care is the best method of preventing damage to joint cartilage is wrong. Patho-physiological studies have shown that well-dosed, undulating stress stimulation in the form of pressure and relaxation is necessary for the supply of nutrients to blood vessel-free cartilage from the extra-chondral synovia or lymph vessels and for the elimination of metabolic waste from cartilage (see also chapter 1).

Dosed stress is apparently a stimulus for the neogenesis of the cartilage matrix.

It has also been established, however, that biomechanical strains on the joints from a variety of different causes can lead to trophic disturbance and cartilage damage. However, to interpret this as a warning against sporting activities would be wrong. In fact, a sedentary lifestyle is an invitation to joint problems. Although many scientifically unfounded claims have been made concerning the osteoarthritis risk to endurance athletes such as marathon runners, racing cyclists, cross-country skiers and walkers, there is in fact no additional risk.

Long-distance runners who in the course of their careers cover 150,000 – 200,000 km or racing cyclists who cover 30,000 km in training runs show no increased incidence to osteoarthritis in the knee or hip joints providing there is no basic axial damage. There is in fact evidence showing that such endurance athletes suffer less with respect to osteoarthritis than the normal population – always providing there is no axial damage, biomechanical problems or trauma.

It has been observed that osteoarthritis of the patella frequently occurs in weight lifters; however, this does not contradict what has been said above. In such cases it is assumed that the massive short-term pressure exerted on cartilage in this type of sport dehydrates the cartilage tissue; it becomes more vulnerable and the risk of micro-trauma is increased. Apparently, it is not the stress itself that causes lesions in the cartilage tissue but more the repeated micro-traumatic events in the cartilage matrix. "It is not so much sports activity itself but the resulting trauma that is the main cause of joint damage" [1]. Thus, the risk involved results from repeated biomechanical problems, weak muscles and joint misalignment on the part of untrained persons carrying out sports activities, from already present joint anomalies (e.g. false axial positions), inadequate loosening up prior to high-performance sports activities or subsequent to non-recognized or untreated trauma.

Metabolic disturbances (including adiposity) and neurological defects also apparently reduce cartilage stability; the result is that in such patients there is

a potentiated risk of osteoarthritis in the case of biomechanical stress, possibly also due to local loss of fluid.

However, it is not only power and endurance sports that can cause multiple and unrecognized micro-trauma on the surface of the cartilage; all sports activities involving movement can bring about the condition. If the body is abruptly stopped at maximum speed, e.g. by accident or collision, the cartilage and joint surfaces can rupture; these then become scar tissue made up of inferior cartilage. Practical experience shows that the administration of collagen preparations may have a favorable influence on cartilage regeneration; thus, sports physicians often recommend the administration of collagen hydrolysate as a preventive measure for those sports activities involving an increased risk of micro-trauma.

The risk of traumatic cartilage damage varies according to the type of sport and the joints involved [2]. Examples of early osteoarthritis as a result of sports trauma are:

- Toe joints: almost 50% of ex-football players over 50 have severe osteoarthritis of the toe joints.
- Ankles: 48% of high-jumpers and 85% of ballet dancers have some evidence of osteoarthritis of the ankles.
- Femur patella: In one report 100% of football players and 90% of weight-lifters have early osteoarthritis of the femur patella joint.
- Lumbar vertebrae: 100% of javelin throwers and 90% of gymnasts and divers have problems with their lumbar vertebrae.
- Shoulder: field athletes (e.g. throwers) and basketball players have frequent problems with the shoulder joint.
- Elbow joints: 90% of weight-lifters, javelin throwers and boxers have trouble with their elbow joints.

Even those sports that are regarded as being joint-friendly, e.g. swimming (including swimming as training for other high-performance sports) is not entirely harmless. In the breast stroke e.g. the medial structure of the knee joint may be traumatized and over-stressed [3], even if this particular risk is much lower than for the other sports mentioned above.

From the sports medicine point of view, the greater risks with respect to joint stability and firmness of joint cartilage are under-stressed joints subjected to too little activity [3]. This is because inadequate muscular stability undoubtedly represents a risk of osteoarthritis.

The correlation in this respect is demonstrated by studies carried out in my laboratory on the isokinetic and isometric development of power under the administration of collagen hydrolysate [4]. This study was carried out between February and September 1999 on a total of 567 persons screened according to specific exclusion criteria. In the final assessment after 14 weeks, 176 volunteers which met American College of Rheumatology (ACR) criteria for

osteoarthritis of the knee were considered. In the 14-week, randomized, prospective, double-blind and placebo-controlled study, collagen-enriched food or placebo were administered (see also chapter 4.1). At the beginning of the study, after 8 weeks and at the end of the study, a 6-minute walking test and the time required for a 50-foot walking stretch were carried out; however, these proved to be too insensitive. Pain levels, radius of movement and degree of mobility produced positive results in the group receiving hydrolyzed collagen. It was surprising to note that of the low-level and slight degree of side effects, the placebo group indicated more symptoms such as diarrhea, headache, nausea etc. than the study group with collagen hydrolysate.

Apart from the predominantly joint parameters employed, a number of isokinetic and isometric measurements were carried out to determine leg power (Biodex Multi-Joint System B 2000™). In the assessment, the 6 isokinetic leg power measurements showed significant increase between weeks 0 and 14 (but not from weeks 0 to 8). There was no such significance in the placebo group; in fact, in part there was a worsening. In the case of the isometric measurements, there was no significance between the groups; there was, however, a positive trend towards the collagen hydrolysate volunteers.

These results indicate the additional stimulating effect of collagen hydrolysate on the joint. These findings suggest that hydrolyzed collagen may improve joint cartilage. Using this mechanism, it was possible to explain the positive effects of dosed physical and sports activity in the prevention of osteoarthritis.

Clinical and sports-medical data on the benefits of collagen hydrolysate in sports nutrition have been available for a number of years. The influence of orally administered collagen hydrolysate on the amino acid concentration in the blood of performance athletes has been regarded as proven for a decade. BEUKER et al. [5] demonstrated in a single-blind, randomized and placebo-controlled study carried out on sports students at the University of Düsseldorf, Germany, over a period of 4.5 months that, under stress power training (3 x 1.5 h per week), the daily administration of 10 g collagen hydrolysate changed the concentration of the amino acids in the blood stream. In the study group e.g. in a total of 6 control measurements, there was a highly significant increase in the concentrations of glycine, proline and hydroxyproline. In the placebo group, under the same training conditions and same meals (no foods containing gelatine), there was no such change in the amino acid profile.

Further studies (see chapter 4.1) confirm these results in various groups of patients. The benefits established on the administration of collagen hydrolysate were confirmed by sports-medical assessment methods whilst those on placebo obtained no benefits.

■ Special aspects in adolescents

Osteoarthritis is commonly regarded as a disease affecting the elderly; however, it can also occur in younger years (see chapter 1). At least early forms and micro-trauma of the joint surfaces apparently occur more frequently than previously thought. In adolescents, such early symptoms often remain undiagnosed or not even registered. Micro-trauma conditions as a rule do not give rise to symptoms at this age; however, they lay the foundation for later degenerative joint conditions in the form of osteoarthritis. Thus, preventive joint protection in adolescent years and for those persons pursuing sports activities is particularly advisable and important. Prevention can avoid threatening degeneration of cartilage or at least slow it down.

Thus, in particular for this group of healthy individuals at risk, the substitution of collagen hydrolysate in food may represent an important preventive measure. It would also appear to be useful according to current opinion in the field of scientific dietetics and sports medicine (see chapter 2):
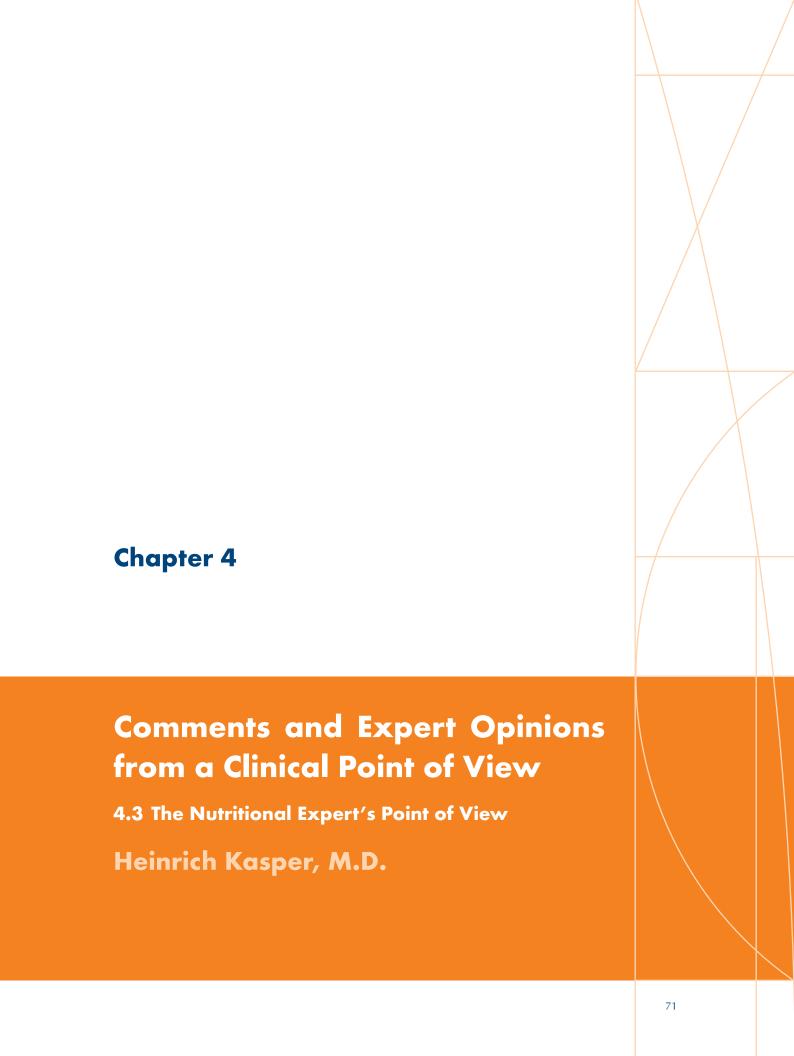
1. It is recognized that the cartilage of adolescents is subjected to more intensive metabolism (see chapter 3). The more rapid turnover requires more amino acids as a substrate for the repair and anabolic process.
2. The diet of adolescents is often consciously of the high-calorie type; collagen-rich and relatively low-energy components tend to be neglected. Imbalance with respect to amino acid availability can thus occur (see chapter 2).
3. Due to the intensive sports activities carried out, athletes may avoid foods of high collagen content; instead, preferring easily digestible, energy-rich carbohydrates.
4. Younger people are more often able and willing to change their eating habits if the benefits can be shown in a convincing way.

Scientific data on the physiological relevance of collagen hydrolysate that are currently available and that have already been dealt with in previous chapters are of particular importance in sports medicine as, especially in power training and in performance sport, the joints, ligaments and tendons are subjected to particular stress. Regular administration of collagen hydrolysate may lead to a more selective provision of cartilage specific amino acids and additionally stimulate chondrocyte metabolism; in this way, the stressed joints, including cartilage, are strengthened and made more resistant [6].

While there are no long-term studies on athletes to answer the question as to whether collagen hydrolysate can prevent stress-induced osteoarthritis, current available data from animal and clinical studies suggest that the benefits may be gained by enhancing athletes' food with this protein. It can be deduced from the clinical and experimental effects achieved by application of collagen hydrolysate and the proven affinity of special amino acids to connective tissue that collagen hydrolysate might have a preventive effect on joint cartilage destruction brought about by micro-trauma and thus protects against the increased risk of osteoarthritis.

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Chapter 4

Comments and Expert Opinions from a Clinical Point of View

4.3 The Nutritional Expert's Point of View

Heinrich Kasper, M.D.

The Nutritional Expert's Point of View

In cases of defined and frequently-occurring metabolic diseases such as diabetes mellitus, hyperlipidemia, adiposity, gout, celiac disease and the rare genetic defect conditions such as phenylketonuria, Wilson's disease etc., nutritional therapy is part of what is usually longer-term treatment. However, nutritional therapy is not just for such primarily metabolic diseases; adapted diets can be most meaningful and beneficial in a whole series of other diseases in the form of concomitant therapy or as a causal or preventive measure. The spectrum ranges from immune deficiency to cancer and includes, at least indirectly, almost all chronic illnesses and those that disrupt the general feeling of wellness.

It is less well known, however, that, amongst the musculo-skeletal diseases, it is not only osteoporosis that can be delayed through a calcium-rich diet ("calcium account"); apparently, other degenerative joint diseases can be influenced by adapting the diet accordingly. Clinical studies showed that the regular administration of collagen hydrolysate might reduce the intensity of pain and the extent of disruption of function caused by osteoarthritis (see chapter 4.1). The molecular mechanism of this therapeutic and chondro-protective effect is still essentially unknown; however, the effect has been confirmed in animal studies and in chondrocyte cultures (see chapters 3 and 5). Thus, optimization of nutrition has become a component of a complex therapy, also in the case of osteoarthritis, as already mentioned in chapter 2.

Osteoarthritis is essentially a disease affecting the elderly; this is undisputed. As the age-related structures in the population will change substantially in the coming years, the prevalence of osteoarthritis will increase correspondingly. From this point of view alone, nutritional optimization, under the aspect of the chondro-protective effect of the collagen fragments in food will become increasingly important practically and clinically, especially as other effective and low-risk alternative therapies do not exist for osteoarthritis. The increasing number of elderly people is on the one hand the result of improved health protection and is a welcome aspect; on the other, it brings about numerous economic problems. For example, in the USA, the proportion of the population aged 75 to 85 increased by 100 % from 1960 – 1980 and the proportion of the over-85s by 140 %. Experts calculate that in the year 2050, 50 % of those who reach the age of 65 will have a life expectancy of more than 85 years. The frequency of degenerative disease of the circulatory and central nervous system, the skeletal system, joints etc. increases, as is well known, with increasing age. The correlation between age and osteoarthritic diseases was clearly established decades ago by pathological-anatomical studies [1] and in more recent studies repeatedly confirmed. In the USA, the incidence of osteoarthritis has been established in the course of extensive epidemiological studies. For example, in the United States Health Examination Survey, 79 % of men and 86 % of women between 75 and 79 were shown to have osteoarthritis of the hands.

The National Health and Nutrition Examination Study (NHANES I) showed that 8 % of men and 18 % of women between 75 and 79 had osteoarthritis of the knee. In the Framingham study, 33 % of those between 63 and 94 suffered from this disease [2]. In a current UK study, 10 % of the population over 55 was established as having osteoarthritis of the knee. The symptoms were established as being severe in a quarter of these patients [3]. A further multi-factor correlation exists between overweight and the frequency of osteoarthritis in the affected joints. On the one hand, this is caused by the high degree of mechanical stress involved in overweight people but also by the lack of activity, static false stress on joints and possible false nutrition on the part of obese people. In Germany, every second person is overweight and every sixth obese. This is a risk potential that has to be taken into account when assessing the development of osteoarthritis in the future. Nutritional medicine thus fulfills an additional function in the prevention of osteoarthritis; it must also take weight reduction into account, for the interrelationship between these two frequently occurring conditions, osteoarthritis and adiposity, cannot be doubted taking into account the comprehensive data already available. Even in European studies published before 1970 osteoarthritis was established as occurring more frequently in those who were obese [4]. Thus, from the nutritional and medical points of view, it is necessary to consider not only those conditions frequently dealt with publicity such as circulatory disease, diabetes mellitus type 2 and malignant tumors as being a serious result of false nutrition but also degenerative joint disease.

Apart from physiotherapeutic measures and the possibility of short-term symptomatic treatment of the consequences of osteoarthritis (see chapter 1), collagen building blocks contained in foodstuffs are of interest for slowing down the progression of osteoarthritis and for relieving pain and functional limitations.

Thus, nutritional medicine with the possibility of nutritional advice and alteration of lifestyle as well as recommendations for optimizing diets play a major role in this indication area.

■ Collagen hydrolysate: what has been established?

The biomedical properties of collagen and its components have been comprehensively dealt with in chapters 1 and 3. Collagen is the dominant protein in mammals; this is what makes collagen and collagen hydrolysate so interesting from the nutritional point of view. Gelatine (that does gel) and collagen hydrolysate (that does not gel) are both prepared by the hydrolysis of collagen.

The biosynthesis of precursor molecules of collagen takes place intracellularly. After proceeding through a number of intermediate stages and release into the extracellular space, fibrils are formed; these are then cross-linked by covalent bonds to become mature, traction-stable collagen fibrils. A regular

amino acid sequence is essential for their functionality. Every third amino acid of the peptide chain is a glycine molecule, mostly followed by proline or hydroxyproline. The proportion of these three amino acids is thus correspondingly high, as is shown e.g. in an analysis of calfskin collagen. Cysteine is completely absent. Of the sulfur-containing amino acids, only methionine is present but in low concentration. This is of nutritional significance as due to these particular characteristics possible serious side effects that would be brought about by the ingestion of large quantities of cysteine and methionine (as is possibly the case with other proteins) supporting the development of osteoporosis and affecting kidney function (see below) do not occur.

Nutritional significance

In chapter 3, basic statements have been made from the nutritional and scientific points of view concerning the problem of collagen building blocks in foods. The principal data are consciously emphasized in this chapter due to their nutritional and medical significance; this is because they reflect not only general trophological aspects but provide an insight into the nutritional and medical significance of collagen hydrolysate in respect of osteoarthritis. There may well be territorial differences. In Germany, the mean daily consumption of meat and sausage is about 180 g in the case of men and 140 g in women. This means that the daily uptake of collagen is about 5 – 5.5 g, whereby there is a considerable degree of variation in individual persons. In the German national food consumption study (Deutsche nationale Verzehrstudie) [5], data are available that would indicate a large degree of variation in the ingestion of meat and sausage products. For example, on one hand this depends on the educational level; with an increase in educational level, the consumption tends to decrease. In spite of this, there are deficits in the availability of information, especially concerning the widespread underestimation of the value of collagen containing connective tissue components in our diets. Exact data on the amount of collagen taken in a normal diet are mentioned neither in the nutritional reports published by the German Nutritional Society (Deutsche Gesellschaft für Ernährung (DGE)) nor in the reports of the German national food consumption study (Deutsche nationale Verzehrstudie). Such data is also not listed in tables indicating the nutritional value of individual foodstuffs of animal origin. As younger consumers tend to eat lean meats, it may be assumed that connective tissue is essentially removed with the fat; the collagen content is hence lower and collagen consumption on the decrease.

Based on its amino acid composition, collagen is of inferior biological value. From the nutritional point of view, however, this is only true to the extent that collagen, in spite of its protein structure, only plays a minor role when it comes to covering the body's protein requirements. However, general amino acid provision, also in the case of patients with osteoarthritis, is covered in the industrialized countries by the protein in food (see chapter 2). Collagen itself

is not necessary for this. However, in respect of collagen synthesis, the protein, with its high concentrations of glycine and proline, is of particularly nutritional value.

From the medical and nutritional point of view, the absence of all risk and side-effects in the application of collagen hydrolysate must be emphasized.

No side-effects are to be expected when regularly consuming 10 g of collagen hydrolysate orally per day in addition to an adequate diet: In the clinical studies carried out to date, no intolerance or deviating laboratory findings have been observed (see chapter 4.1). In this context, the GRAS ("**G**enerally **R**ecognized **A**s **S**afe") status of the American FDA is cited. The Federation of American Societies for Experimental Biology also came to a similar conclusion in 1975 based on the then available animal and human studies that *There is no evidence in the available information on gelatine that demonstrates or suggests reasonable grounds to suspect a hazard to the public when it is used at levels that are now current or that might reasonably be expected in the future* [6].

A further tolerability advantage from the nutritional point of view is the chondo-protective properties of collagen hydrolysate when used as a supplement. Although those persons with osteoarthritis belong to the age group with a high risk of osteoporosis and although high concentrations of protein increase this risk, it has been established that collagen hydrolysate, due to the fact that it does not contain any sulfur-containing amino acids, presents no risk because of this. The protein ingested determines the potential renal acid load factor by its content of sulfur-containing amino acids. In this way, the activity of the osteoclasts is increased and the amount of calcium excreted via the kidney increased. Epidemiological findings indicate increasingly that calcium immobilization in bone brought about by latent acidosis promotes the complex process of osteoporosis [7; 8]. This does not occur as a result of collagen metabolism.

Conclusion

In industrial countries, there is no protein deficiency in normal diets. The mean average value for protein ingestion is, thanks to somewhat luxurious consumption habits, about 70 % over the recommended dose. Based on body weight, protein ingestion is thus, as a median value and irrespective of gender, 1.2 g/kg body weight per day against a recommended 0.8 g. In spite of this value being well over the recommended value there is still an assumed discrepancy between demand and supply with respect to the collagen specific amino acids proline and glycine. According to clinical studies: as daily ingestion of 10 g of collagen hydrolysate leads to a continuous increase in proline and hydroxyproline in plasma [8], the increase in concentration may have a positive effect on cartilage metabolism by covering the requirement resulting from certain mechanical stress conditions or from the increased requirement assumed in the elderly.

From the nutritional and medical point of view, there are additional conclusions that can be made and that make the use of collagen hydrolysate interesting as a preventive measure against osteoarthritis. As demonstrated in animal experiments [9], the intragastric application of collagen hydrolysate leads to the resorption of a heterogeneous mixture of peptides produced during the metabolic process and these, as proven by the use of radio-labeled markers, appear in concentrated amounts in cartilage tissue. This, independent of the supply of desmophilic (cartilage-specific) amino acids, and due to the effect of these large-molecular substances, could possibly have a further positive effect on collagen metabolism (see also chapter 3).

An analogous conclusion can also be made: Collagen hydrolysate ingested orally in quantities above the average contained in normal diets has, considering its composition, a primarily unexpected effect on protein metabolism, reflected in the positive effect on the growth and stability of hair and nails. In contrast to the chondro-protective effects, these effects that can be more easily measured, have been observed in a series of animal studies.
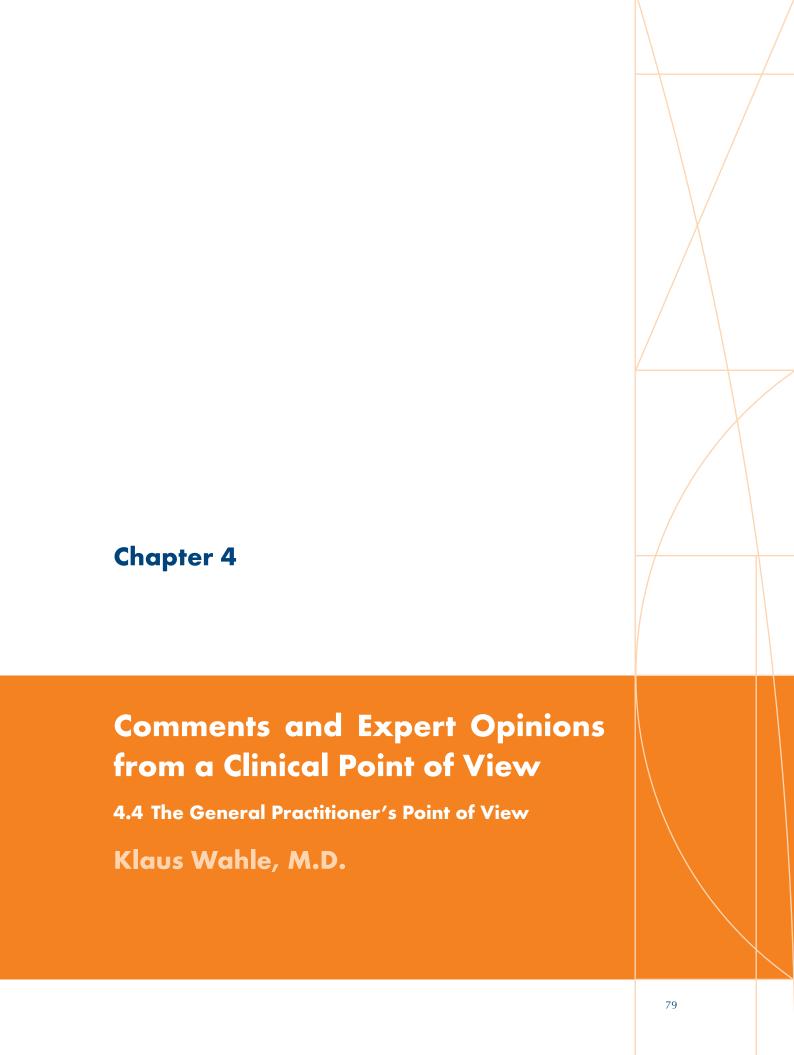
From the nutritional and medical points of view, collagen hydrolysate has a positive effect on chondrocyte metabolism. It also exerts effects, potentially pertaining to prevention of joint disease, furthermore it may slow down the development of osteoarthritis. All these effects represent an important therapeutic option combining low cost with the lack of side-effects and with a high degree of patient compliance.

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Chapter 4

Comments and Expert Opinions from a Clinical Point of View

4.4 The General Practitioner's Point of View

Klaus Wahle, M.D.

The General Practitioner's Point of View

■ Prevention: a task for the GP

A General Practitioner (GP) has to be able to take some 300 different dangerous but preventable and frequently occurring diseases into account if he is to recognize and treat them adequately. This significant number and wide range of indications will increase in future. Apart from the primarily curative tasks he has had to deal with up to now, he will in future have to become more active in prevention, where he will have to do more than just repair already existing damage; in addition, he will have to deal with the causes of health-destroying conditions as well as maintaining and improving general quality of life.

Currently, a paradigm change is taking place in the work of the GP. He is becoming much more involved in preventive medicine which demands a rethinking process and a different form of involvement.

Thus, an understanding of the pathogenetic processes involved in manifest disease is now also necessary in the GP's practice if he is to be able to reverse the course of diseases that have reached a stage where this can be achieved, hence avoiding irreparable future situations. In addition, he will have to be able to assess the **specific risks** of individual patients whilst taking into account exogenous and endogenous factors and imposing a higher degree of **responsibility** on his patients for their own health.

Pathogenesis versus salutogenesis

Currently, medical science is developing in a bifocal manner:
- On the one hand, increasing detailed knowledge of the patho-biochemical processes that occur in the development of disease (pathogenesis) is increasing the chances of being able to intervene in order to stabilize health (salutogenesis). The **therapeutic options will thus become more and more specific** and more selective in the hope of achieving specific repairs, e.g. by the development of highly specific receptor antagonists or the exclusion of specific disease-triggering geneloci.
- On the other hand, this expansion of knowledge concerning the causal factors of disease increasingly includes common roots in the development of various disease states. In order to achieve prevention, the resistance against various disturbances of function or the compensation of exogenous damage must be improved. This can be achieved e.g. by dosed physical stress, immune stimulation, training in psychological processes, optimization of lifestyle and healthy nutrition comprising an adequate diet.

■ Therapeutic targets

There is little doubt that over the next few years there will be some very interesting drug developments. These will be highly selective in the sense of what has been described above, specific and hence without undesired side-effects. Under this aspect, cell wall receptors and biochemical mediators in particular will be given special emphasis by biopharmaceutical researchers. Receptors and mediators regulate the intercellular exchange of information, control metabolism and transport the signals generated by endogenic messengers and drugs. Should these become damaged by a genetic fault, by environmental influence or by the natural process of aging, disease occurs (e.g. circulatory disease, mental dysfunction, cancer, metabolic disturbances, allergies etc.) or the drugs in question will not have the desired effect. Nobel Laureate Professor Dr. Hartmut MICHEL (Max-Planck-Institute for Biophysics, Frankfurt, Germany) regards the structural clarification and crystallization of the membrane proteins that act as receptors as the major challenges facing medical science. This, in his opinion, is the route to the development of highly selective and side-effect-free drugs. The fact that, currently, only three of some 10,000 human membrane proteins have been crystallized [1] emphasizes this. New forms of therapy of the future intervene in these disturbed structures selectively with the help of special mediators and via special receptors and exercise their effect in a causal and specific manner in certain biochemically definable diseases. These new forms include "G-protein-coupled receptors" that inactivate tyrosine kinase inhibitors such as STI 571 in over 70 % of patients, hence "eliminating, either partially or in whole, the cause of this type of cancer"(REICHARDT, P. [1]), in addition, by exerting influence on the alpha-2C-receptors of the cardiac muscle rendering cardiac insufficiency controllable (HEIN, L. [1]).

This is one route to future, curative medicine. The other, in no way to be regarded as an alternative concept, is not based on the highest possible selectivity but more on **non-specific, broad-based, preventive-therapeutic medicine.** One principle, one substance, one active ingredient have differing, even multi-effects. These include the numerous activity programs that, by dosed bodily activity, institute a training effect on the various organ systems, hence exercising a cardio-protective, metabolism-increasing, blood pressure-lowering, blood flow-promoting and musculo-skeletal build-up effect. A preventive broad spectrum also covers immuno-modulating processes as well as mental conditioning. As a rule, the combination of a number of preventive measures increases the overall effect; this is why the GP has come to play a major role in preventive medicine.

Focal point: health-promoting nutrition

These multi-potent concepts are particularly important for the GP and include of course **optimization of nutrition.** The multiple effects of essential

vitamins in human cell metabolism have been known for a long time and are used preventively. The influence of vitamin C in strengthening both humoral and cellular resistance to infection as propagated by L. PAULING is still the subject of considerable controversy. However, a series of studies show that ascorbic acid has a protective effect in numerous metabolic diseases and the consequences thereof, e.g. on the vascular system. Concerning the role of dietary fiber in protecting against intestinal cancer, intestinal motility disturbances and metabolic disease, the manifold roles of minerals and trace elements contained in food with respect to growth, development and regeneration of the entire life cycle have been published in numerous incontestable papers throughout the world.

Inadequate attention, however, has been given to the preventive benefits of collagen and collagen derivatives in health-promoting foodstuffs. On top of this, there has been a trend to one-sided orientation towards fruit and vegetables brought about in part by various food scandals and the consequences of the BSE scare that had a discrediting effect on meat generally. "Luxury" consumers in addition had a preference for so-called "high-quality" pure lean meat containing minimum amounts of connective tissue. Such meat, however, is, from the nutritional point of view, not quite as valuable.

For the GP and his task of advising on health, it is important to be able to implement such health-promoting aspects and to prevent false developments. This of course does not apply to all the unproven but fashionable medical folly that may be propagated. However, medical experience and modern scientific studies on animals and cell cultures have shown that collagen hydrolysate has a positive effect on cartilage regeneration. This is described in detail in previous chapters. This nutritional component can, as confirmed by a series of studies (see chapter 4.1), prevent or at least delay the development of osteoarthritis. The anabolic effect of this protein, with its special amino acid composition, on joint cartilage can, providing there is an adequate number of functioning chondrocytes present, also enhance the analgesic and anti-inflammatory therapy of painful active osteoarthritis. This takes place via an adequate supply of suitable amino acids subsequent to intestinal digestion and resorption of the collagen building blocks but also via stimulation within the cartilage itself (see chapter 3). Nutrition with adequate amounts of collagen (e.g. 10 g of collagen hydrolysate per day) might have a preventive and therapy-enhancing effect.

This is a chance that should be utilized in the primary medical treatment of a disease such as osteoarthritis.

Degenerative joint disease is one of the most common cases faced by the GP in practice. At present, there is no effective conservative possibility of treatment (see chapter 1).

As osteoarthritis is a chronic and progressive disease which, apart from loss of quality of life on the part of the patient and his or her family, also has an immense impact on the national economy, the preventive aspect brought about by advice on the part of the GP on nutrition, eating habits and lifestyle is of critical importance.

Credible advice that leads to a change in behavior can only be based on adequate and confirmed information. In the case of collagen hydrolysate, the data available is convincing, as shown in the previous chapters. This nutritional protein is not a pharmaceutical drug. It is a component of a health-promoting foodstuff – and should be regarded as such by physicians who believe in prevention as well as by sports specialists, company physicians, pediatricians and nutritionists.

■ Possibilities and limitations of the General Practitioner

Practical medicine of the future will find itself going through a paradigm shift between the assessment and the elimination of risk **(risk stratification)** when faced with disease. At present, its orientation towards prevention is inadequately supported by false incentives in the reimbursement system as well as, in many cases, by inadequate scientific knowledge.

The GP of the future will have to see himself more of a case manager providing advice rather than a disease manager trying to treat a specific condition.

This also includes implementation of evidence-based medicine via the preventive effect of certain foodstuff components and the targeted influencing of eating habits.

The increasing preventive orientation of the GP, however, does not mean that he no longer will be involved in normal curative tasks. It also does nothing to cement the postulation that osteoarthritis is the sole domain of the GP (see also chapter 1). The "living anamnesis" that the GP represents, often through knowledge of the patient and his family stretching back many years, is particularly valuable in recognizing the early stages of disease and functional limitations. And, as these patients are often affected by multiple diseases, he may well be able to detect common factors of cause. This also applies fully to the muscular-skeletal diseases that represent the most frequent reasons for the patient consulting the physician in the first place.

However, specific treatment of pronounced osteoarthritis is still the responsibility of the specialist.

There is little doubt that, over the next few years, the possibilities offered by invasive techniques will be further developed; it may well become possible e.g.

to surgically implant in-vitro cultured chondrocytes or artificial cartilage. It is also conceivable that, via receptor-specific mediators as described above, the regenerative process within the joint can be influenced in a selective manner.

Such a view of the therapeutic future, however, should not lessen the importance of utilizing current possibilities of slowing down or even preventing incurable osteoarthritis.

This includes optimization of nutrition, particularly for those patients especially at risk, by the provision of risk-oriented advice on prevention by the GP.

Changes in eating habits and lifestyle cannot be achieved without participation on the part of the patient (and "not yet" patients). They have to implement the scientifically founded advice given by the physician with a high degree of responsibility and self-management. This is especially true for chronic, progressive, almost fate-like diseases such as osteoarthritis. This aspect is also of significance with respect to the World Health Organization (WHO) declaring the decade 2000 – 2010 as the "Decade of Bone and Joint Disease" (see also preface). This will undoubtedly help to place osteoarthritis as a particularly important medical and economic disease at the center of interest in the minds of GPs and public alike.

■ Osteoarthritis – a problem for the General Practitioner

In general practice, what happens on a frequent basis is always of importance. Diseases of the locomotor and skeletal systems are amongst the most frequent reasons for patients consulting their GPs. They are the most frequent chronic diseases suffered by adults and are justifiably regarded as **a general and widespread disease of particular medical, health-economic and socio-economic importance** [3]. As about 80% of those over 75 suffer from some form of x-ray-confirmed osteoarthritic disease and as they make up the majority of those consulting their physicians, the GP in particular is faced with a particular challenge. The absolute number of consultations (for Germany, the estimated number of patients according to KOSSOW [3] is 10 million; however, those receiving adequate treatment is only about 2 million!) is high. The chronic aspect of the degenerative joint disease, the distinct limitations in quality of life of patients (and their families, especially in cases of immobility and those requiring nursing care), the costs involved for nursing care, general help and subsequent treatment as well as the impossibility of curing with conservative methods make it a priority problem for the GP, especially in the case of patients, suffering from multiple clinical problems.

Most patients suffering from osteoarthritis usually consult their GP first and not orthopedic or other specialists.

Practice statistics confirm this priority. DANNINGER [4], in 1997, compiled the most frequent reasons for consulting a physician. According to the list, osteoarthritis ranks second (ICD-10 No. M19.9) in the list of muscular-skeletal diseases and ninth overall. This is far in front of back pain (rank 24) and osteoporosis (rank 234). It is only preceded by myalgia (M 79.1) ranked second, whereby osteoarthritis is certainly also included. Thus, osteoarthritis is far in front of diseases such as cardiac insufficiency (rank 18; acute cardiac insufficiency rank 91!) or varicose veins (rank 26) in the GP's practice.

From the point of view of the GP's practice, it can be said that the GP is able, with the usual inventory of diagnostic and therapeutic methods and at reasonable cost, to slow down the progress of the disease using scientifically founded knowledge, even if the disease as such is not (yet) curable (see below). The slowing down of progress and the maintenance of a pain-free state and mobility are worthy goals for the physician. This still applies even if the structural changes that have taken place in the joints cannot be reversed using conservative medicine on the part of the GP.

"Patients suffer from osteoarthritis and its consequences and not from their x-ray images!" KOSSOW [3]

Therefore, every chance should be utilized to slow down the degenerative processes of osteoarthritis or to prevent activation of the disease with its severe pain and loss of function, even if the disease itself cannot be influenced.

Diagnosis in practice without the need for apparatus

The diagnostic procedure carried out by the GP places greatest emphasis on the **anamnesis,** especially the assessment of pain. It is a considerable advantage if the physician has known the patient for a number of years and is better able, in the sense of a "living anamnesis", to assess the risk and the sensitivity to pain. In addition, having cared for the patient for so long, the physician is in a better position to recognize creeping changes.

GPs – as also described in chapter 1 from the orthopedic point of view – can also differentiate between the pain of early and late symptoms of osteoarthritis:

Early triads:
- Pain on initiating movement
- Pain that occurs when tiredness sets in
- Pain that occurs when stress is applied

Late triads:
- Permanent pain
- Night pain
- Muscle pain

In addition, there are typical **accompanying symptoms** such as:

- Restriction of movement
- Crepitation
- Weather sensitivity and the like

Of course, the findings may vary depending on the joint or joints involved. In the physiotherapy manual of the German Association of General Practitioners (Deutscher Hausärzteverband (BDA)), different diagnostic methods are recommended for Cox arthritis, gonarthritis, omarthritis and osteoarthritis of the elbow [3]. These, however, are based on triad pain, restriction of function and palpatory findings.

For the GP, the **anamnesis** and simple **investigative methods without the need for apparatus** are especially relevant. In Cox arthritis e.g., restricted hip rotation is a primary symptom. Pain radiates towards the groin, buttocks and thigh and back pain may occur as a result of compensatory hyperlordosis. Investigation must also include how the patient walks. A positive sign is given if, when the patient is standing on one leg, the pelvis tends to sink towards the affected side. The maximum bending possibility of the non-affected hip joint when the patient is lying down indicates a stretch deficit – an early symptom of Cox arthritis.

In gonarthritis on the other hand, examination of the patella should be looked at carefully, as should false axial positioning. Such differential examinations can be carried out at little expense and time in the GP's practice.

Independent of such diagnostic specialties, the following may be applied generally for the different sites of osteoarthritis:

Examination in the practice makes use of inspection, palpation and function testing and as a rule no apparatus is necessary.

During the **inspection,** joint changes (swelling, deformation) or false positioning of the joint axis will be obvious things to look for. However, muscle atrophy (especially if it is one-sided) indicates conscious or forced protective positioning of the joint in order to reduce or eliminate pain; or, it indicates an already present retraction of function and loss of mobility.

Palpation of the joint can provide an indication of the presence of pressure pain and, possibly, osteophytes. Bruising and local hyperthermia, although not primary symptoms of osteoarthritis, can indicate inflammation.

Function testing must always be performed if there is a suspicion of osteoarthritis (and documented for later comparison). This includes an assessment of any restriction in mobility, joint instability, pain on movement and final phase pain.

X-ray examination allows objective assessment to be made of any reduction in the articular cavity, subchondral sclerosis, osteophytes, subchondral cysts and the possible presence of chondrocalcinosis.

However, the GP must realize that there is no linear correlation between x-ray and clinical findings.

Even distinct morphological changes may remain clinically unobserved – and vice versa. The x-ray thus serves principally to exclude other possible joint conditions or to clarify the reasons for secondary osteoarthritis. The x-ray also does not establish the indication for surgery or joint replacement ("It is not the x-ray that is going to be operated on but the patient!" [3])

Modern **imaging procedures** are quite dispensable in the GP's practice, especially for cost reasons. Even if according to experts scintographic analysis can indicate activity with respect to subchondral bone restructuring and hence an assessment of the degree of progression, the practical benefits are relatively minor.

Laboratory diagnostic procedures are primarily used to exclude other pathological processes of a secondary nature. Normal laboratory findings indicate little. To exclude inflammatory joint disease, erythrocyte sedimentation and CRP should be determined. If either is positive, further rheumatological analyses by a specialist should be recommended. As to whether the determination of metabolites of cartilage metabolism (e.g. keratan sulfate, aggrecane fragments, hyaluronic acid, chondroitin sulfate) or gene analysis from biopsy material is meaningful for the GP is still uncertain, especially as, at present, there are no practical therapeutic consequences that can be drawn that would improve the treatment.

Arthroscopy, due to possible resulting complications, should be treated with some reserve (see also chapter 1). Such a decision should be made by an orthopedic specialist.

Overall, the diagnosis of osteoarthritis can be made with a high degree of certainty by the GP using normal routine methods available to him.

In the case of complications or special cases involving deviating or additional symptoms, an orthopedic specialist should be involved as soon as possible; this corresponds fully with the GP's function as pilot.

■ Complex therapy – an opportunity

A group of experts established by the Association of General Practitioners (Deutscher Hausärzteverband (BDA)) in 1996 compiled an interdisciplinary paper on the subject. It stated that the designation osteoarthritis is not a uniform etiological unit from the GP's point of view. For the GP, it is a group of diseases of different etiology that are very similar with respect to the processes taking place in the joint, the morphological and functional changes and the symptoms. As in the early stages of the disease there are normally

neither symptoms of pain nor obvious permanent functional restrictions, the GP is recommended to determine risk in as targeted a way as possible (**risk stratification** – see above) in order to be able to identify the early stages of limitation in mobility caused by the disease.

By means of a **complex therapy** involving dosed activity programs, physiotherapy, changes in lifestyle, reduction of other existing risk factors such as overweight and by changes in the diet (collagen-rich food), progression of the disease can be slowed down and the anabolic phase of turnover in joint cartilage stimulated.

Drug therapy in osteoarthritis has its limits – and not only in the GP's practice. As it is not possible to reverse any structural changes by administering drugs, there are two possible therapeutic goals:

- The treatment of acute pain (with rapid but only temporary success)
- A basis regimen to slow down progress by stimulating chondrocyte metabolism (an attempt to have an effect on the cause; however, as it takes time to achieve an effect, there are problems of compliance). This includes changes in diet and, for example, the administration of collagen hydrolysate.

Regarding the symptomatic treatment of pain, there is a whole range of analgesics that can be used. The ABDA database lists over 3,000 (including 1,200 combination and 1,800 mono-preparations). Of these, many (according to N.P. LÜPKE, 1996, a pharmacologist in the BDA Expert Group) are questionable from the scientific point of view and do not produce reliable results in practice. For the GP, the so-called non-steroidal anti-rheumatic drugs and Cox-2 inhibitors as well as corticosteroids can be employed for the short-term treatment of pain (see also chapter 1).

As basic medication for the stimulation of chondrocyte metabolism, experts have recommended oral D-glucosamine sulfate for gonarthritis, ademetionine (oral and parenteral) and hyaluronic acid for intra-articular injection (in cases of gonarhtritis) (see also chapter 1).

In view of the risks involved and the restricted use of these drugs they play a minor role only in the GP's practice.

Only ademetionine was recommended by the BDA Expert Group for the treatment of risk patients in general practice; the other basic therapeutic drugs should be left to the specialists for a more stringently applied indication.
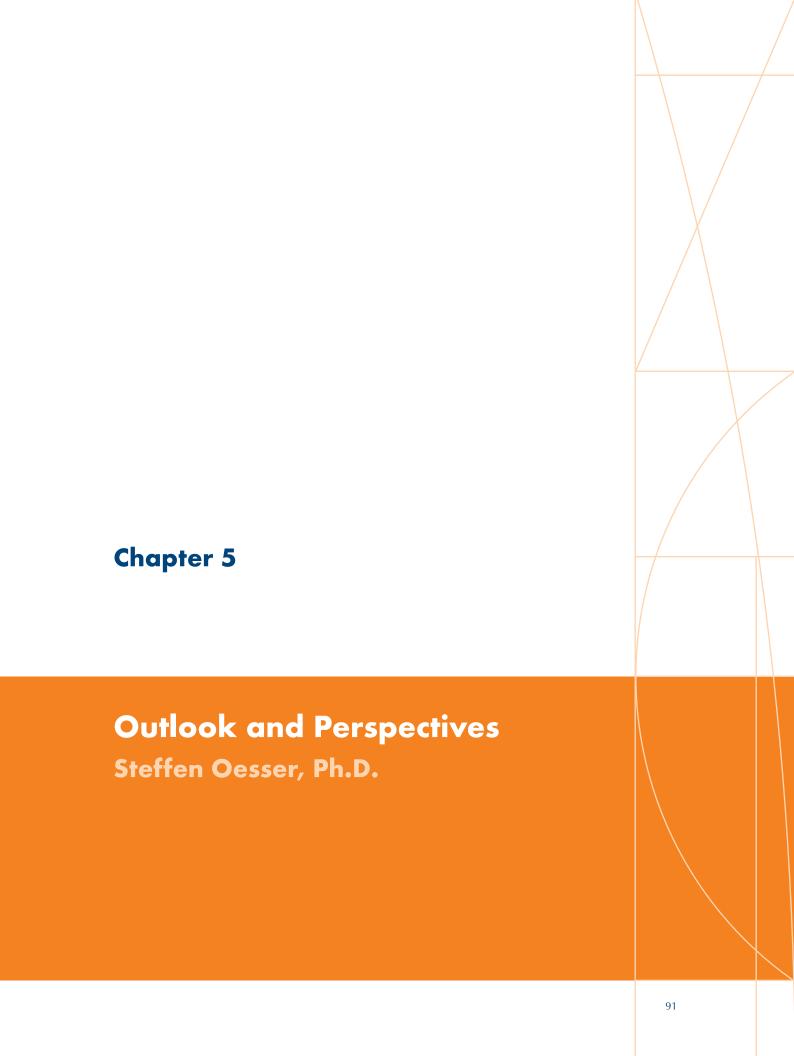
One risk-free method for the optimization of chondrocyte metabolism and prevention or slowing down of the progress of osteoarthritis open to the GP and at the same time an important therapeutic building block is **dietary change.** This publication deals in some detail with the role of collagen hydrolysate. This food, in view of the effects confirmed by numerous clinical studies, is increasingly finding the interest of GPs oriented towards prevention. The BDA Expert

Group in its consensus paper of 1996 mentions, in addition to physical therapy and dosed activity, the change in diet as a concomitant therapy for osteoarthritis. Advice given to risk patients by the GP oriented towards optimized diets before any symptoms of degenerative joint disease appear makes for more responsibility being taken over by the patient for his or her health. In this way, it is a sort of "help to self-help" [4] on the part of the physician; this makes the patient less of simply a receiver of orders and a subject of control by the physician.

Due to its frequency of occurrence and independent of the competence of the orthopedic specialist (see chapter 1), osteoarthritis takes a special place in the GP's practice. However, the GP would never claim to be a specialist for muscular-skeletal disease. Close cooperation with orthopedic, physical and other medical specialists is in the interests of the patient (and the GP himself), and is indispensable in advanced, complex cases. Only in this way is it possible to have a chance of relieving the pain and slowing down the progress of incurable osteoarthritis and of utilizing all further possibilities including surgical joint replacement. However, these patients also who have undergone surgery remain the GP's patients for this and other illnesses they may have. They can continue to receive nutritional advice regarding chondro-protective diets.

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Chapter 5

Outlook and Perspectives

Steffen Oesser, Ph.D.

Outlook and Perspectives

Worldwide, several hundred million people are currently suffering from disease of the locomotor, postural and skeletal systems. The disease of most interest in this respect, principally due to its increasing frequency and the immense socio-economic costs involved, is degenerative disease of the joints such as osteoarthritis.

Osteoarthritis is a chronic and progressive disease that destroys joint cartilage and that can lead to complete loss of joint function. The rapid increase in the number of new cases in the industrialized countries has numerous reasons. Apart from certain types of genetic predisposition, micro-trauma of the joint cartilage, inadequate local anabolic stimulus and trophic disturbances due to a chronic lack of activity, one-sided or extreme mechanical stress and an unbalanced or deficient diet are all important factors. However, the most important reasons for the dramatic increase in osteoarthritic disease are constantly increasing life expectancy and the increasing frequency of over-weight and obese patients. The correlation between age and degenerative joint disease has been clearly demonstrated. Thus, osteoarthritis in advanced age with all the disadvantages for the patient and society would appear to be unavoidable, almost a question of fate – a pathophysiological assessment that is, however, unjustified.

Although almost 90% of orthopedic-rheumatological patients suffer from osteoarthritis, medical research is concentrating mainly on rheumatoid arthritis. Only in recent years has some reorientation taken place internationally in this respect. More recently, there has been a distinct increase in research activities in an attempt to elucidate the pathomechanisms of osteoarthritis. Through the provision of research grants and stimulated by initiatives like the "Bone and Joint Decade" of the WHO it can be expected that this trend will continue, indeed accelerate.

The need for new forms of therapy for osteoarthritis is substantial. According to current knowledge, there is neither an effective generally applicable causal therapy for osteoarthritis nor is a complete restitution of the function of a damaged joint possible. However, as has been described in previous chapters by various specialists, targeted prevention of degenerative joint cartilage by specifically influencing chondrocyte metabolism would appear to be possible. In view of the frequency of osteoarthritis, the enormous effect on quality of life and the immense costs involved, all meaningful and scientifically proven opportunities should be utilized to reduce degenerative joint disease. However, the numerous open questions regarding osteoarthritis research should not lead to already confirmed evidence-based knowledge remaining unused in practice if those suffering can be helped.

Currently, osteoarthritis research is concentrating on developing new methods of precisely diagnosing the disease and on providing effective and gentle
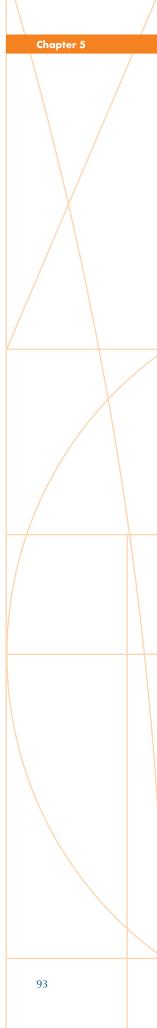
symptomatic therapeutic agents. In this respect much has been achieved in the way of improved anti-inflammatory and analgesic treatment. New and optimized drugs with few side-effects can be expected in future for the treatment of osteoarthritis.

Although symptomatic treatment of osteoarthritis is extremely important for the quality of life of the patient, such drugs can only bring about temporary relief of symptoms; they do not have any causal effect nor do they prevent the disease from progressing. Thus, longer term emphasis should be placed on developing causal treatment drugs and on meaningful preventive measures.

As a result, in the experimental and clinical studies being carried out worldwide, emphasis is being placed on research into the pathomechanisms of the disease, the goal being to develop new therapies for improved intervention or prevention, i.e. to delay, stop or even reverse the degenerative processes that have already started. Even a delay in progression of the disease, in view of its chronic nature, would represent progress for the patient whilst substantially cutting the costs of health care.

In the meantime, consensus exists that the therapeutic goal of causal treatment of osteoarthritis can only occur by targeting chondrocyte metabolism in order to counteract the catabolic processes taking place in the joint cartilage. In principle, two therapeutic concepts are conceivable: on the one hand, by inhibiting the degradation of the structural macromolecules in the extra-cellular matrix (ECM), the continuous loss of cartilage substance could be stopped; and on the other hand, specific stimulation of the biosynthesis of cartilage cells could conceivably compensate for pathologically caused degradation of the ECM. The precondition for both types of therapy would be detailed knowledge of chondrocyte metabolism and the associated regulatory processes. However, this knowledge, in spite of intensive research and the identification of numerous bioactive substances that are involved in the regulation of cartilage metabolism, is still somewhat fragmentary. The pathomechanisms of osteoarthritis in particular are still essentially unclear. However, in future, the key to effective therapy of osteoarthritis could well be found here, e.g. by switching certain genes on or off, a specific modification in the metabolic processes could be achieved within the cartilage cell and hence any pathological changes counteracted.

Currently, much effort is being made to intervene therapeutically to stop the progress of ECM degradation. The idea is to specifically inhibit the activity of the proteolytic enzymes of the family of matrix metalloproteinases (MMPs). Experiments are being carried out with the intention of directly blocking the MMPs by the use of certain antibodies or indirectly by influencing regulation of these enzymes and in turn achieving a reduction in overall activity. These theoretical but promising concepts have as yet to fulfill the high expectations made of them in practice.

A further therapeutical possibility that is being pursued in addition to classical therapy with analgesics and anti-inflammatory agents is the application of substances that are made up of certain components of the ECM or that contain them. Possible mechanisms, however, are still very unclear. Examples of this group of substances are hyaluronic acid, chondroitin sulfate or glucosamine sulfate. Glucosamine sulfate in particular has been shown in a number of clinical studies to relieve the pain in osteoarthritic patients. The reason for these promising results, is, however, unknown; the unambiguous chondro-protective effect on the part of glucosamine sulfate has not yet been confirmed. Furthermore, the analgesic effect of this substance is being increasingly discussed.

Collagen hydrolysate occupies a special position in the prevention and treatment of joint problems. As described in detail in previous chapters, collagen hydrolysate is not a pharmaceutical drug but a food. It is characterized by its high content of amino acids with a high affinity to collagen, e.g. proline and glycine; it can thus contribute to improved nutrition of joint cartilage. On the other hand, it has been demonstrated that treatment with collagen hydrolysate results in a significant increase in the synthesis of ECM. Based on experimental and clinical studies carried out, a chondro-protective effect on the part of collagen hydrolysate can be postulated.

In spite of these positive results, further, more detailed supplemental studies will be necessary in order to underpin the beneficial effects of collagen hydrolysate in joint disease. Confirmation of hitherto obtained results as well as elucidation of the mechanisms involved will be of particular importance in such studies.

Even if the influence of collagen hydrolysate on cartilage cell metabolism has been confirmed at the protein level, some important information is still missing regarding the complete elucidation of the signal transduction involved. One of the primary future challenges will be to identify the particular amino acid sequence within the collagen hydrolysate peptide that is responsible for the stimulation of synthesis of cartilage substance. In addition, for final scientific confirmation of the mechanisms involved, the specific cell receptors will have to be determined and an analysis of qualitative and quantitative change in the gene expression profile of chondrocytes subsequent to application of collagen hydrolysate carried out. Finally, the question has experimentally to be answered as to how far the modification of metabolic activity of the cells can be achieved, not only under physiological but also under patho-physiological conditions.
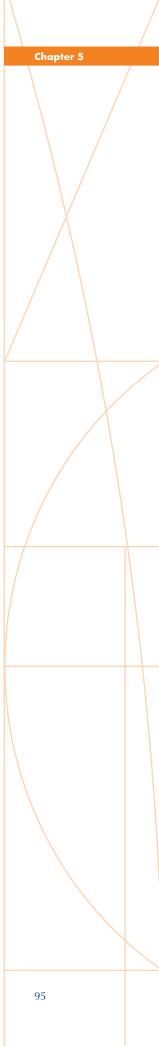
Also, further questions have been raised by the clinical observations and studies carried out to date. For example, the regional differences in the results observed in the international multi-center study carried out by MOSKOWITZ et al. indicate that, apparently, various parameters such as concomitant therapy, therapy regimen, the indication, individual findings and the selection of inclusion criteria of the patients can influence the results. Thus, additional
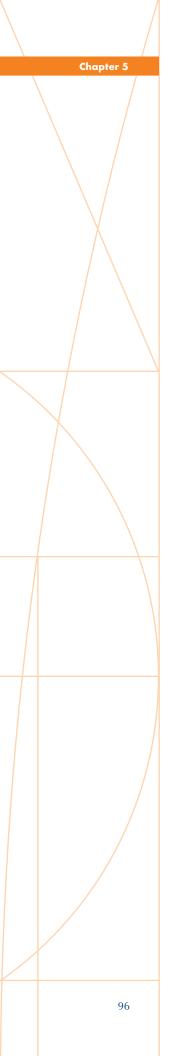
standardized studies should be carried out in order to be able to establish the preconditions for concrete therapeutic recommendations. The question as to the necessary dose for therapy and the period of treatment have also not yet been fully established.
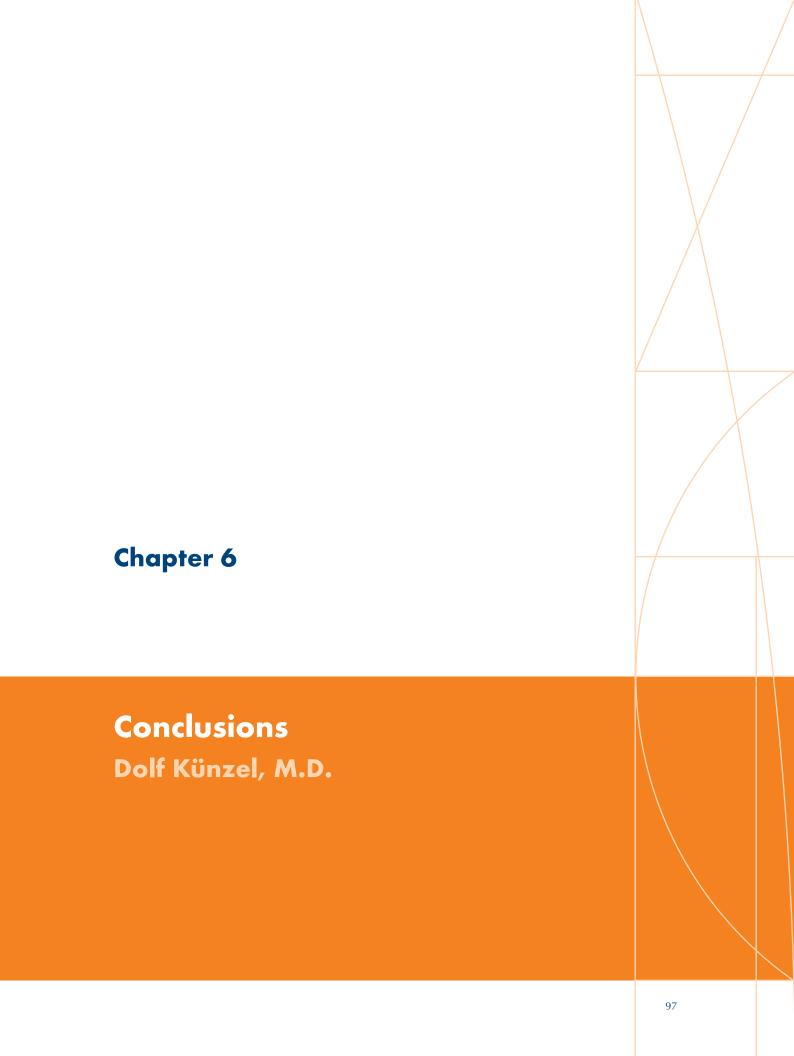
Research also has to be carried out on the postulated preventive effect of collagen hydrolysate on degenerative joint disease. Currently available findings and observations indicate that the daily alimentary ingestion of collagen hydrolysate has a positive effect on joint cartilage. Whether, however, an adequate amount of collagen hydrolysate can actually prevent osteoarthritis or delay it significantly has not yet been scientifically confirmed. Wide-ranging comparative clinical studies will be necessary to establish this.

Many of the open questions described here are either being tackled or are being planned in the form of international research projects. In the medium term, it can be assumed that, through these comprehensive activities, the pathomechanisms of osteoarthritis and the role of collagen hydrolysate in the treatment of joint disease will be better understood.

In spite of the research still required, there is no reason whatever today to dispense with the prophylactic or adjuvant treatment of osteoarthritis with collagen hydrolysate, not least because its application is risk-free.

Chapter 6

Conclusions

Dolf Künzel, M.D.

Conclusions

In previous chapters, information on the benefits of the oral application of collagen hydrolysate has been given, from the viewpoint of a number of specialist areas, with respect to its qualities in preventing osteoarthritis and as a concomitant therapy of the disease as a nutritional supplement.

Now, the principal goal is to ensure that this knowledge is utilized in practice.

In doing so, some considerable skepticism on the part of both physicians and patients regarding the use of natural methods of healing and such "banal" treatments as nutritional optimization first has to be overcome. More, in fact, has to be achieved: generally, in modern medicine, a paradigm change has to take place from cure to prevention of disease. Prevention is better than cure – this is still completely valid in reality. Those who propagate proven methods as opportunities for the prevention of disease are in no way old-fashioned but completely up-to-date as far as modern medicine is concerned. Nutritional optimization based on experimental and clinical data is part of this process.

■ Optimized nutrition is an opportunity for prevention

Collagen hydrolysate has (again) generated some considerable interest in medicine and science in recent years. Some aspects no doubt require further scientific work; and, results of long-term prospective clinical studies are not yet available. However, confirmed results already obtained indicate that collagen hydrolysate might influence cartilage metabolism and prevent degenerative disease as well as enhancing and supporting the complex therapy involved.

■ Osteoarthritis is a primary health problem

"What happens frequently is always important", is one of the creeds in medical practice. As far as disease is concerned, there should be no value hierarchy; for the patient, "his" disease is always the most important. However, degenerative joint disease is particularly of medical and social importance due to its high frequency, its chronic and progressive course, the lack of causal cure with conservative methods, its high degree of disturbance of quality of life and the immense costs involved. In view of increasing life expectancy and the increasing number of people of old age, osteoarthritis is in fact increasing in frequency. This development is enhanced by a predisposition brought about by lifestyle in the way of overweight, lack of activity, false mechanical stress on joints and false nutrition. These aspects have been comprehensively dealt with in previous chapters to show that osteoarthritis has many and various causes and that lifestyle and working conditions have an enormous influence on the disease.

The World Health Organization (WHO) has declared this decade as **"Bone and Joint Decade"** to bring the problem to the public's eye.

It is a particular challenge to use suitable preventive measures to exert an influence on the development and progress of joint "wear and tear".

■ The major benefits of collagen hydrolysate

Even though definite proof of the preventive effects of collagen hydrolysate on joint degeneration still needs to be furnished by long-term prospective clinical studies with larger patients pools, the read-out of data available from experimental and clinical investigations is positive: collagen hydrolysate has been confirmed as having a positive effect on chondrocyte metabolism and the stability of cartilage matrix.
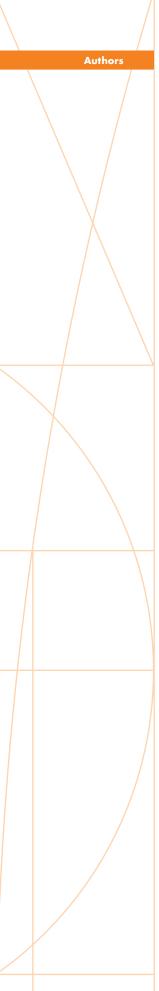
In summary, it can be established that collagen hydrolysate possesses a number of benefits that make it interesting for use in the prevention and therapeutic support of joint degeneration.
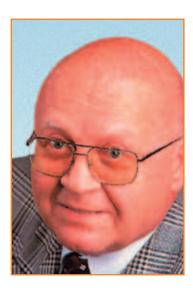
The major benefits are:

1. **Excellent tolerability** – a major reason why the US authority FDA has classified collagen hydrolysate as **GRAS ("Generally Recognized As Safe").** Also, WHO and the German Federal Institute for Drugs and Medicinal Products have accorded collagen hydrolysate the highest possible safety status.

2. Its **amino acid composition** corresponds to that of the cartilage matrix (threefold amount of glycine and proline / hydroxyproline compared to other proteins). Thus, collagen hydrolysate is a "customized" building block for the synthesis activity of the chondrocytes.

3. Collagen hydrolysate is **well resorbed.** Its **low-molecular structure** allows transmural persorption through the intestinal wall with resulting temporary concentration within the joint cartilage and confirmable metabolic activation of the chondrocytes.

4. It is a **natural product** produced from natural raw materials; there are thus no problems of stability associated with oral application.

5. Collagen hydrolysate **has practically no undesired side-effects nor does it react with drugs or other food / food ingredients.**

6. Administration of collagen hydrolysate **stimulates the anabolic phase** of cartilage matrix turnover; this brings about a phase of regeneration and stability in joint cartilage.

7. Clinical studies have shown that it might have synergy effects with analgesics and anti-inflammatory drugs; this in turn can result in a **reduced consumption of analgesics** and hence a reduction of overall risk.

8. There is **no risk of infection** due to microorganisms; the stringent veterinary controls applied to the raw materials and the production process itself (treatment with acids, alkali and heat) render all such microorganisms inactive.

9. There are **no undesired alimentary effects such as weight increase or dietary imbalance** as collagen hydrolysate is a protein comprising only amino acids, water and minerals and contains no fat, carbohydrates or preservatives.

10. **Oral administration** of collagen hydrolysate is uncomplicated as it is available in numerous product variations (powder, capsules, beverage) and in various flavors. There is thus a high degree of compliance on the part of the user.

11. The **cost-benefit relationship is favorable;** thus there is every chance that the user will consume it on a permanent basis.

12. There are **no restrictions on its use.** Adolescents, pregnant women, manual workers, diabetics, obese people and all who do not have protein metabolism problems, problems of elimination or other rare diseases can take it without risk.

Appendix

Milan Adam, M.D.

Curriculum vitae

Professor Adam completed his university education in the *Medical Faculty at the Karls University of Prague*, Czech Republic. In the course of his professional career, Professor Adam has been a visiting scientist at many international universities and research facilities-among others, at the *Max Planck Institute (MPI) for Protein and Leather Research* in Munich and at the MPI for Biochemistry, Martinsried at Munich. Furthermore, he worked on the *Medical Faculty at the University of Reims*, France, where he was awarded *Dr. Honoris Causa.* In his Czech homeland, he has worked as a scientist at the Rheumatism Research Institute in Prague since 1954. In the seventies and eighties he lectured at the *Medical Faculty of the Karls University of Prague* and also at the *Chemical University of Prague.* Additionally, Professor Adam was the Vice-President of the *UNESCO Conference on Education* in Mexico City in 1990. From 1991 to 1997 he headed the University Rheumatism Hospital of the *Postgraduate Medical School* in Prague.

Since 1990 Professor Adam has been President of the *Society for Connective Tissue Research,* Prague and an honorary member of a number of professional scientific associations. From 1987 to 1997 he was a member of the *Editorial Board of Rheumatology* in New York, USA; in addition, he is a member of the editorial boards of various other journals. To date he has published more than 270 scientific publications and investigations. After the Velvet Revolution he was a member of the Czech government as Minister for Education, Youth and Athletics.
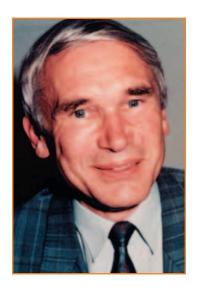
Kristine Clark, Ph.D., R.D., FACSM

Curriculum vitae

Dr. Kristine Clark is the Director of Sports Nutrition for *Penn State University's Athletic Dept.* where she counsels more than 800 varsity athletes from 29 teams. In addition, she advises head coaches, team physicians, athletic trainers, strength and conditioning coaches, and athletic administration on policies regarding eating disorders, weight management, and supplement use among athletes. While most of Dr. Clark's time is devoted to athletics, she also holds a position of assistant professor in the dept. of nutrition at *Penn State* teaching a course titled, "Nutrition for exercise and health throughout the lifecycle."

Dr. Clark was appointed to the *Sports Medicine Advisory Board* of the *United States Olympic Committee* in 1999. She began working as the nutritionist for the *United States Women's Soccer Team* in 1995 and continues as their nutrition consultant. In addition, she serves as the nutritionist for the *United States Soccer Federation.* Clark is the nutrition columnist for the *Women's United Soccer Association* website.

Dr. Clark holds a Ph.D. in Nutrition Science from *Penn State University*, a Masters degree in Health Education from the *University of Wisconsin-LaCrosse,* and a B.S. degree in Nutrition and Dietetics from *Viterbo College,* LaCrosse, WI. She is a registered dietitian, a Fellow in the *American College of Sports Medicine,* a Board of Trustees member of the ACSM, and is active in the *Am. Dietetic Association.*
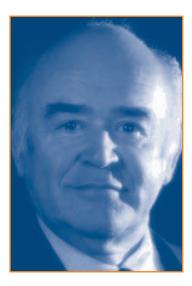
Heinrich Kasper, M.D.

Curriculum vitae

Professor Kasper studied medicine at the university of Gießen, Germany, and subsequently qualified as a specialist in internal medicine in 1966. In 1968, he qualified as a lecturer and was appointed Senior Physician and Head of the Dietetics Teaching Facility of the hospital in Gießen. From 1970, he worked at the university hospital in Würzburg (gastro-enterology and metabolism) and also headed the Dietetics Teaching Facility. In 1974 he was appointed Professor of Internal Medicine and, in 1981, Department Head Gastro-Enterology and Metabolism. Professor Kasper has done much scientific work in both areas and in clinical dietetics.

He was a long-term member of the steering committee of the *German Association for Nutrition* and is currently honorary member of the association.

He is a member of the *German Society for Nutrition (DGE)* and Deputy Chairman of the *German Academy for Nutritional Medicine*.

Professor Kasper is author of the standard textbook on nutritional medicine and dietetics "Ernährungsmedizin und Diätetik".

Dolf Künzel, M.D.

Curriculum vitae

Dr. Künzel completed his studies in medicine and journalism at the universities of Leipzig and Berlin before qualifying as a specialist in internal medicine at the *Humboldt University in Berlin (Charité),* Germany. Subsequent to a number of years heading medical research, he was appointed Editor-in-Chief of the publishing group *Gustav Fischer Verlag Jena, Georg Thieme Verlag Leipzig, Johann Ambrosius Barth Verlag Leipzig* and *Verlag Volk und Gesundheit Berlin* in 1985, where he became Director in 1987. In 1992/93 he was General Manager of the American-German publishing house *Ullstein Mosby* (subsidiary of *Mosby Yearbook Chicago*). Since 1993, Dr. Künzel has been a freelance author of medical and popular science books, Editor-in-Chief of a number of specialist technical journals, consultant and moderator, especially for the *German Association of General Practitioners (Deutscher Hausärzteverband BDA).*

Roland W. Moskowitz, M.D.

Curriculum vitae

Roland W. Moskowitz, M.D. is Professor of Medicine at *Case Western Reserve University,* and Director of the *Arthritis Translational Research Program of the Case Research Institute.* Following his training in Rheumatology and Internal Medicine at the *Mayo Clinic,* Dr. Moskowitz was on the medicine faculty at *Temple University School of Medicine* and, since 1962, a member of the faculty at *Case Western Reserve University.*

Dr. Moskowitz has served on the Board of Trustees of the *American College of Rheumatology* and the Board of Trustees of the *National Arthritis Foundation.* He has been a member of the *Advisory Council of the National Institute of Arthritis and Musculoskeletal and Skin Diseases,* Chairman of the *Subspecialty Board of Rheumatology*, and a member of the *American Board of Internal Medicine.*

He is currently President of the *Osteoarthritis Research Society International.* Dr. Moskowitz's primary research interest relates to the pathophysiology and genetics of osteoarthritis; in 1990 he received international recognition for research linking osteoarthritis to a defective collagen gene.

Dr. Moskowitz is the author of over 200 published articles, and is editor of 10 textbooks including "Osteoarthritis – Diagnosis and Medical/Surgical Management".

In 2000 he received the President's Gold Medal Award from the *American College of Rheumatology* for his contributions as a researcher, educator and clinician.

Steffen Oesser, Ph.D.

Curriculum vitae

Steffen Oesser studied biology and chemistry at the *University of Kiel* in Germany. As a Scientific Assistant at the *Institute for Physiology of the University of Kiel,* he initially concentrated on the areas of cell physiology and protein chemistry. Since 1993, Dr. Oesser has been active in medical research at the *Hospital for General and Thoracic Surgery* at the Kiel campus of the *University Hospital of Schleswig-Holstein,* Germany. He is principally involved in researching the pathophysiology of osteoarthritis and the development of new therapy possibilities for the treatment of degenerative disease of joint cartilage.

Since October 2003 Dr. Oesser is managing director of the *Collagen Research Institute* in Kiel, Germany.

Wolfgang Pförringer, M.D.

Curriculum vitae

Professor Pförringer studied medicine at *Munich University* and worked after his studies as a house doctor and registrar in hospitals in Munich, Baltimore, USA, Capetown, South Africa and Davos in Switzerland. In 1978 he qualified as a specialist in orthopaedics with an additional qualification in sports medicine, and he concluded his university education in 1981 with a PhD. Further professional periods were spent after 1986 in Great Britain, Canada and the USA as a holder of a fellowship from the *German Association of Orthopaedics and Traumatology (DGOT)* for Austria, Germany and Switzerland *(ASG Fellow).* Since 1987 Prof Pförringer has worked as professor of orthopaedic surgery at *Ludwig Maximilian University in Munich.* In 1997 he was appointed medical director of the *Orthopaedic Clinic Munich-Harlaching* and has had a private practice with admitting rights since 1998 in the *Dr. M. Schreiber Surgical Clinic* in Munich.

Professor Pförringer is founding member of the *Orthopaedic and Traumatological Sports Medicine Association (GOTS)* and was its general secretary until 1994. He is honorary president of the *German Orthopaedic Sports Traumatology Union (DVOST)* and honorary member of the *Japanese Orthopaedic Society of Sports Medicine (JOSSM)* and of the *Helenic Orthopaedic and Traumatology Society.* Prof Pförringer holds the position of general secretary of the *South African-German Orthopaedic Foundation (SAGOF).* From 1979 to 1997 he was chairman of the *Health Policy Group* of the CSU (party).

Furthermore, Prof Pförringer is a member of a range of other national and international specialist associations. He is the author of over 250 publications and is the editor of several textbooks on the subject of orthopaedics.

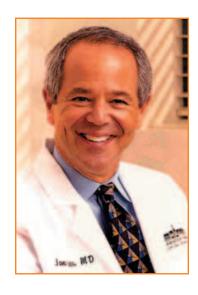# Wolfhart Puhl, M.D.

Curriculum vitae

Professor Puhl studied medicine at the universities of Marburg, Freiburg and Göttingen and completed his training as a specialist in orthopaedics at the *Orthopaedic Clinic and Polyclinic of Heidelberg University*. He obtained his PhD there and was appointed as a consultant the same year at *Heidelberg Orthopaedic Clinic and Polyclinic* where he became a senior consultant in 1974. In 1982 he was chosen as Medical Director of the *Ulm Rehabilitation Hospital* and of the *Orthopaedic Clinic and Paraplegic Centre of Ulm University*. He has held this position up to the present.

Professor Puhl has been a member of the board of the *German Association of Orthopaedics and Traumatology (DGOT)* and of the *German Association of Orthopaedics and Orthopaedic Surgery (DGOOC)* since 1980. Professor Puhl has been working since 1996 as first chairman of the *Association of Leading Orthopaedists (VLO)*. He also holds the office of president of the *Endoprosthetic Working Group (AE)*. Moreover, Prof Puhl is a founding member and member of the board of the *European Federation of National Associations of Orthopaedics and Traumatology (EFORT)*, and will be its president from 2005 to 2007.

The *European Orthopaedic Research Society (EORS)* made him an Honorary Member in 1997.
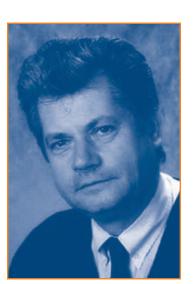
James M. Rippe, M.D.

Curriculum vitae

Professor James Rippe, M.D. is a graduate of Harvard College and Harvard Medical School with post graduate training at Massachusetts General Hospital. He is currently the Founder and Director of the Rippe Lifestyle Institute and Associate Professor of Medicine (Cardiology) at Tufts University School of Medicine. Dr. Rippe is founder and director of the Rippe Health Assessment at Celebration Health in Orlando, Florida, USA.

Dr. Rippe is regarded as one of the leading authorities on preventive cardiology, health and fitness and healthy weight loss in the United States. He has written over 200 publications on issues in medicine, health and fitness, and weight management. He has also written 25 books including 15 medical texts and 10 books on health and fitness for the general public. His two walking books were recipients of *National American Health Book Awards.*

Dr. Rippe has developed corporate fitness programs for a variety of companies. He serves as Chairman of the Advisory Board for the "Healthy Growing Up" program—a curriculum linking health and fitness for children. Dr. Rippe's work has been featured on several TV programs. He comments regularly on health and fitness for *USA Today, American Health and Prevention.* He served for three years as Medical Editor for the *Television Food Network (TVFN).*

Jürgen Seifert, M.D.

Curriculum vitae

Professor Seifert studied medicine at the University of Munich, Germany, and, having qualified as a Medical Assistant, worked in the *Institute for Surgical Research* at the university from 1967-1981. In 1974 he qualified as a university lecturer with his work on the enteral resorption of large molecular proteins and was awarded his professorship in 1979. In 1981 he was appointed Professor of Experimental Surgery at the *Christian-Albrechts University* in Kiel, Germany, and is currently Head of Surgical Research at the *Hospital for General and Thoracic Surgery* at the Kiel campus of the *University Hospital of Schleswig-Holstein.* Apart from numerous studies on circulatory regulation and other clinical problems, Professor Seifert did much research work on the enteral resorption of foodstuffs, particularly proteins. He was able to show that proteins, even in large molecular form, could be resorbed whilst remaining biologically active. He followed up this work with studies where special emphasis was placed on the immunological aspects of the resorption-dependent influence of humoral defense mechanisms. Professor Seifert has been awarded a number of prizes for his scientific work. He is a member of numerous national and international specialist societies and associations.

Klaus Wahle, M.D.

Curriculum vitae

Having studied chemistry and medicine at the universities of Bochum, Aachen and Essen, Dr. Wahle qualified as a physician in 1981 and completed his qualification as specialist in general medicine in 1986. He acquired his Ph.D. in the same year and established himself in practice. Since 1992, he has been working with Dr. med. Ursula Wahle (specialist in gynecology and psycho-therapy) in a communal practice in Münster-Nienberge. He is honorary professor at the *Westfälischen Wilhelms-Universität Münster* (2001) and, since 1992, associate lecturer for general medicine and Head of the *Working Group on General Medicine* at the university.

Professor Wahle has published numerous medical papers. He holds the position of *Deputy Head of the Institute for Practice Research (PRAFO)* within the *German Association of General Practitioners (Deutsche Hausärzteverband)* in Nittendorf and is active in several other research and scientific organizations. Since 1997, Professor Wahle has been responsible for training and further education within the *German Association of General Practitioners.* Under his management, some 18 comprehensive inter-disciplinary manuals and numerous guidelines for General Practitioners have been compiled.

The GELITA Health Initiative has been set up by the GELITA Group, the world's leading manufacturer of gelatine. The aim of the initiative is to promote research into collagen hydrolysate and its use in the field of joint health, and to disseminate the findings from this research to physicians, nutritionists and patients.

GELITA has more than 2600 employees worldwide working in research, production and distribution of around 250 types of gelatine, including collagen hydrolysate. Apart from edible gelatine, the company also produces high quality gelatines for the pharmaceutical and photographic industries from its Eberbach headquarters in Baden-Württemberg, Germany. Almost 130 years of experience are a guarantee for products of highest quality.

A subsidiary, the GELITA Health Products GmbH, has developed *GELITA mit CH alpha®,* a nutritional supplement that is available in German pharmacies. Each ampoulle contains 10 g collagen hydrolysate.

For more information please visit our website at
www.gelita-health-initiative.com
www.ch-alpha.com