



universität
wien

DIPLOMARBEIT

Titel der Diplomarbeit

The role of nutrition in joint diseases

Verfasserin

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angestrebter akademischer Grad

Magistra der Naturwissenschaften (Mag.rer.nat.)

Wien, Oktober 2012

Studienkennzahl lt. Studienblatt: A 474

Studienrichtung lt. Studienblatt: Ernährungswissenschaften

Betreuer: Univ.-Prof. Dr. Karl-Heinz Wagner

Danksagung

Während der Zeit meines Studiums und während der Erstellung der vorliegenden Arbeit haben mich viele Menschen unterstützt. Und dafür möchte ich mich bedanken.

Bei Univ.-Prof. Dr. Karl-Heinz Wagner für die Betreuung der Diplomarbeit.

Bei Mag. Brenda Laky, Ph.D. für die wunderbare Unterstützung und Hilfe während der Erstellung der Arbeit.

Bei meinen Arbeitgebern für ihre Flexibilität die es mir erlaubte mein Studium berufsbegleitend abschließen zu können.

Bei meinen Eltern, die mir dieses Studium ermöglicht haben, immer an mich geglaubt haben und jederzeit für mich da waren.

Bei meinen Geschwistern, Freunden und meinen Mitbewohnern für ihre Hilfe, ihr Verständnis und ihren Beistand während meines Studiums und vor allem während der letzten Monate.

Bei meinem Freund Georg, der die größte Stütze in meinem Leben ist. Ohne ihn hätte ich das alles nie geschafft.

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4 List of Abbreviations

OA	osteoarthritis
NSAID	non-steroidal anti-inflammatory drug
COX-2	cyclooxygenase-2
COX-1	cyclooxygenase-1
PUFA	polyunsaturated fatty acid
IgG	immunoglobulin G
IgA	immunoglobulin A
n-3 FA	omega-3 fatty acid
n-3 PUFA	omega-3 polyunsaturated fatty acid
DGE	Deutsche Gesellschaft für Ernährung
ATP	Adenosintriphosphate
AA	arachidonic acid
UVB	ultraviolet B
ROS	reactive oxygen species
DMSO	dimethyl sulfoxide
MSM	methylsulfonylmethane
RCT	randomized controlled trial
ASU	avocado and soybean unsaponifiables
ALA	alpha-linolenic acid
GLA	gamma-linolenic acid
EPA	eicosapentaenoic acid
DHA	docosahexaenoic acid
IL- α 1	immunoglobuline-alpha 1
FLAP	5-lipoxygenase-activating protein
MMP	matrix metalloproteinase
ADMAMTS	a distintegrin and metalloproteinase with thrombospondin motif
LDL	low density lipoprotein
PGE2	prostaglandin E2
RC	rotator cuff

5 Introduction and Aims

Joint disorders are frequently occurring problems involving cartilage as well as muscles, tendons, and ligaments, rather than bones; and often cause significant pain and dysfunction. Non-operative medical treatment is aimed to reduce pain and inflammation and include pharmacological approaches such as corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs). Due to negative side effects of such medication, permanent treatment is not recommendable. Non-pharmacological approaches such as lifestyle changes including a healthy diet may be an alternative way to reduce symptoms and slow down progression of joint diseases.

The main objective of the present diploma thesis was to evaluate and critically examine essential associations between selected nutritional components and their impact on joint disorders. The first part of the work outlines the role of selected nutritional compounds and their possible influences on joint disorders. The protocol of a critical review focusing on potential effects of omega-3 fatty acids (n-3 FAs) in shoulder disorders including osteoarthritis (OA) and rotator cuff (RC) pathologies is integrated as second part of the diploma thesis.

6 The joint

The first part of this diploma thesis is an introduction into the joint anatomy and physiology as well as an explanation of selected, nutrition-related joint disorders and possible influences of special nutrients on pathogenesis.

6.1 Anatomy and physiology of the joint

The part where two or more bones are joined to each other is described as joint or articulation [GRAY 1918]. Such constructs not only provide mechanical support, but also allow movements. Joints are therefore either classified according to their functions, which are determined by the degree of movement between the articulating bones, or to their structures, which are differentiated in how the bones connect to each other.

The three functional classifications of joints are

1. synarthrosis (immovable joints)

The surfaces of the bones are almost in direct contact. The joint space is filled with connective tissue or hyaline cartilage. The bones of the skull, except the mandible, are examples for this type of joint.

2. amphiarthrosis (slightly movable joints)

This type of joint is composed of joint space, capsule, synovia and special types of ligaments. Because of the strength of the ligament-bonding, movement is limited, which is the only difference to diarthrosis. An example for this kind of joint is the connection between pelvis and spine.

3. diarthrosis (free movable joints)

The main part of joints refers to this class. The parts of the joint are the same as explained above – joint space, capsule, synovia, and ligaments, but ligament-

bonding is less strong, therefore free movement is possible. Examples for diarthrosis are the shoulder joint or the knee joint.

[ROHEN and LUTJEN-DRECOLL 2006, GRAY 1918]

In the following only the diarthrosis will be described, because this group of joints is affected by joint diseases relevant for this work.

The free movable joints, the diarthrosis, can be structured into three subgroups:

1. joints with one degree of freedom

Motion in one plane is possible, which is either a forward and backward motion or a limited rotation. Both types are parts of the elbow joint.

2. joints with two degrees of freedom

This type of joint allows motion in two levels, bending and rotation axes. An example is the knee joint.

3. articulations with three degrees of freedom

Motion in all dimensions is possible. Shoulder and hip are joints with three degrees of freedom.

[ROHEN and LUTJEN-DRECOLL 2006]

The three structural classifications of joints include

1. fibrous joints

The bones are connected to each other with tissue rich in collagen fibers.

2. cartilaginous joints

The bones are joined by cartilage.

3. synovial joints

The bones are not directly connected to each other. [IQBAL 2012]

In general the basic structure of a joint is always the same (Figure 1). It is composed of the joint bodies, whose articular surfaces are coated in hyaline cartilage-tissue, and the articular capsule. The synovial membrane is the inner coat of the joint capsule. Additionally, the joint is passive stabilized by strong ligaments. Muscles and tendons are responsible for active and dynamic stabilization as well as for motion of the articulation. The space between two joint bodies, the joint space, is filled with synovial fluid. The hyaline cartilage is made of matrix-tissue and chondrocytes. [NIETHARD and PFEIL 2005]

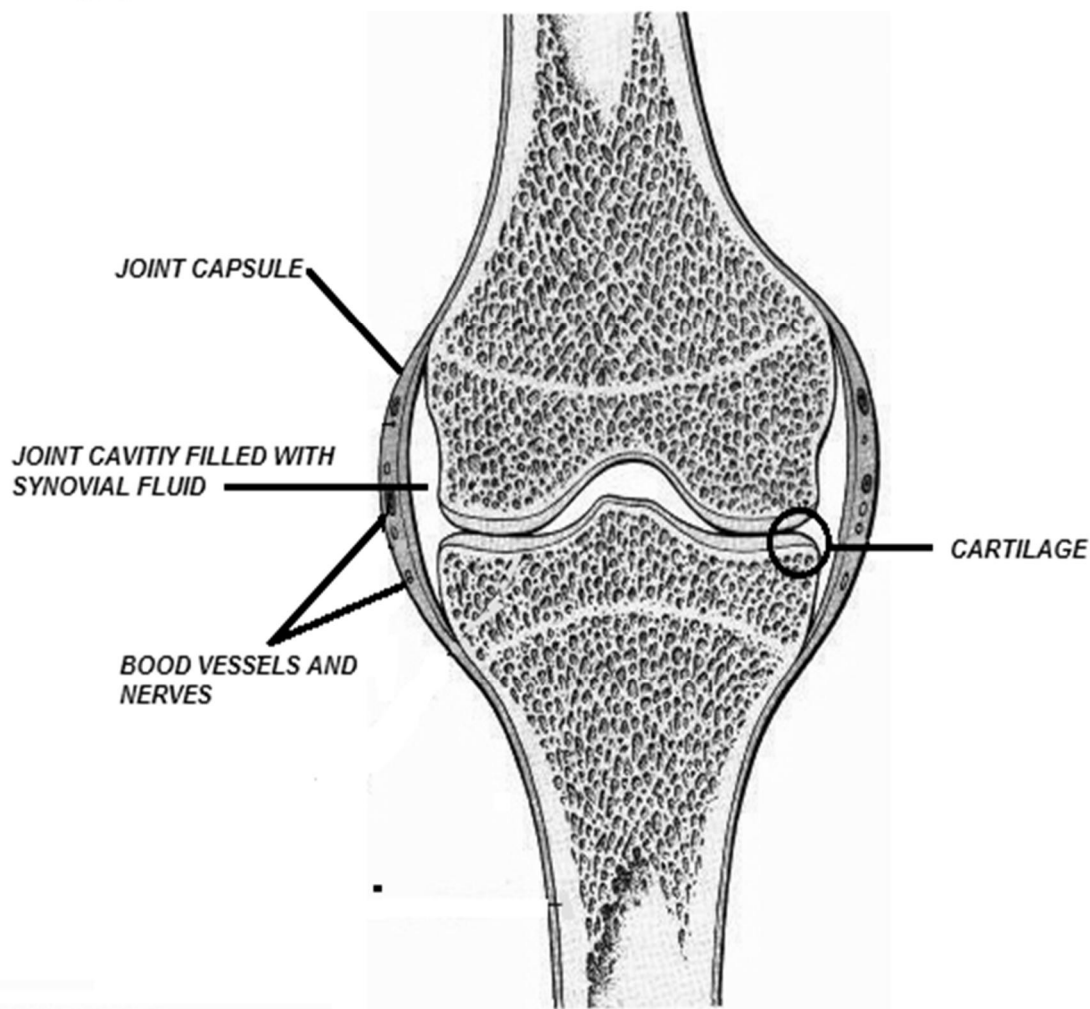


Figure 1: A typical joint structure

[modified according to NIETHARD and PFEIL 2005]

During childhood and adolescence chondrocytes are responsible for the cartilage growth and regeneration. Hormones, metabolites and enzymes are important factors in the

regulation of the cell growth. With higher age normal chondrocytes lose their mitotic activities and a regeneration of cartilage in case of degeneration is only possible by using alternate tissue from spongy bones or synovial tissue of the border areas of the cartilage. [NIETHARD and PFEIL 2005]

As seen in Figure 2, the articular cartilage is divided into 4 zones with individual matrix regions. The cell-free superficial zone includes the gliding surface of the joint. A layer of elongated chondrocytes are organized parallel to the articular surface. The matrix shows fine fibrils with few polysaccharides, endoplasmic reticulum, Golgi membranes, and mitochondria but the cells of this area are almost inactive. The transitional zone is the second layer and contains active chondrocytes including endoplasmic reticulum, Golgi membranes, mitochondria, glycogen and intracytoplasmic filaments. Compared to the superficial zone, the fibrils of the transitional zone are larger and columnar organized.

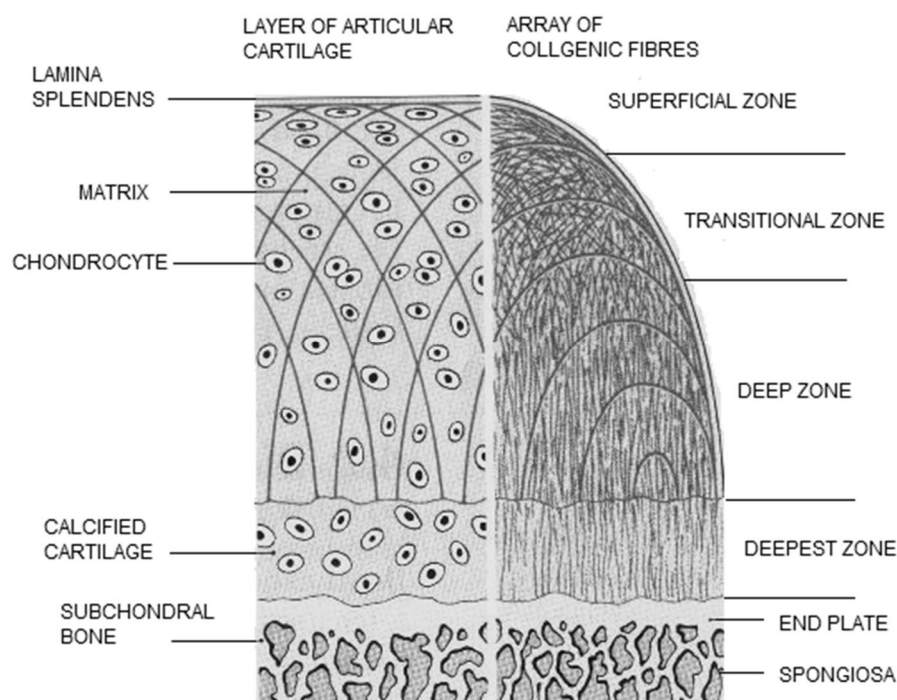


Figure 2: Composition of the joint cartilage

[modified according to NIETHARD and PFEIL 2005]

Third layer is the deep zone with chondrocytes quite similar to the transitional zone but with a different organization (perpendicular to the joint surface).

These cells contain large amounts of intermediate filaments, glycogen granules, large collagen fibrils and the highest amount of proteoglycans. An increasing number of proteoglycans leads to a decreasing amount of water from the superficial zone to the deep zone.

The deepest zone of cartilage is the border between softer cartilage and subchondral bone. The chondrocytes contain low amounts of cytoplasm and endoplasmic reticulum. [JAMES and UHL 2001]

For an adequate supply of the joint with all necessary nutrients two delivery-systems are responsible. The systems are termed as subchondral and synovial drift.

Subchondral drift is the supply with nutrients and oxygen of those parts of the joint, which are directly connected to the blood supply. [NIETHARD and PFEIL 2005]

The hyaline cartilage itself is avascular. That means that the chondrocytes are not directly connected to the blood supply. Thus, the synovial fluid is responsible for nutrient transport into the cartilage-cells as well as for the evacuation of metabolic waste from the chondrocytes. This exchange of substances is induced by exposure of the joint. A- and B-cells of the synovial membrane produce hyaluronic acid, which are free or bonded to proteins, and proteins, which are parts of the synovial fluid. [NIETHARD and PFEIL 2005, DÖLL 2007]

The detailed composition of the synovial fluid, as listed below, is similar to blood plasma.

Composition of synovial fluid

- approximately 94% water
- sugar content of approximately 66 mg/100 ml
- hyaluronic acid content of 2,5 - 2,7 g/l (consists of free hyaluronic acid chains or proteoglycan aggregates) Hyaluronic acid is highly hydrophilic, but it declines with ageing. Concentration of hyaluronic acid defines viscosity of the synovial fluid.
- protein content of approximately 15-25 g/l (synoviocytes, monocytes, lymphocytes and granulocytes) [BERG 2003, TITTEL 2003]

Additional to the nutrition based function, the synovial fluid is also responsible for the lubrication and shock absorbance of the joint. [NIETHARD and PFEIL 2005, BERG 2003, TITTEL 2003]

Inflammation within the articulation results in composition changes of the synovial fluid, which leads to reduced lubrication and less slippage. [TITTEL 2003]

6.2 Joint disorders

Joints, especially the cartilage, can be damaged by many types of injuries or diseases, however cartilage destructions are either mechanically or biologically induced.

Biological factors are nutritional disturbances within the cartilage (age-related or cytotoxic substances) but also enzymatic destruction by enzymes secreted by cells of the synovial membrane (e.g. leucocytes in case of joint-maturation). [NIETHARD and PFEIL 2005]

Reasons for mechanical destruction are trauma, acute or chronic overstress and immobilization. [NIETHARD and PFEIL 2005]

The following chapter describes only those joint disorders regarding etiology and clinical course, which may be related to or influenced by the daily diet.

6.2.1 Osteoarthritis

Degenerative joint disorder or osteoarthritis (OA) is primarily associated with the aging process. With the third decade of life degeneration of connective and supporting tissue is a normal process of aging, and at the age of 65 nearly everybody is affected, but with differences in medical condition. [NIETHARD and PFEIL 2005]

6.2.1.1 Pathogenesis

OA is caused by an increasing breakdown and loss of cartilage in joints. Affected are weight-bearing joints, the vertebral column and peripheral and axial joints. The most affected peripheral joint is the knee followed by shoulder and hip. [NIETHARD and PFEIL 2005, BERKSON 1991]

Causes for the incidence of OA are

- physical overstress
- traumata
- inflammatory articulation-processes
- metabolic disorders
- endocrine disorders

Physical overstress of the joint is always part of the pathogenesis of OA. This mechanical stress in the articulation leads to irritation, such as wear and inflammation. Severe wear leads to a greater degree of inflammation and this higher degree of inflammation leads to an increased amount of wear and cartilage degradation. [NIETHARD and PFEIL 2005, BERKSON 1991]

Development of degenerative joint disorders is a slow progressive process. One of the first symptoms is the loss of elasticity with changes in the joint tissue such as decreased cartilage-thickness, fissure formation in the cartilage and subchondral sclerosis. This damage of the articulation causes thrust and shear forces, which lead to a typical deformation of the joint. If the process of degeneration is accelerated, the symptoms of OA become clinically relevant.

OA clinically appears with pain, swellings, muscle tension, limitation of motion and stiffness after prolonged periods of immobility and increasing joint deformation. [NIETHARD and PFEIL 2005, BERKSON 1991]

6.2.1.2 Therapy

Prevention of the progression of degenerative joint disorder and the reduction of pain, swelling and immobility are the most important treatment options, since there is no direct cure for OA. Obesity and physical inactivity are main risk factors for the incidence of OA and should also be considered in the therapy. Therefore, in acute phases immobilization and steroidal and non-steroidal antiphlogistic medication, later on remedial gymnastics and is recommended. In advanced stages of OA surgical intervention is recommended. [NIETHARD and PFEIL 2005]

The focus of medical intervention to treat or reduce symptoms of OA as well as other joint disorder is to reduce pain and inflammation. In acute phases of diseases a medical intervention is necessary, because symptoms (pain, swelling, immobility) are too strong.

In the following non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids and their mechanism of action will be explained.

6.2.1.3 NSAIDs

NSAIDs have analgesic and antipyretic and, in higher doses, anti-inflammatory effects. In the therapy of OA and rheumatoid arthritis NSAIDs is one of the most commonly used drugs.

Due to their selectivity NSAIDs can be classified into COX-2 selective or non-selective NSAIDs, non-aspirin or aspirin and salicylate drugs and acetaminophen [CHOU et al. 2011]

Mechanism of action

NSAIDs decrease pain, inflammation, and fever by blocking cyclooxygenase (COX) enzymes. In particular NSAIDs affect the isoenzymes COX-1 and COX-2. COX-1 acts as a mediator in the gastrointestinal tract and protects the gastrointestinal mucosa from

acid and platelet aggregation. COX-2 mediates processes concerning inflammation and pain and is located throughout the body, including joints and muscles. NSAIDs reduce pain (occurring with OA or rheumatoid arthritis) by blocking COX-2.

Permanent medical treatment with NSAIDs has to be taken with caution due to strong side effects. The drawback of so called non-selective NSAIDs is that both enzymes, COX-1 and COX-2, are being blocked. One of the most dreaded consequences is the destruction of the gastric mucosa caused by the blocking of COX-1. [CHOU et al. 2011] NSAIDs vary in their selectivity for COX-2 meaning how much they affect COX-2 relative to COX-1. Thus, if they only block COX-2 but not COX-1, they are called COX-2 selective NSAIDs, they might reduce inflammation and pain without any negative side effects on the gastrointestinal tract. [CHOU et al. 2011] However, as explained above, NSAIDs are associated with several other negative effects.

In addition to the side effects interactions between NSAIDs and other drugs, e.g. blood thinner, cardio-active drugs, diuretics, preparations against hypertension and anti-depressants will occur. A parallel intake of NSAIDs and other drugs can either increase or lessen the effect of NSAIDs. [DÖLL 2007]

6.2.1.4 Corticosteroids

Corticosteroids (corticoids) are also often used to treat joint disorders. The best known member of this group is cortisone.

Cortisone is a steroid hormone synthesized in the human body by the adrenal gland in response to stress. In extended periods of hunger glucocorticoids initiate the proteolysis and gluconeogenesis in the liver. Additionally cortisone suppresses the immune system and subsequently decreases inflammation, pain and swelling. [LÖFFLER 2004]

In its function as immune suppressor, cortisone weakens the organism if taken over a long period of time. [LAXMAIAH MANCHIKANTI 2002]

In case of long-term, high dose medical treatment with steroid hormones such as cortisone several negative side effects may occur. Examples are hyperglycemia,

immunosuppression, hypertension, precipitation of diabetes mellitus, osteopenia and osteoporosis, muscle and joint pain, psychological imbalances, gastrointestinal disturbances, as well as dermatological and metabolic problems. [LAXMAIAH MANCHIKANTI 2002]

Due to the long list of possible side effects, an alternative to NSAIDs and corticosteroids could be of special interest. Therefore nutritional components are under discussion to be such an alternative or an additional way to treat symptoms of OA as well as other joint disorders.

6.2.1.5 Dietary factors associated with osteoarthritis

Obesity and metabolic syndrome

As explained above OA is a disease where weight-bearing joints, such as knee and hip, are affected. Therefore obese people whose weight-bearing joints are under greater strain have a higher risk of developing OA. It has been reported that weight loss reduces pain, and improves function for patients with OA who are obese or overweight. [LEE and KEAN 2012, BROSSEAU et al. 2011] However, not only weight-bearing joints, but also other joints, such as the hand joint, are also affected in case of obesity or overweight. Responsible is a systemic effect including adipokines with pro-inflammatory and degenerative effects, secreted by adipose tissue, as well as some joint cells. [SELLAM and BEERENBAUM 2012] OA is also associated with the metabolic syndrome including type-2 diabetes, a reason for cardiovascular mortality. Early-onset OA is suspected to be a reason for the incidence of the metabolic syndrome. [SELLAM and BEERENBAUM 2012]

In either case weight loss strategies including diet and physical activity are recommended to prevent OA and reduce related symptoms. [LEE and KEAN 2012, BROSSEAU et al. 2011, SELLAM and BEERENBAUM 2012]

Anti-inflammatory nutrients

Not only obesity is a nutrition related risk factor to cause OA, inflammatory processes could be influenced by the diet as well. Antioxidants, vitamin D, chondroitin and glucosamine, polyunsaturated fatty acids (PUFAs) and phytochemicals are under discussion to have positive influence on the progress and intensity of arthritis. [AMEYE and CHEE 2006, MCALINCON and BIGGEE 2005]

6.2.2 Inflammatory-rheumatic joint disorders

Rheumatism is a hyponym for about 100 diseases with different clinical presentation, pathogenesis, etiology, localization, prognoses and characteristic. Therefore, a classification by localization and type is sensible.

- inflammatory-rheumatic joint disorder with affection of one or several articulations
- degenerative-rheumatic joint disorder
- osteoarthritic disorders without inflammatory background
- rheumatic soft-tissue disorder
- degenerative and inflammatory disorders of muscles, tendons, ligaments and ligament sheaths [NIETHARD and PFEIL 2005]

Rheumatoid arthritis

According to the Austrian Medical Chamber approximately 0.4 - 1 % of adults in industrial countries are affected by rheumatoid arthritis [ÖAK, 2012], women three times more than men. [NIETHARD and PFEIL 2005, RHEUMA-ONLINE 2012]

6.2.2.1 Pathogenesis

Typical for rheumatoid arthritis is the poly-articular involvement, symmetric allocation and chronicity. Pathogenesis is almost unknown. Most hypotheses emanate from hereditary disposition and environmental antigens, especially viruses and bacteria, as triggers of rheumatoid arthritis [NIETHARD and PFEIL 2005, IDELBERGER 1978, HAIKE 1974].

Additionally nutrition, mental stress and unknown environmental contaminants as influencing and interacting factors are under discussion. The immune system reacts with hyperactivity which leads to aggressive synovitis with degeneration of cartilage and joint. [NIETHARD and PFEIL 2005]

In some cases blood serum of affected people shows specific antibodies, so called rheumatoid factors. Rheumatoid factors are predominantly anti-immunoglobulin G (anti-IgG) directed autoantibodies of the immunoglobulin M (IgM) class. However, at early-stage diseases not everyone with a rheumatoid factor found in the blood has a rheumatic disease. Later, in an advanced stage, about 80% of the affected patients show a positive rheumatoid factor test. In most cases a significant anemia is diagnosed. [NIETHARD and PFEIL 2005]

First place of manifestation are joints of the hand or feet. Symmetric swellings of the metacarpophalangeal and interphalangeal joints often occurs at the beginning, followed by the articulations of knee, shoulder, hip, elbow and the ankle joint. In other cases, among younger people, rheumatoid arthritis can also start as an acute mono-arthritis, where the bigger joints, such as knee, elbow, shoulder, and the vertebral column are affected. [NIETHARD and PFEIL 2005, HAIKE 1974]

6.2.2.2 Therapy

Depending on stage and activity of the inflammatory changes of the disease, different treatments are necessary. Medical treatment with NSAIDs and cortisol is recommended

at all stages; at advanced stages with strongly affected joints, surgical excision of the immunological active tissue is needed. Additional physiotherapy and exercise therapy is required. [NIETHARD and PFEIL 2005]

6.2.2.3 Dietary factors associated with rheumatoid arthritis

Dietary factors associated with rheumatoid arthritis are rather uncertain and not evidence based. Lahiri et al concluded that dietary antioxidants and breastfeeding may be protective, and high coffee consumption (more than four cups per day) may increase the risk to develop rheumatoid arthritis. An increased risk with obesity is also discussed. [LAHIRI et al 2012]

In a review by Miles and Calder a moderate positive effect of marine n-3 FA on symptoms of rheumatoid arthritis such as duration of morning stiffness, pain and swelling in joints has been reported. Reasons are anti-inflammatory and immune-modulating effects of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) present in fish oil and fatty fish. Arachidonic acid (AA) is the precursor of inflammatory eicosanoids involved in rheumatoid arthritis. EPA and DHA decrease the production of inflammatory eicosanoids from AA. EPA and DHA could also affect other immune related systems relevant in rheumatoid arthritis, such as dendritic cells, T cell function and production of inflammatory cytokines and reactive oxygen species. [MILES and CALDER 2012]

The German Nutrition Society (DGE) published recently nutritional recommendations for inflammatory diseases especially for rheumatoid arthritis. Nutritional treatment of rheumatoid arthritis can be seen as an additional treatment to medication. A lacto-vegetarian diet based on vegetables and fruits, low in fat milk products, low meat and fat intake and fish twice a week (at least one portion of fatty fish per week), could have positive impact, if practiced over a period of at least 3 months. [DGE 2008]

6.2.3 Metabolic Arthropathy – Articular Gout

Gout is a metabolic disease which occurs in recurrent attacks. Due to the deposit of uric acid crystals in the peripheral joints and tissues, it leads to destruction of the joints. The onset of the disease is in middle age of life. Men are more affected than women. [NIETHARD and PFEIL 2005, DÖLL 2007] According to Mikuls et al., who analyzed the UK General Practice Research Database from 1990 to 1999 including approximately 1.7 million patients (49 % men), the overall prevalence of gout is about 1.4%, the overall male to female ratio is 3.6:1. Prevalence rises up to 7.3 % in men between 75 and 84 years. [MIKULUS et al. 2005]

6.2.3.1 Pathogenesis

There are two types of gout classified. Primary gout is caused by a genetic defect concerning the purine metabolism. This disorder leads to a reduced renal excretion of uric acid as well as to an increased synthesis.

Reasons for the incidence of the secondary gout are an increased synthesis or supply of uric acid and a decreased elimination of uric acid due to a kidney disorder.

The high level of uric acid in blood plasma results in deposition of urate crystals in cartilage, capsule and tissue in joints of the toe, finger and elbow. [NIETHARD and PFEIL 2005, DÖLL 2007]

6.2.3.2 Therapy

Acute gout attacks necessitate medication to reduce pain, maintenance treatment to reduce the plasma level of uric acid with dietary measures and medication to increase excretion and reduce synthesis [NIETHARD and PFEIL 2005]. NSAIDs are the most common drugs used in the treatment of gout and oral corticosteroids are a possible alternative. [RICHETTE and BARDIN 2010]

6.2.3.3 Dietary factors associated with gout

Acute gout attacks require medical treatment, but modifiable risk factors such as diets high in purine, high alcohol consumption, overweight, diabetes and hypertension should be addressed. [EGGEBEEN 2007, HAYMAN and MARCASON 2009]

Huang et al. investigated the effects of Vitamin C supplementation on serum concentrations of uric acid in a RCT involving 184 hyperuricemic patients. In this study Vitamin C supplementation (500 mg/d, duration of 2 month) reduced serum uric acid concentration statistically significant (mean change of - 0.5 mg/dl). [HUANG et al. 2005]

6.3 Muscles and tendons as part of the joint

In the following anatomy and physiology of muscles and tendons are described, because of their importance in maintaining joint stability and movement.

6.3.1 Anatomy and physiology of muscles and tendons

As seen in Figure 3 the skeletal muscle consists of bundles of muscles, which, themselves, are comprised of various numbers of muscle fibers or muscle cells. The main parts of the muscle cell are so called myofibrils with the contractile protein components actin and myosin. The sarcomere is the smallest unit of the myofibril. It consists of thin layers of active actin filaments (I-Band) and actin and myosin filaments next to each other (A-Band), connected to the Z-disc, and thicker myosin filaments (H-Band). Several muscle fibers are innervated by one single nerve, the so called motor neuron. Nerve and muscle fiber form the motor unit (M). This M is in the focus of the muscle contraction.

The contraction of the muscle can be isotonic, isometric, auxotonic or isokinetic. In case of isotonic contraction the myofibrils generate a tension and get shorter. The actin

filament glides over the myosin filament and the H-zone gets narrower. Contraction requires energy as adenosine triphosphate (ATP), and calcium is released from the cells. In relaxation periods actin and myosin returns in off-position and the muscle reverts to the initial situation. [NIETHARD and PFEIL 2005, HOHMANN et al. 2003]

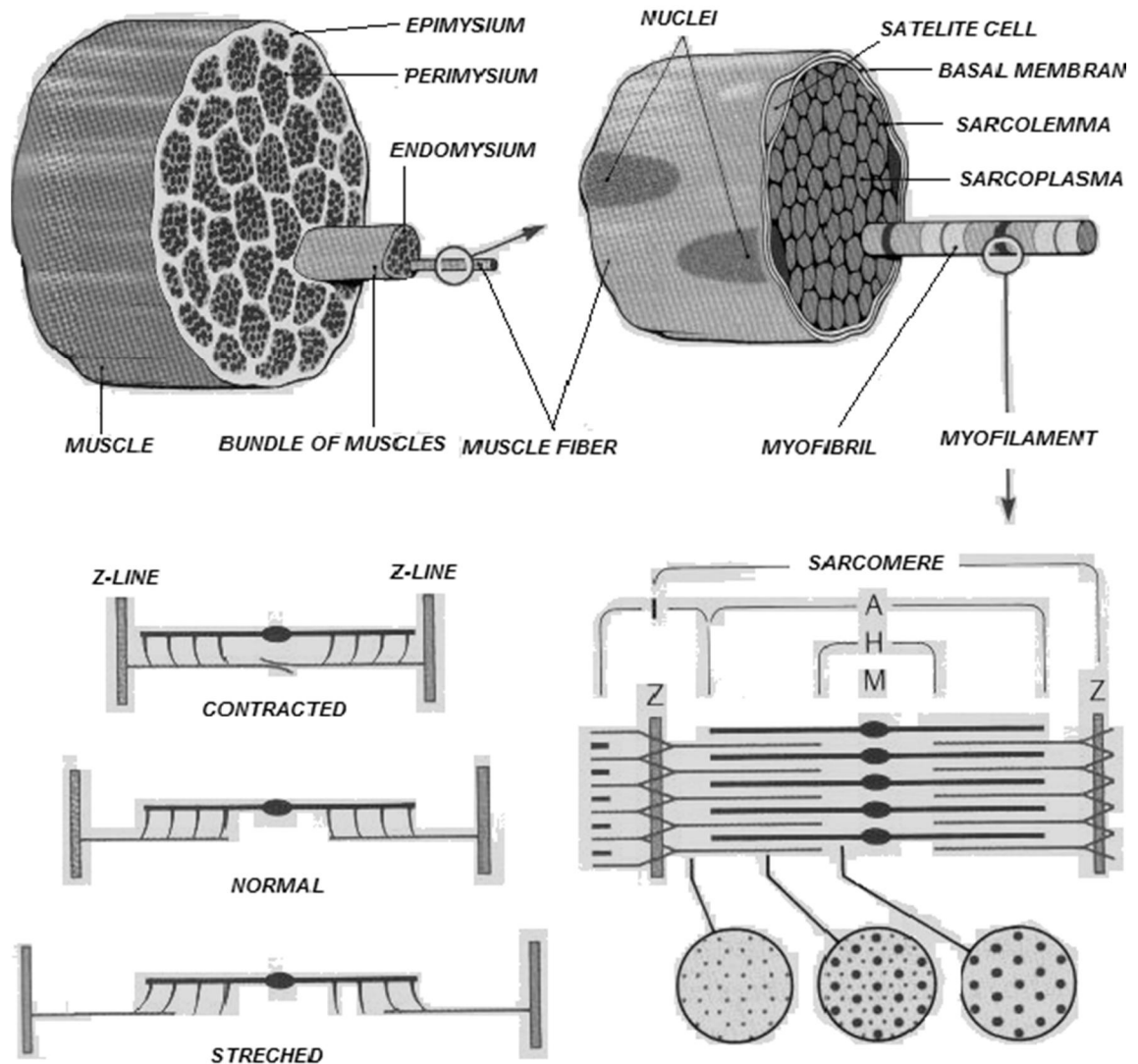


Figure 3: Anatomy of the muscle

[modified according to NIETHARD and PFEIL 2005]

Tendons and ligaments vary in their structural composition because of their different functions. Due to the fact that they work by tension, they are typically made of tight, parallel arranged connective tissue with spindle-shaped cells, the tendocytes. [NIETHARD and PFEIL 2005]

According to Niethard and Pfeil the components of the connective tissue are

- collagen
- proteoglycan
- glycoprotein
- elastin

Collagen fibrils ensure tensile strength, elastic fibers act as damper. In case of loss of elasticity there is an increased risk for rupture. The tendon is covered in loose connective tissue, the so-called tendon sheath. In case of overstress inflammation could be a consequence. In the transitional area, as seen in Figure 4, where the tendon is connected to the bone (tendon-insertion), chondrocytes are enclosed to the tendon tissue to compensate the tension. [NIETHARD and PFEIL 2005]

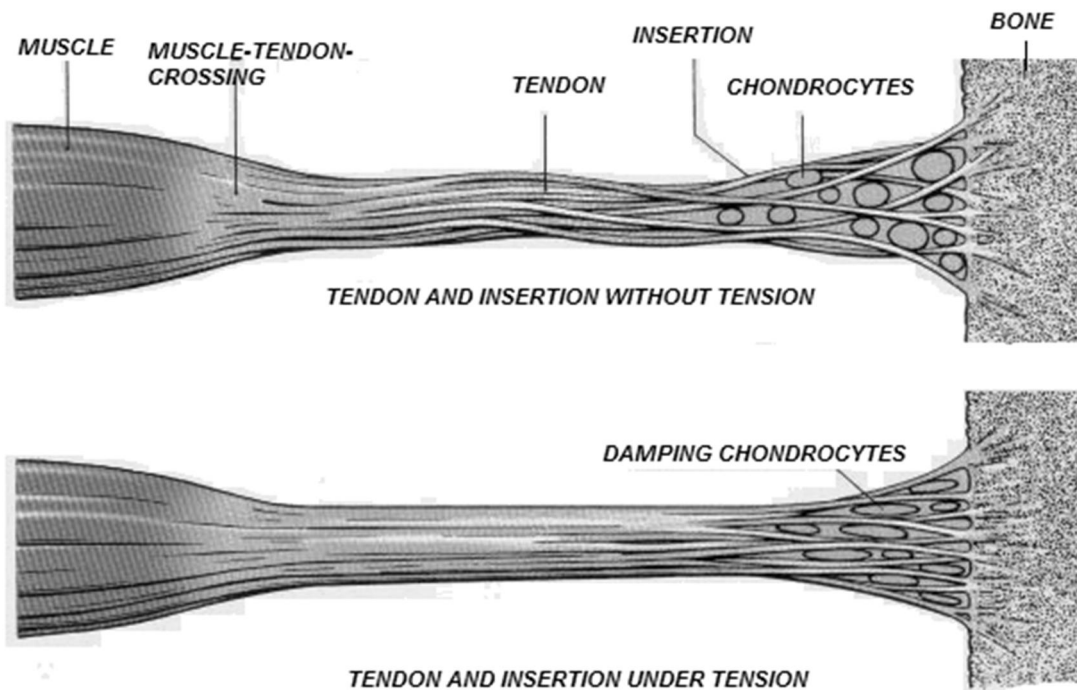


Figure 4: Tendon-bone insertion

[modified according to NIETHARD and PFEIL 2005]

6.3.2 Muscle diseases

In the following chapter only those muscles disorders were selected and described regarding their etiology and clinical course, which may be related to or influenced by nutritional components.

6.3.2.1 Muscle inflammation

6.3.2.1.1 Pathogenesis

Causes for the incidence of myositis are bacterial, viral or parasitical. A bacterial induced inflammation as a consequence of injections into the muscle is the most common cause for myositis. Lymphocytic myositis is also possible in patients with inflammatory-rheumatic disorders.

In aging people a special form of myositis, polymyalgia rheumatic, is a frequent occurring disorder. The joints of shoulder and hip are most commonly affected. [NIETHARD and PFEIL 2005]

The only symptom of myositis is unspecific muscle pain, and in the case of polymyalgia rheumatica symptoms are shoulder and hip joint pain and an extremely disturbance of the general condition. [NIETHARD and PFEIL 2005]

6.3.2.1.2 Therapy

Abscesses as consequences of injections require surgical excision. Medical treatment with corticosteroids is the recommended intervention for polymyalgia rheumatica. [NIETHARD and PFEIL 2005]

6.3.2.2 Tendovaginitis

Tendovaginitis is an inflammatory disorder of the tendon sheath.

6.3.2.2.1 Pathogenesis

Mechanical irritation and physical over stress lead to swelling of tissue and tendon sheath. In few cases, bacterial infections and rheumatic inflammations are causes for the incidence of tendovaginitis. Extraction of fibrin into the tendon sheath is the reason for the typical creaking of sliding fabric. [NIETHARD and PFEIL 2005]

6.3.2.2.2 Symptoms

In most cases tendovaginitis affects the joints of the hand. Symptoms are swelling, acute pain and pain in motion after unique or chronic physical overstress. [NIETHARD and PFEIL 2005]

6.3.2.2.3 Therapy

Immobilization and injections into the affected tissue with corticoids are common ways to treat tendovaginitis. [NIETHARD and PFEIL 2005]

6.3.2.2.4 Dietary factors associated with myositis and tendovaginitis

To best of our knowledge, there are no scientific studies approaching effects of dietary intervention on myositis and tendovaginitis. However, as myositis and tendovaginitis are inflammatory diseases, the anti-inflammatory effects of n-3 FAs (EPA and DHA in fatty fish or fish oil) could be of interest to reduce pharmacologic treatment. n-3 FAs show anti-inflammatory activity by inhibiting membrane AA metabolism, and at the

same time synthesizes of pro-inflammatory prostaglandins from AA is reduced. [BRIEN 2008, WANN 2010, EFTHIMIOU and KUKAR 2010]

6.3.2.3 Degenerative disorder of tendon, meniscus and bursa

Tendons and menisci work by tension. In cases of strong physical strain degenerative changes are possible. Most affected areas are spinea and hip. The main symptom is pain. Disorders of bursa are inflammations with swelling and consequently associated pain. Inflammations in deeper tissue regions such as in the shoulder or hip often remain undetected.

Degenerative disorders of tendon, meniscus or bursa require immobilization of the affected region. In some cases, if the inflammation is chronic, medical treatment with corticosteroids is recommended. [NIETHARD and PFEIL 2005]

6.3.2.3.1 Dietary factors associated with degenerative disorders of tendon, meniscus and bursa

From the scientific point of view, there are no nutritional recommendations concerning degenerative disorders of tendons, meniscus or bursa. In case of chronic inflammation, an additional treatment with anti-inflammatory nutritional compounds could be taken into consideration, to reduce corticosteroid or NSAID intake. n-3 FAs could be of interest, due to their important role in the initiation and regulation of inflammatory mediators. [GOLDBERG and KATZ 2007]

7 The shoulder joint

As the shoulder will be in the focus of the following critical review, the following chapter will describe selected shoulder pathologies and the effects of nutritional components on shoulder diseases will be discussed.

7.1 Shoulder Joint

The shoulder joint (Figure 8) has the greatest mobility compared to other joints in the human body. It permits the arm to be rotated, elevated, and extended both forward and backward. This flexibility is also the reason why the shoulder joint is an extremely unstable joint, thus has the greatest predisposition to injuries.

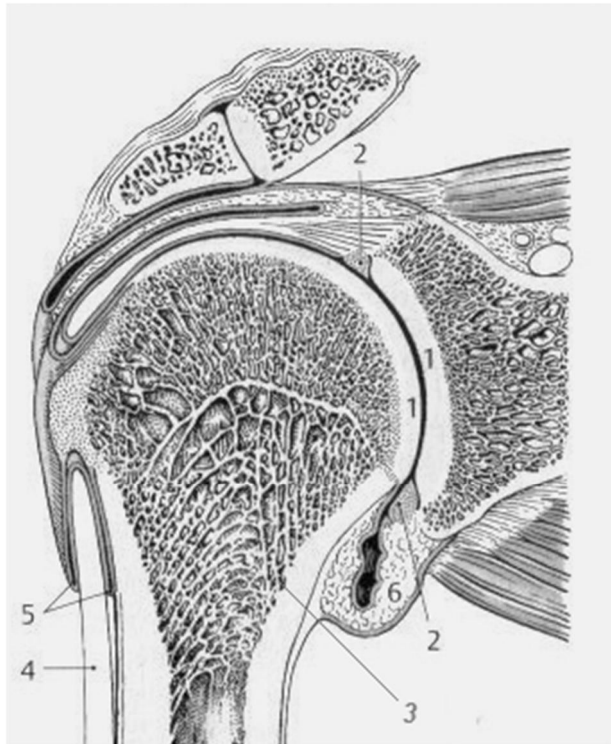
7.1.1 Anatomy

The shoulder joint assembles the following diarthrodial joints:

- the glenohumeral joint
- the acromioclavicular joint
- the sternoclavicular joint
- and the layer between scapula and posterior chest wall (scapulothoracic articulation).

Shoulder joint bones are covered by articular cartilage and surrounded by fibrous articular capsules.

A total of 80 % of all shoulder disorders are changes in the soft tissue. Problems concerning the rotator cuff (RC) are the most common reasons for pain in the region of the shoulder. [PLATZER 2005, NIETHARD and PFEIL 2005]



- 1 CARTILAGE
- 2 GLENOID LABRUM (PART OF THE CARTILAGE)
- 3 CAPUT HUMERI (HEAD OF THE HUMERUS)
- 4 TENDON
- 5 SYNOVIAL MAMBRANE
- 6 PART OF THE JOINT CAPSULE

Figure 5: The shoulder joint

[modified according to PLATZER 2005]

7.1.2 Rotator cuff muscles

The RC (Figure 9) is a group of muscles and related tendons in the shoulder of the human body. Functions are stabilization and movement of the shoulder. The RC consists of 4 muscles, named supraspinatus, infraspinatus, teres minor and subscapularis. These muscles have their source at the scapula and connect to the head of the humerus, forming a cuff at the shoulder joint. On the one hand this construction ensures a high degree of mobility; on the other hand this dynamic stabilization involves a potential instability of the shoulder which often leads to luxation. [PLATZER 2005, NIETHARD and PFEIL 2005]

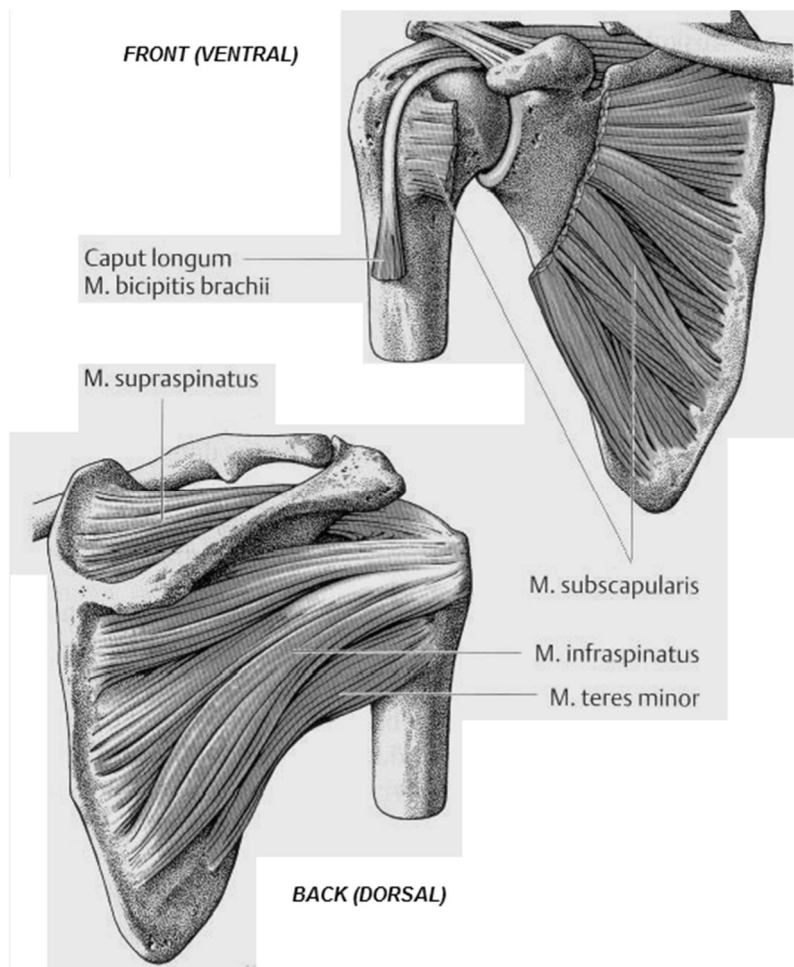


Figure 6: The rotator cuff

[modified according to NIETHARD and PFEIL 2005]

7.2 Shoulder pathologies

As explained above, the shoulder is a very flexible joint and therefore prone to injuries. In the following chapter selected shoulder disorders and will be explained. At the end of this chapter the nutritional influences on shoulder disorders will be discussed.

7.2.1 Shoulder instability

Shoulder instability or dislocations of the shoulder can be classified into three groups:

- habitual dislocation without traumatic background
- arbitrary dislocation of the shoulder where patients are able to dislocate the shoulder whenever they want to
- post traumatic recurrent habitual dislocation after traumatic dislocation
[NIETHARD and PFEIL 2005]

A constant feeling of instability within the shoulder is a typical clinical sign. Mobility is restricted leading to limitations at work and leisure time. Possible complications and long-term consequences are chronic shoulder instability or OA of the shoulder.
[NIETHARD and PFEIL 2005, MILLETT et al. 2008]

Surgical intervention is recommended in the treatment of recurrent shoulder dislocation.
[NIETHARD and PFEIL 2005]

7.2.2 Osteoarthritis of the shoulder

Shoulder OA is a gradual, progressive, mechanical, and biochemical degeneration of the articular cartilage, bone and joint capsule of the shoulder.

As a conclusion of wear of the cartilage surface, friction within the joint increases which leads to pain and disability. Risk factors for shoulder OA, or also known as

degenerative joint diseases of the shoulder, are various including age, genetics, gender, weight, joint infection, previous shoulder dislocation or injury. Physical overstress of the shoulder, such as overhead sports is a further risk factor. [MILLETT et al. 2008]

The main objective in the treatment of OA is to lower pain and restore function. Therefore medication with NSAIDs and corticosteroids is recommended. Due to the numerous side effects (as explained in chapter 6.2.1.3. - 4) alternatives are of high interest. In some cases, if conservative therapies fail, surgical intervention is necessary. Non-surgical and non-pharmacologic intervention such as physiotherapy and exercise are unproven in the treatment of shoulder OA. [MILLETT et al. 2008]

7.2.2.1 Dietary factors associated with the shoulder joint (cartilage)

Shoulder dislocation is a disorder where nutritional intervention is not applicable. But as explained above, chronic shoulder instability could lead to shoulder osteoarthritis [MILLETT et al. 2008]. The main nutritional components in the treatment of OA are glucosamine and chondroitin. However, at the moment a general recommendation for the use of glucosamine and chondroitin is not possible, since heterogeneity among glucosamine and chondroitin sulfate trials is high [RICHMOND et al. 2009, BRUYERE et al. 2008, VLAD et al. 2007]. As inflammation of the synovial membrane is a symptom of osteoarthritis [KAPOOR et al. 2011] treatment with anti-inflammatory nutrients such as n-3 PUFAs should be taken into consideration.

7.2.3 Rotator cuff pathologies

RC tears are ruptures of the tendons related to the four muscles supraspinatus, infraspinatus, subscapularis and teres minor. Traumatism or degeneration of the tendons are reasons for the occurrence of tears. But a traumatic rupture without previous degeneration is rather infrequent.

Tears range from small partial tears to full thickness tears. Acute traumatic tears are painful but pain decreases over time. In case of degeneration of the RC over a long period, symptoms are rather mild. Pain is much more in focus than function restriction. Degenerative RC tears are very present in elderly with a prevalence of about 30%. [NIETHARD and PFEIL 2005]

In the therapy pain and limited function are decisive factors. Among young patients with extensive clinical symptoms surgical intervention is recommended. [NIETHARD and PFEIL 2005] For painful partial RC tears NSAIDs and injections of corticosteroids in combination with supervised exercise should be considered. [ROBB et al. 2009]

7.2.3.1 Dietary factors associated with the shoulder joint (tendons)

There is a lack of scientific studies regarding tendon-related joint disorders and dietary supplementation [LEWIS and SANDFORD 2009]. However, nutritional alternatives to NSAIDs and corticosteroids could be of interest in the treatment of tendon and muscle related shoulder disorders. Reduction of inflammation processes with n-3 PUFA supplementation is even of high interest in chronic shoulder disorders. Treatment with proteoglycans as natural components of the soft tissue of the shoulder (tendons and muscles of the RC) could also be of interest.

8 Diet and joint disorders

In this chapter a selection of frequently discussed nutrients related to joint disorders are explained and the clinical relevance is evaluated. Table 1 gives an overview of the reviewed nutrients and studies.

Substance	Reference	Design	Population	Dosage/Parameter Duration	Results
Glucosamine sulfate	Towheed et al.	Review	2570	500 or 1500 mg/day 3 weeks–3 years	significant improvement in pain and joint function
	Reginster et al.	Review	624	1500 mg/d 6–36 month	significant improvement in pain and joint function
	Wandel et al. 2010	Meta-analyses	3803	800-1500 mg/day 1–156 weeks	no clinical relevant effect on joint pain and joint space narrowing
	Lee et al. 2010	Meta-analyses	414	1500 mg/day up to 3 years	a small to moderate protective effect on minimum joint space narrowing
	Vlad et al. 2007	Review	2613	1500 mg/day 1 month–3 years ⁹	no significant outcome
Chondroitin sulfate	Hochberg 2010	Meta-analyses	1179	800-1200 mg/day 2 years	significant effect of slowing the rate of joint space narrowing
	Reichenbach et al. 2007	Meta-analyses	3846	800–1200 mg/d (1x 200 mg/d 1-32 weeks	minimal or nonexistent symptomatic benefit
	Lee et al. 2010	Meta-analyses	1088	800mg/day up to 2 years	small but significant protective effect on minimum joint space narrowing
Collagen hydrolysate	Benito-Ruiz 2009	RCT	250	10 g/day 6 month	improvement of knee joint comfort
	Bruyere et al. 2012	RCT	200	1200 mg/d 6 month	significant improvement in pain
	Zuckley et al. 2004	RCT	190	10 g/day with calcium (300 mg/day) and vitamin C (60 mg/day) 14 weeks	improvement of knee functional mobility
Vitamin D	Bergink et al. 2009	Cohort	1248	serum level of 25-hydroxyvitamin D	low levels of vitamin D intake are related to an increased risk of OA progression
	Brejawi et al. 2009	Cross-section	117	serum level of 25-hydroxyvitamin D	high prevalence of low vitamin D status in patients with knee OA
	Felson et al. 2007	Cohort	993	serum level of 25-hydroxyvitamin D	no association between vitamin D levels and joint structure

Substance	Reference	Design	Population	Dosage/Parameter Duration	Results
AO	Canter et al. 2007	Review	460	150-200 mg/day Selenium 400-1200 mg/day Vit E 3 weeks-12 month	no significant outcomes for Vit A, C and Selenium, contradictory outcomes for Vit E
	Brien et al. 2008	Review	681	DMSO topical MSM topical or orally 4-20 g/day 3-4 weeks	significant improvement in pain
Rosehip powder	Christensen et al. 2008	Meta analyses	287	5 g/day or more (pain related – patients decision) 3 month	clinically relevant reduction of pain
	Chrubasik et al. 2008	One-year-Survey	296	5 g/day or more (pain related – patients decision) 1 year	improvement in pain
ASU	Henrotin et al. 2011	Review	435	300-600 mg/day 3 month-2 years	reduced progression of joint space loss, decreased NSAID and analgesic intake, beneficial effects on pain and joint function
	Christensen et al. 2008	Meta analyses	664	300 mg/day 3-12 month	neither worse nor better than other medications for treating OA in knee and hip
n-3 FA	Brien et al. 2008	Review	402	630-5750 mg mussel extract/day or capsules of green lipped mussel extract(dose not reported) 2-6 month	improvement in pain and joint function
	Dawczynski et al. 2011	RCT	60	3 g n-3 PUFA or 3.2 g GLA or 1.6 g PUFA + 1.8 g GLA/day 12 month	n-3 PUFA and GLA increased EPA and DHA in plasma lipid cells
	Adam et al. 2003	RCT	68	diet low in AA and fish oil capsules (30 mg/kg body weight/day) 8 month	significant improvement in tender and swollen joints, increased EPA and erythrocyte lipids, lower formation of prostaglandin metabolites

Substance	Reference	Design	Population	Dosage/Parameter Duration	Results
n-3 FA	Galarraga et al. 2008	RCT	97	10 g cod liver/day (2.2 g EPA and DHA) 9 month	reduced NSAID intake
	Berbert et al. 2005	RCT	34	3 g fish oil n-3 FAs	improvement in joint pain intensity, handgrip strength, duration of morning stiffness
	Stammers et al. 1992 in Henrotin et al. 2011	double-blind placebo-controlled trial	86	10 ml cod liver/day (786 mg EPA) 24 weeks	no effect on pain and ability
	Cho et al. 2003 in Henrotin et al. in 2011	multicenter open trial	60	4 capsules of green lipped-mussel (200 mg extract) 8 weeks	improvement of OA signs and symptoms (joint pain and function)
	Goldberg and Katz 2007	Meta analyses	823	1,7-9,6 g n-3 FAs/day (fish oil or capsules) 1-12 month	reduced joint pain intensity, morning stiffness, number of painful and/or tender joints, and NSAID consumption

Table 1: Summery of the reviewed studies concerning nutrients relevant in the treatment of joint disorders

8.1 Cellular components of the connective and supporting tissue

Relevant cellular components of the connective and supporting tissue of the joint are glucosamine (glucosamine sulfate), chondroitin (chondroitin sulfate) and collagen (collagen hydrolysate).

8.1.1 Glucosamine sulfate

From a chemical point of view, glucosamine is a monosaccharide with an amino group instead of the hydroxyl group at the second carbon-position (C-2 position). This amino sugar is an important precursor in the biochemical synthesis of glycosaminoglycan, which are the side chains of proteoglycans. Therefore, glucosamine is an essential part of the extracellular matrix including ligaments, tendons, cartilage and synovial fluid. [THE AMERICAL HERITAGE® SCIENCE DICTIONARY 2005]

D-fructose-6-phosphate and the amino acid L-glutamine are the precursors in synthesis of glucosamine in human organism.

Dietary supplements are, in most cases, produced by hydrolysis of crustacean exoskeletons or fermentation of vegetarian sources. The precursor is chitin, which is a common nitrogenous polysaccharide in animal and funguses. [THE AMERICAL HERITAGE® SCIENCE DICTIONARY 2005] In 2006 Hathcock and Shao evaluated food safety of glucosamine sulfate. Based on the included clinical trials an upper safe level for supplements (USL) of 2000 mg/d has been determined. There was no toxicological basis to determine whether a no observed adverse effect level (NOAEL) nor a lowest observe adverse effect level (LOAEL). [HATHCOCK and SHAO 2006] Glucosamine sulfate is approved as a pharmaceutical product in Austria with a daily dose of 1250 mg glucosamine. Products with lower amounts of glucosamine are available as dietary supplements. [BUNDESMINISTERIUM FÜR GESUNDHEIT 2009] In the USA glucosamine sulfate is classified as a dietary supplement and is available over the counter. [VLAD et al. 2007] In the United Kingdom only one of the glucosamine products is licensed and available as a “prescription only medicine”. In

Europe most of the products are sold as dietary supplements and available over the counter. [BLACK et al. 2009] According to Reginster et al. a daily oral dose of 1500 mg glucosamine sulfate per day is effective and safe, and used in most of the existent trials concerning glucosamine sulfate. [REGINSTER et al. 2012]

In the work of Bruyere et al. three meta-analyses and reviews met the study requirements. [TOWHEED et al. 2005, VLAD et al. 2007, REGINSTER 2007] In all of them, a significant improvement in pain and also in joint function was found. However, heterogeneity was high among the trials included. [BRUYERE et al. 2008] In almost every older trial a daily dose of 500 mg has been administered. In more actual trials doses of 1500 mg/day are administered. [TOWHEED et al. 2005]

A meta-analysis of Wandel et al. included ten trials incorporating 3.803 patients with knee or hip OA. The group found no clinical relevant effects with glucosamine (800 - 1500 mg/d) or with glucosamine in combination with chondroitin on joint pain. There was also no effect on the joint space narrowing compared with placebo. [WANDEL et al. 2010]

Lee et al. reported in their meta-analysis on structural efficacies of glucosamine sulfate and chondroitin on knee OA, that glucosamine sulfate in long-term daily treatment over at least 3 years has small to moderate protective effects on minimum joint space narrowing. [LEE et al. 2010]

However, a general recommendation is not possible, since heterogeneity among glucosamine sulfate trials does not allow definitive conclusions or recommendations about efficacy of glucosamine sulfate in the treatment of OA or pain related joint disorders in general. [VLAD et al. 2007]

8.1.2 Chondroitin sulfate

Chondroitin sulfate, a natural compound of the body, structurally made of a chain of alternating amino sugars containing sulfuric acid, is a so-called sulfated glycosaminoglycan and therefore, as well as glucosamine sulfate, part of the side chains of proteoglycans. Chondroitin sulfate as a proteoglycan is a major intracellular component of connective tissue, cartilage and skeleton. [THE AMERICAN HERITAGE® SCIENCE DICTIONARY 2005] The ULS for chondroitin sulfate is 1200 mg/d. [HATHCOCK and SHAO 2006] In Europe chondroitin sulfate is declared as a dietary supplement and available over the counter. [BLACK et al. 2009]

Hochberg reported in his meta-analysis that an oral daily dose of 800 mg chondroitin sulfate appears to have a small but significant effect on slowing the rate of joint space narrowing over a period of 2 years in patients with symptomatic radiographic knee OA. [HOCHBERG 2010]

Reichenbach et al. reported in a meta-analysis (total of 3846 patients, duration up to 132 weeks) a small effect of chondroitin sulfate (800 – 1200 mg/d) on symptoms of osteoarthritic disorders such as pain. [REICHENBACH et al. 2007]

Lee et al. reported in their meta-analysis, that chondroitin sulfate may delay the natural radiological progression of knee OA. Long-term daily treatment, over at least 2 years with a daily oral intake of 800 mg, may retard degeneration of cartilage affecting the knee. [LEE et al. 2010]

8.1.3 Collagen hydrolysate

Collagens are the most prevalent proteins in human organism and are responsible for mechanical stability of tissue and organs. All of the 20 different collagen types have the typical triple helix in common. This structure is responsible for the high stability of collagen. [LÖFFLER 2004]

Collagen hydrolysate is the enzymatic hydrolyzed form of collagen. Such as collagen type II, the main characteristics of collagen hydrolysate are the amino acids proline and

glycine which are responsible for stability and regeneration of cartilage. [HENROTIN et al. 2011]

In the randomized, double-blind, controlled multicenter trial of Benito-Ruiz et al., 250 subjects with primary OA of the knee were given collagen hydrolysate (10 g/d) as a dietary supplement over a period of six month. There was a significant improvement in knee joint comfort. [BENITO-RUIZ et al. 2009]

In the RCT of Zuckley et al., 190 patients with mild symptoms of knee OA were given 300 mg collagen hydrolysate per day as a dietary supplement over a period of 14 weeks. Results show a significant improvement of certain strength and work performance tests; that means an improvement of knee functional mobility. [ZUCKLEY et al. 2004]

A recent RCT by Bruyere et al. examined the effect of collagen hydrolysate in articular pain. A treatment with 1200 mg collagen hydrolysate per day over a period of 6 month showed significant improvement in joint pain. [BRUYERE et al. 2012]

8.2 Vitamins and Antioxidants

Vitamins are essential nutrients and must be obtained from the diet. From a chemical point of view vitamins are structurally not related and have different functions in human body. Some vitamins have no upper level of intake, because of their low bioavailability and fast metabolism at high doses of intake. Some vitamins have pharmacologic or toxic potential at higher intake. Vitamin A and D for example could have lethal dosages at very high intake, but overdoses with the daily diet are unlikely.

Vitamin needs are individually different and depend on factors such as age, gender, health status etc. They are part of this chapter due to their role in radical metabolism. Free radicals can lead to destruction of macromolecules, and as a consequence to so-called oxidative stress, if the body is not able to inactivate them. Endogenous sources of free radicals are the arachidonic acid cascade (AA-cascade), inflammation, phagocytosis, respiratory chain or physical activity.

The body comprises of an effective non-enzymatic and enzymatic defense system. Non-enzymatic defense is performed by antioxidants, among them also vitamins. They have either individual antioxidant potential, but can also act as synergist by regenerating

primary antioxidants. Therefore, vitamin supplements are often administered as supplement-complex. For example vitamin C is able to enhance the antioxidant effect of vitamin E since vitamin C regenerates the active form of vitamin E. Also vitamin E and selenium is a synergistic couple with antioxidant potential. [ELMADFA and LEITZMANN 2004]

8.2.1 Vitamin D

Vitamin D can be synthesized in the human organism in case of enough ultraviolet B (UVB) radiation (exposure of the sun), and therefore, in definition, vitamin D is not a “real” vitamin. Vitamin D represents a pro-hormone, and a precursor for the hormone calcitriol. There are two forms of fat soluble vitamin D, also called calciferol, in human diet. One is cholecalciferol (vitamin D3), which is from animals and synthesized in the skin, and the second form is the plant derived ergocalciferol (vitamin D2). The potential for synthesizing vitamin D3 in skin decreases with age. [ELMADFA and LEITZMANN 2004, DGE et al. 2012]

Nutrients containing vitamin D in relevant doses are fish-liver, fish oil, fatty fish, egg yolk and some edible mushrooms. Milk and milk products contain vitamin D, but only in very low doses. In some regions vitamin D enrichment of food (e.g. margarine or milk) is a way of protecting against vitamin deficiency. [ELMADFA and LEITZMANN 2004, DGE et al. 2012]

Functions of Vitamin D

- increases calcium absorption
- regulation of gene-transcription (function as steroid-hormone) with the consequence of increased intestinal absorption of calcium
- bone formation and degradation
- controls cell proliferation in skin

[ELMADFA and LEITZMANN 2004]

Recommended daily intake: 20 µg in case of non-endogenous synthesizes. The average intake with normal food is only 2-3 µg/day. Therefore, differences must be compensated with endogenous synthesise or dietary supplements. [DGE et al. 2012]

Three observational studies in humans have been performed in the last 10 years [BERGINK et al. 2009, BREIJAWI et al. 2009, FELSON et al. 2007]. The serum level of 25-hydroxyvitamin D was reported. One study showed no association between serum level and structural joint degradation [FELSON et al. 2007]. Whereas, in the other two studies a correlation between low vitamin D serum level and joint degradation was observed. [BERGINK et al. 2009, BREIJAWI et al. 2009] Therefore, further studies are required to investigate if there is an association between vitamin D intake and osteoarthritic disorders, or not.

8.2.2 Antioxidants

Antioxidants prevent other substances from the undesired effect of oxidation. In their capacity as radical scavenger antioxidants have a high physiological importance. In the human organism they inactivate reactive oxygen species (ROS), which lead to oxidative stress in high doses. Oxidative stress itself is one of the reasons for the aging process, and is also one major aim in the development of chronic diseases. ROS have been associated with the inflammation process of several diseases including rheumatoid arthritis and OA. [CANTER et al. 2007]

In a review by Canter et al. the antioxidant potential of the vitamins A, C, E and selenium and their role in the treatment of arthritis (inflammatory arthritis and OA) was critically discussed. Twenty randomized clinical trials were considered, but the quality of the studies was generally poor because most of the included studies did not adequately describe the study design and statistical analyses. However, the conclusion of the review was missing evidence that vitamins A, C and selenium have any effect in the treatment of arthritis. The results for vitamin E were contradictory. [CANTER et al. 2007]

A review by Brien et al. included six studies concerning OA and the nutritional supplements dimethyl sulfoxide (DMSO) and methylsulfonylmethane (MSM). Both supplements have antioxidant potential, possible actions are slowing down or stopping

leakage from injured cells, stabilizing cell membranes or scavenging hydroxyl radicals which trigger inflammation.

Due to the poor methodology of the included DMSO studies no final conclusion can be drawn for any effects of this supplement. Data from MSM studies on the other hand are more rigorous and there is moderate positive but not clear evidence that MSM is more effective than placebos in the treatment of knee OA. Therefore further studies are mandatory, also to identify optimal dosage and long-term safety. [BRIEN et al. 2008]

8.2.3 Rosehip powder

Rosehips are the pseudo fruits of *Rosa Canina*, commonly known as dog rose. *Rosa Canina* is a wild rose species native in Europe, Northwest Africa and Western Asia. Rosehips are known for their high vitamin C levels (500mg/100g) which is the highest in middle European fruits. Rosehips puree has 20 times more vitamin C compared to lemons. Additionally, the fruits are rich in provitamin A, B-vitamins, minerals and the trace elements copper and zinc.

The raw fruits of *Rosa Canina* are not suitable for consumption. Therefore, dried fruits as powder, tea, syrup, jam are the most common products. [BIELENBERGER 2007]

Standardized hip powder and antioxidant and anti-inflammatory effects have been evaluated in several trials.

A review by Christensen et al. comprised only three randomized controlled trials (RCTs) with 287 patients over a small period of 3 month of low quality, so the results should be taken with care. They concluded that a small to moderate short-term efficacy of preparations with *Rosa Canina* hip powder (5 g/d), with a small but clinically relevant reduction of pain in OA patients was possible. Further long-term studies are needed to confirm the results of this review. [CHRISTENSEN et al. 2008]

A One-Year-Survey (77 patients out of 296 completed the survey) by Chrubasik et al. of moderate quality (no representative sample, no control group, no defined dose/day) suggested a positive effect of rosehip and seed powder (Litozin®) on patients with chronic pain as well as unspecific low back pain and osteoarthritic pain. [CHRUBASIK et al. 2008] A review by Chrubasik et al. in 2008 could not assure the anti-inflammatory

and anti-oxidative effects of Rosa Canina with clinical significance. Therefore further research is needed. [CHRUBASIK et al. 2008]

8.3 Phytochemicals

Phytochemicals are physiologically active plant components of different chemical structure. To date approximately 100.000 different phytochemicals have been identified, and 5.000 to 10.000 are present in the human diet. [DGE 2010]

Due to their chemical structure and function phytochemicals can be classified into

1. Polyphenols
2. Carotenoids
3. Phytoestrogens
4. Glucosinolates
5. Sulfides
6. Monoterpenes
7. Saponines
8. Protease-Inhibitors
9. Phytosterols
10. Lectins

Phytochemicals are part of the daily diet in fruits, vegetables, legumes, nuts, as well as whole grain products and fermented foods. In plants, phytochemicals have several responsibilities, for example protecting the plant from predators or microbes, growth regulation and some of them are plant pigments. Phytochemicals are not established as essential nutrients, but in their function as bioactive substances they could have biological significance in human metabolism. [DGE 2010]

Phytochemicals are discussed to have anti-oxidative, anti-carcinogenic, immune-modulating, anti-microbial, anti-thrombotic, anti-inflammatory, blood pressure regulating, cholesterol level reducing, and blood-glucose level regulating and digestion-furthering potential. [ELMADFA and LEITZMANN 2004]

Recommendations for daily intake of phytochemicals are not reasonable because of the lack of scientific data. It is possible that some of these nutrients develop their special effects only in synergism with others. Therefore, the German Nutrition Society (DGE) recommends a high consumption of fruits and vegetables to ensure a sufficient supply of phytochemicals. [DGE 2010]

8.3.1 Avocado-soybean unsaponifiables

Avocado and soybean unsaponifiables (ASU) are phytochemicals. ASU is an extract of oils generally mixed in the ratio one-third avocado oil and two-thirds soybean oil. Main components of ASU are β -sitosterol, campesterol and stigmasterol which are phytosterols.

The underlying premise is that this ASU-mixtures stimulates the synthesis of aggrecan and extracellular matrix components such as type II collagen (collagen is a natural component of tendons, joints, ligaments and muscles) because of their positive effects on human chondrocytes. ASU is discussed to reduce the production and the action of inflammatory substances and reduces the production of catabolic mediators. Thus, ASU could prevent cartilage degradation and support the repair of damaged cartilage. [AMEYE and CHEE 2006, ARC 2009, HENROTIN et al. 2011] Henrotin et al. reported positive effects of ASU (300 mg/d up to 2 years) on joint space loss, NSAID intake, pain and joint function. [HENROTIN et al. 2011]

The conclusion of the meta-analysis of randomized controlled trials of Christensen et al. is that ASU (300 mg/d over an average trial duration of 6 month) are neither worse nor better than other medications for treating OA in knee and hip. There is no evidence of significant negative side effects. There are better chances of success in patients with knee OA than in patients with hip OA. [CHRISTENSEN et al. 2008]

8.4 Lipids

The term lipid includes a variety of different molecules with similar chemical and physical properties. From the chemical point of view a classification into lipids with FA as structural component and so called lipid-like substances, which are isoprene

derivates. The majority of natural fats consist of triglycerides, which are esters of glycerin with long chain FA, and traces of mono- and diglycerides, free FA, phospholipids and non-saponifiable components. [ELMADFA and LEITZMANN 2004]

Classification of natural fats and oils with relevance in human diet

- simple lipids (neutral fats, waxes)
- complex lipids (phospholipids, glycolipids, lipoproteins)
- fat-derivates/fat-soluble substances (FA, glycerin, sterols, fat-soluble vitamins, lipochromes, antioxidants, flavors) [ELMADFA and LEITZMANN 2004]

Biological functions of lipids

Structural function: lipids are present in all cells of the body, especially in the cells of the nervous system. They are essential parts of the cell membrane as well as the membrane of cell organelles such as mitochondria and lysosomes.

Energy support: lipids supplies humans and plant organism with energy, and are responsible for long-term reserves. 1 g fat provides 37.7 kJ.

Body functions: unsaturated long-chain FAs are essential for brain and retina.

Immune function: one of the most important functions of lipids is their function as precursor for the biosynthesis of eicosanoids.

Thermal insulation: fats below the skin protect against body heat loss.

Protective function: simple lipids protect inner organs against mechanical influences.

Carrier of fat-soluble vitamins, flavors and odorous substances: lipids are essential for the bioavailability of lipid-soluble agents.

[ELMADFA and LEITZMANN 2004, LÖFFLER 2004]

8.4.1 Fatty acids

Fatty acids (FAs) consist of a hydrocarbon chain and a carboxyl group. In most cases FAs contain an even number of C-atoms and in some cases one or more double bonds. [LÖFFLER 2004]

Main characteristics of FAs are chain length, degree of saturation and localization of the double bonds.

Chain length

FAs with up to 4 C-atoms are defined as short-chain, with 6-12 C-atoms as medium-chain and with more than 12 C-atoms as long-chain FAs.

Degree of saturation

Saturated FAs have no double-bond in the molecule, mono-unsaturated FAs have one double-bond and PUFA have more than one double-bond in the molecule.

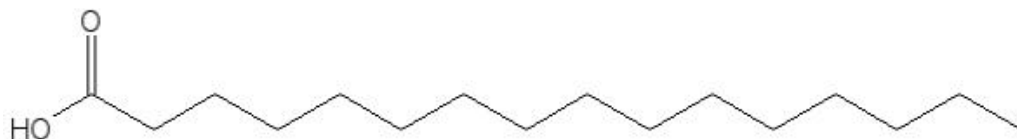
Localization of double bonds

Furthermore a classification by the localization of the first double-bond from the methyl end is possible. n-3 FAs have their first double-bond at the third C-atom, n-6 FAs at the sixth C-atom and n-9 fatty acids at the ninth C-atom. Finally a differentiation into cis-FA and trans-FAs is possible. In cis-configuration adjacent hydrogen atoms are on the same side of the double bond and in trans-configuration hydrogen atoms are on opposite sides of the double bond [ELMADFA and LEITZMANN 2004, LÖFFLER 2004]

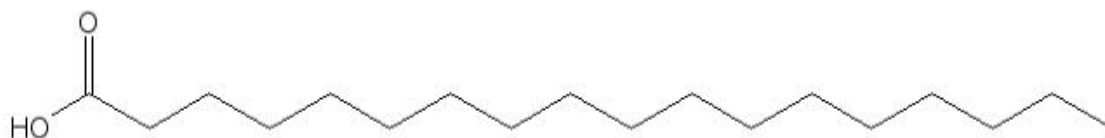
Nomenclature

Both, trivial names and chemical designations are used in literature.

Saturated FAs



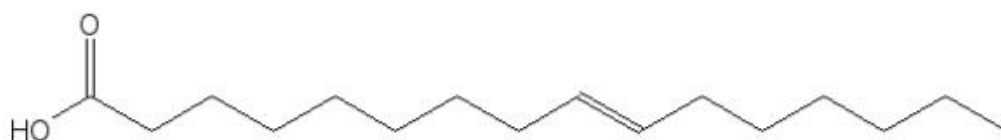
Palmitic acid – Hexadecanoic acid – $C_{16}H_{32}O_2$ – C16:0



Stearic acid – Octadecanoic acid – $C_{18}H_{36}O_2$ – C18:0

Figure 7: Saturated FAs

Unsaturated FAs

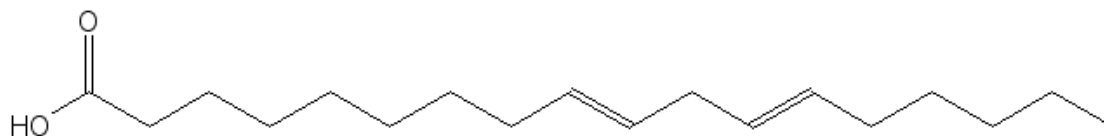


Palmitoleic acid – cis-9-Hexadecenoic acid – $C_{16}H_{30}O_2$ – C16:1n-7

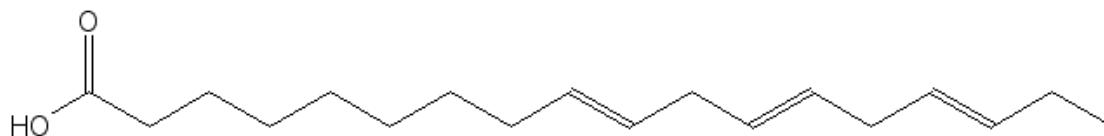


Oleic acid – cis-9-Octadecenoic acid – $C_{18}H_{34}O_2$ – C18:1n-9

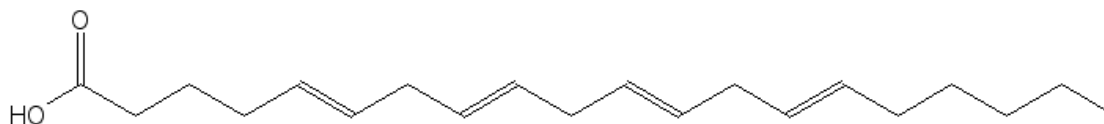
Figure 8: Unsaturated FAs

PUFAs

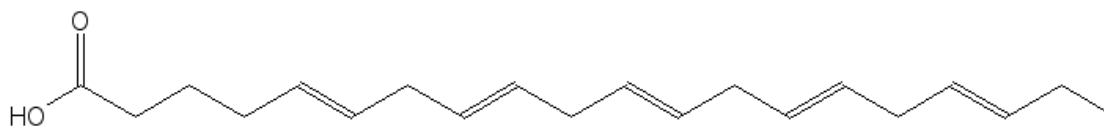
Linoleic acid – cis-9,12-Octadecadienoic acid – $C_{18}H_{32}O_2$ – C18:2n6



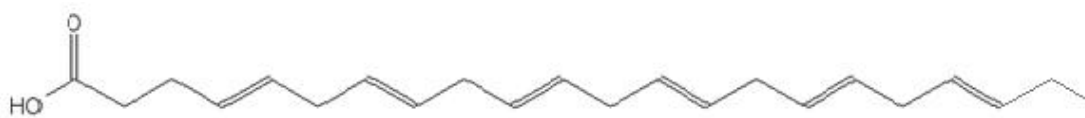
Alpha-linolenic acid (ALA) – cis-9,12,15-Octadecatrienoic acid – $C_{18}H_{30}O_2$ – C18:3n3



Arachidonic acid (AA) – cis-5,8,11,14-Eicosatetraenoic acid – $C_{20}H_{32}O_2$ – C20:4n-6



Eicosapentanoic acid (EPA) – cis-5,8,11,14,17-Eicosapentanoic acid – $C_{20}H_{30}O_2$ – C20:5n-3



Docosahexaenoic acid (DHA) – cis-4,7,10,13,16,19-Docosahexaenoic acid – $C_{22}H_{32}O_2$ – C22:6n-3

Figure9: PUFAs

8.4.1.1 Essential fatty acids

N-3 and n-6 FAs belong to PUFAs. PUFAs contain two or more double bonds. The classification whether n-3 or n-6 depends, as explained above, on the location of the last double bond relative to the terminal methyl end of the molecule. The human organism is not able to synthesize the two fatty acids linoleic acid and ALA. Therefore these so called essential FAs must be obtained from the diet. Any other n-3 or n-6 FA can be derived from those two essential FAs. [LÖFFLER 2004]

PUFAs are essential parts of all cell membranes due to their influence on membrane fluidity and their functions as membrane-bound enzymes and receptors. PUFAs are regulators of a broad range of functions in the body, including blood pressure, blood clotting, and optimal brain and nervous system development and function. [WALL et al. 2010]

n-3 and n-6 FAs play an important role in the initiation and regulation of inflammatory mediators and can influence them significantly. [GOLDBERG and KATZ 2007]

These PUFAs are the precursors for the inflammatory mediators termed eicosanoids (prostaglandine, prostacycline, thromboxane, leukotriene). [WALL et al. 2010, LÖFFLER 2004]

8.4.1.2 Biosynthesis of eicosanoids

Linoleic acid, supplied from food, is the precursor for AA in the human body and is formed via several intermediates and inserting of double bonds by enzymes (elongase and desaturase). AA itself is the precursor for the prostaglandins of series 2, thromboxane of series 2, leukotriene of series 4, resolvins and the lipoxines. Further biosynthesis leads to docosapentaenoic acid. In human organism the ALA is the precursor for the biosynthesis of EPA, which is the initial substance to synthesize prostaglandins of series 3, thromboxane of series 3, leucotrienes of series 5, resolvins and the lipoxines. DHA is a product of further biosynthesis and the precursor for resolvins and neuroprotectins. [WALL et al. 2010]

The series 2 prostaglandins are defined as pro-inflammatory, the prostaglandins of series 3 as anti-inflammatory, due to their potential of reducing inflammatory mediators such as IL-1 α , COX-2, 5-lipoxygenase and its activator FLAP (five lipoxygenase activating protein), as well as catabolic factors (metalloproteinase MMP or ADAMTS). [AUSMAN 2006, AMEYE 2006]

8.4.1.3 Requirements

The recommended dietary intake for adults for linoleic acid is 100 mg/kg normal weight/day on average. That means approximately 6.5 g linoleic acid/day or 2.5 % of the daily needed energy.

For ALA a daily intake of approximately 1 g, 0.5 % of daily needed energy respectively is recommended. Accordingly the n-6 to n-3 ratio is preferably 5:1. [ELMADFA and LEITZMANN 2004, DGE 2012]

Due to the numerous positive effects of n-3 fatty acids EPA and DHA a therapeutic intervention with high amounts of purified n-3 FA could be possible. Regularly consumption of fish (1-2 times a week) could have a preventive effect. [ELMADFA and LEITZMANN 2004, DGE 2012]

Dietary sources of n-3 FA

EPA and DHA are mainly present in fish oil from fatty fish such as menhaden, herring, sardine, sprat, and in liver oil from fish and wale. In plant oils like linseed oil, soybean oil, flax oil, as well as in nuts and dark green leafy vegetables high amounts of ALA are found. [ÖGE 2012, EBERMANN and ELMADFA 2008]

Dietary sources of n-6 FA

Oils obtained from sunflower, thistle, pumpkin seed, corn germ and grape seed are rich in linoleic acid. Animal source food such as meat, butter, milk and milk products and egg yolk contain high amounts of AA. [ÖGE 2012]

8.4.1.4 PUFAs and health effects

Since years PUFAs are of special interest regarding cardiovascular diseases, cancer, mental health and degenerative disorders. In the following the most important and most discussed diseases will be explained.

8.4.1.4.1 Cardiovascular diseases

In a review by Delgado-Lista et al. the effects of marine omega-3 PUFAs on subjects with high cardiovascular risk have been evaluated. A reduction of cardiovascular events of 10 %, cardiac death of 9 % and coronary events of 18 % is possible when administered marine n-3 PUFAs as food or in supplements for at least 6 month. There is also a trend for lower total mortality compared to control groups. The included studies are highly heterogenic regarding dosages, and therefore not easy to compare. [DELGADO-LISTA et al. 2012]

The German Nutrition Society summarized the results of more than 100 studies of different evidence classes including RCTs, intervention, cohort and case control studies. According to the resulting fat-guidelines the efficacy of ALA in the primary and secondary prevention of coronary heart diseases is possible. Primary prevention of cardiovascular diseases through higher intake of PUFAs is also possible. There is high evidence for lower mortality in case of increased intake of fish, fish oil and n-3 FAs. Secondary prevention of coronary heart diseases by PUFA supplementation is of insufficient evidence. [DGE 2006]

8.4.1.4.2 Cancer

The latest review of epidemiological studies of Gerber in 2012 evaluated that α -linolenic acid is neither a risk nor a protecting factor of different types of cancers. There is limited evidence for a possible role of n-3 PUFAs in cancer prevention concerning colorectal, prostate and breast cancers due to insufficient homogeneity of the different studies [GERBER 2012]. Results of the latest RCT by Murphy et al. reported a positive role of n-3 PUFAs as adjuvant in lung cancer patients. Fish oil supplementation

may increase chemotherapy efficacy without affecting treatment toxicity (e.g. nausea, vomiting). [MURPHY et al. 2011]

The German Nutrition Society reviewed more than 90 studies with different study designs (cohort, case control and intervention studies) could not find any relation between PUFA intake and cancer risk. An increased intake of long chain n-3 FAs (EPA and DHA) can possibly lower the risk of colon cancer. [DGE 2006]

8.4.1.4.3 Metabolic syndrome

A recent review by Lopez-Huertas showed that the supplementation with n-3 PUFAs of >1 g/day for at least 3 months leads to a significant reduction (7 – 25 %) of triglycerides confirming a hypotriglyceridemic effect of n-3 PUFAs. [LOPEZ-HUERTAS 2012] In the fat-guidelines of the German Nutrition Society the hypotriglyceridemic effect of n-3 PUFAS is also reported (25 % in healthy people and 34 % in hyperglyceridemic patients). [DGE 2006] The potential of n-3 FAs to reduce triglyceride concentration is related to their effects on reducing hepatic production and secretion of VLDL, their positive effects on plasma lipolytic activity and the stimulation of β -oxidation of FAs in the liver. [JACOBSEN 2008] Lopez-Huertas associates, that this hypotriglyceridemic effect may lead to reduced small dense low density lipoprotein (LDL) particles and therefore maybe to lower inflammation processes in metabolic syndrome patients. However, no clear effects were found on other metabolic syndrome markers such as high blood pressure, increased risk for coronary heart diseases, insulin resistance and glucose intolerance and typ-2 diabetes as a consequence. [LOPEZ-HUERTAS 2012]

8.4.1.4.4 Osteoporosis

Orchard et al. reviewed the impact of n-3 FAs on osteoporosis. Three included RCTs of the past 10 years showed significantly positive effects of a n-3 FA mixture combined with calcium, n-3 FA fortified dairy products and a high ALA diet on bone related osteoporosis marker [GRIEL et al. 2007, MARTIN-BAUTISTA et al. 2010, DAWCZYNSKI et al. 2009]. Whereas four of the included RCTs found no significant effects regarding n-3 FA intervention. [SALARI et al. 2010, CORNISH and CHILIBECK 2009, DODIN et al. 2005, APPLETON 2011] Due to the small number of

RCTs and the heterogeneity of the published studies, recommendations for n-3 FA supplementation for skeletal health are not needed at the moment. [ORCHARD 2012]

8.4.1.4.5 Fish Oil and Perna Canaliculus (green-lipped mussel)

Fish and fish oil is rich in PUFAs. As shown previously PUFAs are precursors for inflammatory mediators and therefore are crucially involved in the process of inflammatory diseases. [WALL et al. 2010]

In the 1990s the influence of Perna Canaliculus on arthritic diseases was of increased interest, since Maoris with a high and frequent consumption of green-lipped mussels had a significantly reduced risk for arthritic diseases. Therefore, a stabilized powder of green-lipped mussel was produced and marketed.

Green-lipped mussel extracts contain concentrated n-3 FA such as EPA and DHA. [BRIEN 2008] As explained above n-3 FAs show anti-inflammatory activity by inhibiting membrane AA metabolism, and at the same time synthesizes of pro-inflammatory prostaglandins (PGE₂) from AA is reduced.

[BRIEN 2008, WANN 2010, EFTHIMIOU and KUKAR 2010]

A review by Henrotin et al. reported effects of n-3 FAs on OA. Only two clinical studies of low [CHO et al. 2003] to moderate [STAMMERS et al. 1992] quality could be found, therefore a definitive conclusion is not possible. A treatment with the New-Zealand green-lipped mussel extract (200 mg/d over a period of 8 weeks) improved symptoms including pain and joint function. [CHO et al. 2003] A treatment with cod liver oil (10 ml/day for 24 weeks) as an adjunct to NSAIDs did not show any effects on pain and joint function. [STAMMERS et al. 1992]

The results of the meta-analysis of Goldberg and Katz (17 studies with 823 patients included), where n-3 PUFA supplementation in patients with rheumatoid arthritis or joint pain has been reviewed, suggest that EPA/DHA supplementation for 3 – 4 month reduces joint pain intensity, morning stiffness, number of painful and/or tender joints, and NSAID consumption. The author's conclusion is that n-3 PUFA supplementation is an attractive adjunctive treatment for joint pain, but further studies in humans are required. [GOLDBERG and KATZ 2007]

In their RCT Dawczynski et al. examined the influences of n-3 PUFAs and gamma-linolenic (GLA) acid on disease activity in patients with rheumatoid arthritis. 60 participating patients in four test groups received PUFAs (3g/d), GLA (3.2g/d), a combination of both (1.6g PUFAs/d and 1.8g GLA/d) or olive oil (3g/day) over a period of 12 month. Intake of n-3 PUFAs or GLA led to an increased incorporation of EPA and DHA in plasma lipids and cell suggesting a possible positive effect in the treatment of chronic inflammatory diseases such as rheumatoid arthritis. [DAWCZYNSKI ET AL. 2011] Adam et al. reported in their RCT a positive effect of a diet low in AA (< 90 mg/d) and the intake of fish oil capsules (30 mg/kg body weight). Significant improvement in tender and swollen joints, as well as enrichment of EFA in erythrocyte lipids and lower formation of prostaglandin metabolites has been results of the 8 month trial including 68 patients with rheumatoid arthritis. [ADAM et al. 2003] Galarraga et al. demonstrated in their RCT of 9 moth duration that oral supplements of 10 g cod liver/day (containing 2.2 g EPA and DHA) reduces the daily intake of NSAIDs in 39 % of the patients with rheumatoid arthritis without any negative effects on their disease activity. [GALARRAGA et al. 2008] Berbert et al. figured out, that a daily treatment with 3 g fish oil n-3 FAs in combination with olive oil significantly improves joint pain, hand grip strength and morning stiffness in patients with rheumatoid arthritis. Although the trial was of parallel randomized design there were only 34 patients involved. Therefore results should be taken with care. [BERBERT et al. 2005]

9 Critical Review - Protocol

The review protocol follows the principle of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.

[LIBERATI 2009, MOHER 2009]

JOURNAL

The Journal of Nutrition

TITLE

The Role of Omega-3 Fatty Acids in Shoulder Joint Disorders – A Critical Review

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INTRODUCTION

The introduction will give an overview of n-3 PUFAs and their role in health and disease. Since patients with inflammatory joint diseases may benefit from n-3 FAs, special focus will be placed on shoulder joint disorders. Background information will be obtained from other chapters of the diploma thesis.

AIM

The main objective of the critical review will be an overview of the current knowledge of n-3 PUFAs in shoulder disorders including OA and RC pathologies. A specific aim of the review will be an investigation regarding the potential effects of n-3 PUFAs supplementation on the treatment or as a treatment adjuvant of shoulder pathologies.

METHODS

Scientific relevant studies will be identified using systematic searches of electronic databases of Medline (PubMed), ExcerptaMedica Database (Embase), and Cochrane Registry of Controlled Trials (CENTRAL) and manual searches from January 1990 to

May 2012. The manual search will include abstracts presented at meetings, ongoing clinical trials (www.clinicaltrials.gov), reference lists, and reviews on the topic to identify eligible trials. The search strategy will involve combining specific terms related to n-3 PUFAs AND specific shoulder joint disorders including terms relating to OA OR RC pathologies. Medical Subject Headings (MeSH) will be used wherever possible.

STUDY SELECTION

The search will be performed according to the following predefined criteria: (1) only scientific publications with FAs related terms linked to either OA or RC pathologies; (2) only studies on human adults; (3) all study designs; and (4) only publications in English or German will be considered. All studies not meeting inclusion criteria will be excluded from the review.

STUDY CHARACTERISTICS

The following study characteristics will be extracted: (a) publication details (e.g. first author); (b) quality criteria of study design (e.g. level of evidence); (c) study participants details (e.g. age, gender); (d) shoulder pathology details; (e) primary outcome variable(s) (e.g. n-3 PUFA supplement and risk of RC retears); (f) secondary outcome variable(s): e.g. inflammation related parameters; (g) reported confounding factors (e.g. co morbidities, funding sources)

Two independent reviewers (MTH and BL) will perform all aspects of the search strategy including article search, examination of the abstracts for relevance, assessment of inclusion criteria and review the full text articles in detail as indicated. All collected data will be recorded and compared; disagreement will be resolved via mutual consensus, and thereafter summarized. The review protocol will not be registered; however it will follow the principle of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement. [LIBERATI 2009, MOHER 2009]

RESULTS

Bibliographic search results: The role of n-3 FA in shoulder joint disorders

Bibliographic search results: The role of n-3 FA in OA

Bibliographic search results: The role of n-3 FA in RC disorders and tendon related disorders

DISCUSSION

The main findings including the strength of evidence for each main outcome will be summarized. A general interpretation of the results in the context of other evidence will be provided. Limitations of the critical review and outcome level will be discussed. The conclusion will include the main outcome result and implications for future research will be given.

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10 Conclusion

The main objective of the present diploma thesis was to evaluate and critically examine associations between selected nutritional compounds and their impact on joint disorders. Osteoarthritis (OA) and ways of alternative intervention are well discussed in the scientific literature. Especially glucosamine and chondroitin as natural occurring parts of the cartilage are of high interest concerning cartilage repair further reduction of pain and related medication. Literature research allows no definitive recommendation neither for glucosamine nor chondroitin. Collagen seems to influence cartilage but also here no recommendation is possible. Studies concerning the influence of vitamins and antioxidants on joint disorders are of low quality and therefore results should be taken with care. To better define their influence on inflammatory processes in human organism, further research is recommended. The role of vitamin D in bone metabolism and therefore in osteoporosis is already known, but is also discussed against cartilage disorder like OA, and interesting for rheumatoid arthritis (RC) disorders. Further research is necessary to investigate whether a low serum vitamin D concentration correlates with cartilage disorders and if supplementation with vitamin D is of interest in treating OA and RC disorders.

The antioxidant and anti-inflammatory effect of rosehip powder is also discussed in several short term studies of different quality, which might be also of interest for cartilage related joint disorders. But long term studies of high quality are necessary to clarify relevant effects of rosehip powder on OA and RC disorders.

Avocado-soybean unsaponifiables (ASU) are under discussion in treating cartilage related joint disorders since ASU stimulates the synthesis of aggrecan and extracellular matrix components such as collagen (collagen is a natural component of tendons, joints, ligaments and muscles) due to their positive effects on chondrocytes. Further, ASU show anti-inflammatory potential. Therefore ASU are discussed to prevent cartilage degradation and support the repair of damaged cartilage. However, literature shows no positive effect of ASU on joint disorders, but further studies could be of interest to test the anti-inflammatory effect of ASU on joint disorders.

n-3 FAs and their health potential in general are well discussed in literature. Research showed that n-3 FAs are involved in several diseases with inflammatory background. Therefore, n-3 FA should be of high interest in the prevention and treatment of OA and RC disorders. Due to the fact that shoulder disorders are a common orthopedic problem,

nutritional intervention associated with weight loss could be of interest in this kind of disease as well.

Therefore, a critical review focusing on potential effects of n-3 PUFAs in shoulder disorders especially in OA and RC pathologies will be a next step. A protocol for a critical review investigating the potential effects of n-3 PUFAs supplementation on the treatment or as a treatment adjuvant of shoulder pathologies was established and is part of this diploma thesis.

In general, the daily diet should be considered in the treatment of OA and RC. NSAIDs and corticosteroids are the common way in treating joint diseases but additional supplementation or a diet high in nutrients can lead to a reduced medication and therefore higher quality of life. But further research is necessary to determine positive effects of the discussed nutritional components.

11 Summary

Joint disorders are frequent problems involving cartilage as well as muscles, tendons, and ligaments, rather than bones; and often cause significant pain and dysfunction. Non-operative medical treatment is aimed to reduce pain and inflammation and include pharmacological approaches such as corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs). Due to negative side effects of such a medication, permanent treatment is not recommendable. Non-pharmacological approaches such as lifestyle changes including a healthy diet may be an alternative and additional way to reduce symptoms and slow down progression of joint diseases.

The main objective of this diploma thesis was to investigate whether there are positive effects of selected nutrients on joint disorders or not.

Joint disorders with a possible link to dietary compounds are explained. A literature research focusing the nutritional components glucosamine, chondroitin, collagen, vitamins and antioxidants, avocado and soybean unsaponifiables, rosehip powder and n-3 fatty acids and their effects on joints disorders has been conducted using the data bases PubMed and SCOPUS. Several reviews, on low and high quality studies, showed that recommendations or conclusions are neither possible for glucosamine nor for chondroitin. Collagen seems to influence cartilage but also here data are not convincing. Also further studies are needed to clarify if low serum vitamin D correlates with cartilage disorders and if supplementation with vitamin D might be of interest in treating OA and RC disorders. Literature research showed also no significant protection of joint disorders by ASU. Rosehip powder is also under discussion, but possible anti-inflammatory effects need confirmation. Published data showed that n-3 FAs are involved in several diseases with inflammatory background. Therefore, n-3 FA are of high interest in the treatment of OA and RC disorders since they show anti-inflammatory activity by inhibiting membrane AA metabolism, and at the same time synthesizes of pro-inflammatory prostaglandins from AA is reduced.. In general, diet is an important factor in treating OA and RC. NSAIDs and corticosteroids are the common way in treating joint diseases but an additional dietary support with specific nutrients could lead to reduced medication and increased quality of life, due to fewer side effects caused by NSAID and corticosteroid intake over a long treating period.

12 Zusammenfassung

Gelenkserkrankungen sind häufig auftretende gesundheitliche Probleme welche sowohl Knorpel als auch Muskeln, Sehnen und Bänder, weniger jedoch die Knochen betreffen und oft starke Schmerzen und Bewegungseinschränkungen hervorrufen. Medikamente wie nichtsteroidale Antirheumatika und Corticosteroide werden zur Linderung der Schmerzen und zur Entzündungshemmung eingesetzt. Aufgrund der Nebenwirkungen dieser Medikamente ist eine Langzeittherapie nicht empfehlenswert. Nichtpharmazeutische Behandlungsmöglichkeiten wie eine Lebensstiländerung, (inklusive eine gesunde Ernährung) könnte eine Alternative zur Reduktion der Symptome und einer Verlangsamung des Krankheitsverlaufs von Gelenkserkrankungen sein.

Ziel der vorliegenden Arbeit war herauszufinden, ob ein Zusammenhang zwischen ausgewählten Nahrungskomponenten und Gelenkserkrankungen besteht.

Im ersten Teil der Arbeit wurden Gelenkserkrankungen die möglicherweise mit der Ernährung beeinflusst werden könnten erläutert. Eine Literatursuche mittels SCOPUS und PubMed spezialisiert auf die Nahrungsbestandteile Glucosamin, Chondroitin, Kollagen, Vitamine und Antioxidantien, die unverseifbaren Bestandteile aus Avocado- und Sojabohnen Öl, Hagebutten und Omega-3 Fettsäuren und deren Effekte auf Gelenkserkrankungen wurde durchgeführt. Die dabei gefundenen Reviews, welche Studien von sehr unterschiedlicher wissenschaftlicher Qualität enthalten, erlauben folgende Aussagen. Weder für Glucosamin noch für Chondroitin sind definitive Empfehlungen zur Supplementierung möglich.

Kollagen scheint die Knorpelzusammensetzung zu beeinflussen, eine Empfehlung ist aber auch hier nicht zu geben. Weiter Studien sind auch in Bezug auf Vitamin D nötig um herauszufinden, ob niedriges Serum Vitamin D mit Knorpelschäden in Zusammenhang steht und ob Vitamin D deshalb in der Behandlung von Osteoarthritis und Rotatorenmanschetten-Rupturen eingesetzt werden könnte. Auch für den Einsatz von unverseifbaren Bestandteile aus Avocado- und Sojabohnen Öl (ASU) ergab die Literatursuche keinen definitiven Beweis. Das Pulver aus Hagebutten wurde in den letzten Jahren sehr häufig untersucht. Aber auch das entzündungshemmende Potential der Hagebutte muss noch weiter erforscht werden.

Die Literatursuche ergab, dass n-3 Fettsäuren an einigen Erkrankungen mit Entzündungshintergrund beteiligt sind. Deshalb sollten n-3 Fettsäuren auch in der

Behandlung von Osteoarthritis und Rotatorenmanschetten-Rupturen vermehrt in Betracht gezogen werden.

Zusammengefasst könnte die Ernährung eine alternative zusätzliche Behandlungsmöglichkeit im Falle von Osteoarthritis und Rotatorenmanschetten-Rupturen sein. Um die Einnahme von nichtsteroidalen Antirheumatika und Corticosteroiden zu verringern könnte eine Supplementierung mit zuvor genannten Nahrungsbestandteilen in Erwägung gezogen werden, bzw. zusätzlich zur medikamentösen Therapie eingesetzt werden. Eine verringerte Einnahme dieser Medikamente würde in weiterer Folge zu einer höheren Lebensqualität führen, da die Nebenwirkungen durch die Langzeiteinnahme reduziert werden könnten.

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