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Low grade chronic inflammation and anti-inflammatory diet: effect on Rheumatoid arthritis

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Index

Abstract

Rheumatoid arthritis is related with chronic inflammation and among the autoimmune rheumatic disease with an incidence about 1% of overall population that affect primarily the joints and the bones, it's a progressive disease that can lead to disability if not treated. To discover the disease there are a combination of clinical analysis and an interview that allows to asses the presence of the disease from the early stages till the sever condition. The assessment of the severity is based on a score parameter that is the combination of the clinical and interview analysis, the score is based on the 2010 American College of Rheumatology and European League Against Rheumatism and only with the use of this "degree" system is possible to identify the stage of the disease.

Since rheumatic disease interest is increased in the last years new scientific evidences have increased the ability of the early diagnosis thanks to some specific parameters like rheumatoid factors, c-reactive protein, citrullination of proteins and fibroblast-like synoviocytes that are specific cells found in subject with RA. Genetic plays a crucial role for the susceptibility of a subject to the disease but environmental factors play another important role in its development. The immune system has a big role in the disease development over time since inflammation is modulated by immune system and at the same time the immune system keeps the inflammatory modulation active, the understanding the correlation between the two is important to understand in which way is possible to act and how the joint damage happens.

This work wants to put interest in the RA disease and in the anti-inflammatory diet that can be used to improve the general health of a person. It will be discussed what is the meaning of an anti-inflammatory diet, what are the main characteristics of this diet pattern and in which way the diet can influence Rheumatoid arthritis with a focus on the principal component that can be found in food. The modulation of the inflammatory process can be influenced by the bioactive components in the food and what are the most effective one, where they can be found and if adequate dietary pattern can be considered as therapy for the disease.

1 INFLAMMATORY PROCESS CHARACTERISTICS

The inflammatory process is defined as the response of the body's immune system to a stimulus that can be harmful for the body.

The inflammatory process is characterized by the presence of five macroscopic physiological phenomena, these are: *tumor*- swelling of the tissue, *calor*- increased tissue temperature, *rubor*- redness in the inflammation site, *dolor*- intense sensation in the inflammation site, *function laesa*- impaired function in the area of inflammation [1]. This process is fundamental for the body to keep the homeostasis but often is considered as a bad reaction because it can be kept active for too long or the response is too strong, and the body is unable to stop the process that cause damage to the body itself.

Even if inflammation can be seen under a positive light thanks to its first effect on the defence of the body through lysis of external microorganisms, unknown substances and the modulation of the immune system through inflammatory mediators such as cytokines, chemokines, cell adhesion molecules to increase the efficiency of the process; the second true defence mechanism is the anti-inflammatory mechanism [1] that takes action on these common mediators. Only through anti-inflammatory signalling process the inflammation can be keep under control and the resolution can take place with the return to a normal condition of the body, the homeostasis. The signalling pathway is the critical zone where more interest takes place because the gene expression for pro-inflammatory molecules has a negative effect on the anti-inflammatory expression, only a very strict control and balanced expression of pro- and anti-inflammatory molecules can guarantee a stop to the process.

Inflammation is not a unique reaction, it can be divided into two specific categories: acute inflammation and chronic inflammation. These two categories have common mediators, but chronic inflammation or low-grade chronic inflammation, as it's called more frequently, is associated with non-communicable diseases such as Rheumatoid arthritis, cancer, autoimmune disorders, obesity, inflammatory bowel disease and others.

1.1 Acute inflammation characterization

The acute inflammation is the first process that the body use as a defence, during this process the immune system has an important role in the inflamed site, neutrophil, leukocytes, macrophages are some of the most important cell for the "killing machine" system used as

defence against external substances and for the production of the intermediates that have a central role in the modulation of the inflammatory system.

In the acute phase takes place a massive production of pro-inflammatory mediators that positively affect the immune system intervention in the site of inflammation, chemicals mediators such as TNF-α, IL-1, IL-6, IL-8, IL-11, IL-16 are produced to guide the immune cells to the site of infection, increased vascularity of the tissue.

The CRP (C-reactive protein) and ESR (erythrocyte sedimentation rate) are the markers used to identify an acute phase inflammation. The CRP is preferred thanks to its rapid increase in the blood, the half-life is 19 hours, and it's produced by the liver in response to pro-inflammatory cytokines in particular to IL-6 while ESR increased its levels as response to fibrinogen production [2]. As clinical markers CRP nowadays is preferred to ESR even if new markers of acute phase inflammation are searched.

1.2 Chronic-inflammation process

The term "chronic inflammation" often is used to describe the "low grade chronic inflammation" process, this process is often a consequence of the acute inflammation but can be present even before the acute process or can be completely unrelated to the acute inflammation, in the last case is caused by the so called autoimmune chronic inflammatory diseases. Some common mediators with acute inflammation are produced like TNF-α, IL-1, IL-6 and even the CRP, the CRP is used as marker of chronic inflammation [3] where the levels in the serum are increased but lower compared to the level on the acute phase [4].

The chronic inflammation is the centre of attention of numerous studies because if strictly related with a malfunctioning of the inflammatory mediators with an uncontrolled modulation of the immune system [5] that has severe consequence on the whole body and is proved as one of the causes of the non-communicable diseases such as autoimmune diseases, cancer, Rheumatoid arthritis and type 2 diabetes mellitus [4].

2 RHEUMATOID ARTHRITIS

Rheumatoid arthritis is one of the most common and severe autoimmune rheumatic diseases affecting primarily the joints and secondarily extra-articular organs [6]. Genetic has a predominant role in the development of the disease, about 50%, with other factors like inflammatory state, metabolic diseases such as diabetes, obesity, dysbiosis, cigarette smoke, sex and age [6, 7, 8, 9]; even if the etiology of the disease is not yet fully clear the immune cells and their mediators have a crucial role in the joint destruction and systemic complication. Rheumatoid arthritis can be defined as an immune-complex disease since an autoantibody called rheumatoid factor (RF) has been identified in 70-80% of RA patients [7], the RF is able to link with IgG and deposit on various tissues in particular the joints or the synovium where it promotes inflammation and as consequence cause tissue damage [7].

Rheumatoid arthritis is one of the major autoimmune diseases with an estimated incidence rate of 5-50 in 100,000 person per year [5], the normal condition of the synovium is altered in persons affected by RA. The synovium is a specialized connective tissue that lines the inner surface of capsules of synovial joints and the tendon sheath, in RA synovium is thicker and the joints becomes swollen and puffy [5] the continuous inflammation causes a progressive destruction of the cartilage and the bone within the joint.

2.1 Clinical identification of arthritis

The diagnosis of rheumatoid arthritis is based on the 2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) in which classification criteria for RA evaluates a set of variables ie risk factors, number and type of joints involved, duration of the symptoms, based on the score ≥6 it's possible to identify a RA patient [6]. The typical identification is polyarticular with pain, stiffness and swelling of multiple joints, usually symmetrical and the first joints affected are the hands in particular the wrists and metacarpophalangeal, metatarsophalangeal and proximal interphalangeal joints [10]: swelling, bogginess tenderness and warmth with atrophy of the muscle near the joints is always present.

There is not a single test to identify arthritis, but the laboratory test includes a complete blood analysis to identify rheumatoid factor, erythrocyte sedimentation rate or C-reactive protein. Even for experts the macro-identification of this disease is difficult since it can affect

simultaneously not only the hands/wrists but also other joints, the help of the patients is fundamental to evaluate the characteristics of the ACR-EULAR classification; possible stiffness of the joints are more visible in the morning, and it can last for more than an hour [10] till all day long in severe cases. An extra identification of the disease is made thank to X-rays of the bones, in particular of the hands that are usually the first attacked by the disease.

The identification of the disease is not easy, and more markers are searched to be able to identify RA in the early stage. As shown anti CCP, anti-cyclic citrullinated peptide antibodies, could be a better indicator for rheumatoid arthritis compared to RF [11] but more evidence are needed to establish which one is a better predictor. The importance of the early diagnosis is fundamental to slow down the progressive joint damage and for the prevention of irreversible disability [10] that is the final stage of the disease.

2.1.1 Nephelometric tests

This test is used to measure the amount of RF in blood, the test is easy thanks to its automation; the principle of the methodology relies on the use of a polystyrene particles coated with an immune-complex, consisting of human γ-globulin/anti-human γ-globulins from sheep [7], the agglutination reaction is measured by a nephelometer.

The nephelometer is based on the light that goes through the sample, more agglutination means more light is scattered, by the small particles, rather than being absorbed, the amount of scattered light is measured collecting the light at an angle.

2.1.2 Citrullination

Citrullination, called peptidyl-arginine deamination, is the irreversible process of conversion of protein-contained arginine to citrulline [12]; by which the amino group of the guanidine of arginine is hydrolysed leading to the substitution of the amino group with an oxygen atom. The process is catalysed by a specific enzyme called peptidyl-arginine deaminase (PAD) that in a calcium rich environment is activated [13], another important aspect for the PAD regulation is the reducing environment that is needed to keep it active [13]. Thanks to this discovery a biochemical ELISA test is used to detect anti-citrullinated antibodies (ACPAs) in patients affected by RA.

Numerous clinical tests showed that the presence of the anti-citrullinated protein antibodies (ACPA) predicts a more aggressive disease course [6].

2.1.3 Fibroblast-like synoviocytes (FLS) in RA

These cells are abundant in the synovial fluid of patients affected by RA, these cells are strictly related to the sCD14, a soluble form of CD14, that are responsible for the expression of pro-inflammatory cytokine, chemokines, and mediators in RA-FLS via TLR-4 (toll-like receptor 4) and promote the proliferation of these cells [14]. Even if the pathway is not fully clear numerous studies focused on the action of sCD14 in RA founding an important relationship between CD14 and RA-FLS, the sCD14 are responsible for the production of chemokines, cytokines and mediators by RA-FLS and this suggest that sCD14 could be responsible for the infiltration of immune cells in synovial fluid, stimulation of pro-inflammatory molecules, neoangiogenesis, osteoclastogenesis and matrix destruction [6, 14]. TNF-α and IL-17 have shown a significant importance thanks to their capacity of stimulating the production of IL-6 [6, 14, 15] and increase the expression of TLR-4 in RA-FLS, both cytokines TNF-α and IL-17 are able to augment the expression of the TLR receptors by the sCD14 stimulation in RA-FLS [14]. IL-6 production, that plays a key role in the development of RA, is increased in RA-FLS by sCD14; higher levels of sCD14 can be found in patients with RA even if this value is not influenced by genetic factors but by specific non-genetic factors such as age, race, body composition, and inflammatory disease burden.

This complex interaction of inflammatory molecules can be used as a base for possible new form of treatment through TNF-α antagonist [10], with consecutive decrease of sCD14 effects, or through the TLR-4/RA-FLS expression in RA. An example of the progression of inflammation in joints of RA mice is summarized in *Figure* 1

2.2 Mediators modulation effect on RA

As saw before the autoimmune disease rheumatoid arthritis is related to inflammation, the antigen presenting cell are unable to recognize the citrullinated proteins (vimentin, type II collagen, fibrin, histones, fibronectin) as self-structure due to the susceptibility genes HLA-DR1 and HLA-DR4 [6] and the specific anti-citrullinated protein antibodies (ACPAs) are directed against the citrullinated antigens, important are the citrullinated protein of fibrinogen that stimulate the TNF-α production in macrophage via TLR-4 receptor [16]. This reaction cause an increase in the mediators of RA inflammatory process with the uncontrolled prolonged stimulators of inflammation thanks to cytokines such as: IL-1, IL-6, TNF-α, the last two in the

last years are the one of interest to understand better how the RA works and which can be new therapeutic solution to reduce the disease severity.

Prostacyclin (referred as PG) and TXA_2 are lipidic molecules produced by cyclooxygenase (COX) from the arachidonic acid cycle as some of the final products [17, 18], these molecules have roles both in physiological immune response associated with inflammation and tissue damage especially in RA. PGD_2, PGE_2, PGI_2, PGJ_2, are produced by cell on demand and the receptors for these molecules are called P receptors [19], even if PGI_2 has shown an anti-inflammatory action with a protective action on cardiovascular diseases [17], it has shown an opposite effect in RA since PGI_2 is the most abundant PG present in synovial fluid in the joints of people affected by RA, experiments in mice IP receptor deficient has shown how PGI signal is crucial to the inflammatory response in arthritis with a reduction in the clinical and histological arthritic score compare to control mice [17, 19], these suggest that PGI-IP pathway has a significant role in the development of inflammatory reaction in RA.

PGE_2 and its receptor called EP, EP4 particularly important in RA, has an important role in the modulation of interleukins on the one that regulate differentiation and function of T helper type 1 cells and promote inflammation [19], data showed that PGE_2 is involved in articular cartilage erosion [18]. Some studies demonstrated how the regulation of the PGE_2/EP4 system can be used to reduce inflammatory state and through this modulation it can be used to improve symptoms in patients with RA.

TXA_2/TP system is a mediator produced by platelets in tissue damage or inflammation [19], this molecules are rich in synovial fluid of RA patients and they have a function on the rheumatoid arthritis fibroblast-like synovial cells proliferation and activity [19]. These cells have both characteristics of “passive responders” and “aggressors”, they are an indicator of a proinflammatory milieu and at the same time promoters of inflammation through synthesis of cytokines, chemokines and adhesion molecules [14].

The LTs are a family products formed by the pathway of arachidonic acid metabolism and include different types of LT (LTA_4; LTB_4; LTC_4; LTD_4; LTE_4) and the effect of LTs are mediated via the surface receptor for LTB_4 (BLT1 and BLT2) [19, 20]. The principal effect of LTB_4 is to enhance the movement of the immune and inflammatory cells in the site of tissue damage [20]. LBT are produced by neutrophils has shown the ability to induce arthritis [19] however there are

not many studies about it and this leaves a window of opportunity to find a better connection between the LTs and RA. Two studies were done to focus on the possible use of inhibitory molecules but there was not significant evidence since the clinical studies on different duration of treatment in different patient have never been made.

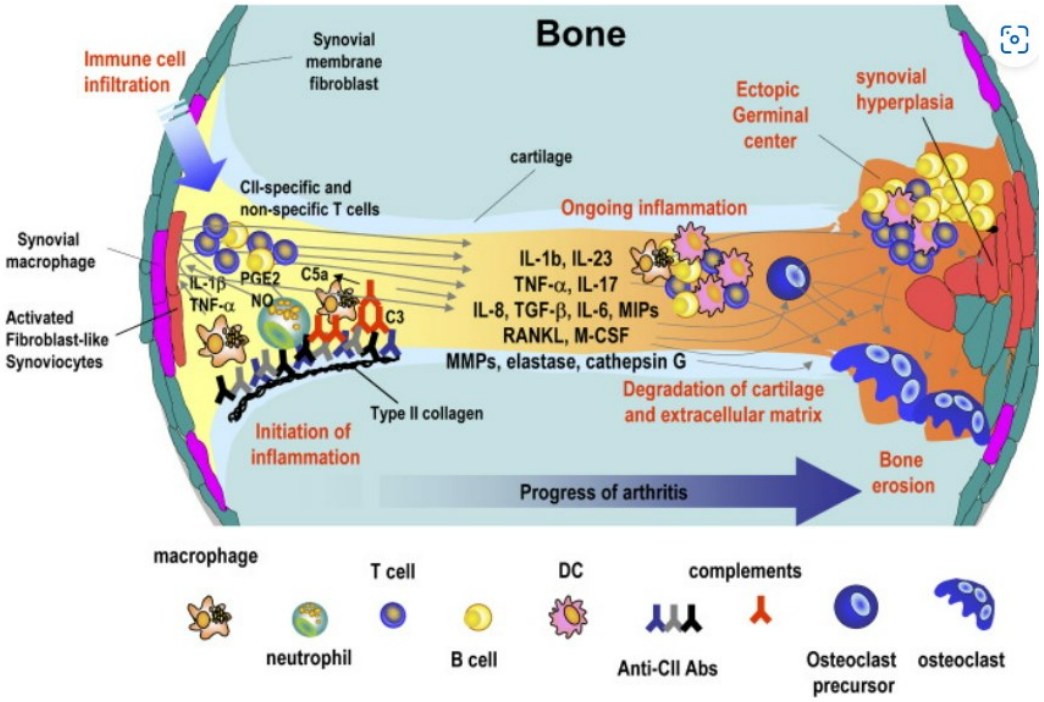

*Figure 1 I*nflammatory process progression in Rheumatoid arthritis *(Young-Gyu Cho, Mi-La Cho, So-Youn Min, Ho-Youn Kim)*

3 ANTI-INFLAMMATORY DIET

The term anti-inflammatory diet means the specific dietary pattern that thanks to the natural compounds present in food is able to intervene by down-regulating the inflammatory state through modulation of its messengers such as interleukins, cytokines or to the compounds that, once inside the human body, have the ability to reduce ROS and modulate cortisol and insulin.

With this broad definition is not really clear what kind of diet can be identify as anti-inflammatory, as today the diet should be made to maximise the intake of food rich in natural active compounds like flavonoids, vitamins, fibres and catechins while others such as caffein, simple sugar/refined carbohydrates, dairy products, high quantity of red meat should be limited or, if possible, avoided. As today the anti-inflammatory diet main characteristics is the fusion of the Mediterranean diet and the Okinawan diet [21, 22], both of them have in common high intake of fruit and vegetables, moderate quantity of carbohydrates, not refined but whole one, low quantity of red meat and dairy products; the difference is the overall intake of fat that is lower in the Okinawan diet [21]. The most important element of both diets is the encouragement to consumption of a balanced calory intake with a well distributed macronutrients consumption throughout the whole life of a person.

3.1 Fruit and vegetables

Fruit and vegetables should be the base for the anti-inflammatory diet, up to two third of the total volume of food of the diet, many studies have shown the efficiency of vegetables and fruit in the reduction of inflammatory markers in the blood [21] thanks to the rich presence of polyphenols, but fruit should be limited in the consumption compared to vegetables due the rich presence of simple sugars. The positive effect can be attributed to the phytochemical compounds known as polyphenols that has shown a positive effect in the reduction of inflammation through modulation of NF-kB an important transcription factor responsible of activating inflammatory pathways [21, 23] and for the natural ability to neutralize free radicals. Genistein, a flavonoid compound rich in soybean, has shown anti-inflammatory, anti-angiogenesis, immunomodulatory properties in particular is able to inhibit IL-1B and TNF-α and gene expression in FLS-RA [22, 24, 25] with a positive effect in the reduction of joint damage.

Quercetin mostly found in vegetables, fruits and is generally safe but at high doses greater then 1'000 mg per day can cause stomach pain and headache [23]. Quercetin has been investigated for its anti-inflammatory, antioxidant, neuroprotective and anti-diabetic properties; quercetin as dietary source can be found in apples, citrus fruits, broccoli, red onions, coriander, tea and berries.

B-cryptoxanthin and supplemental zinc have shown a possible protective effect against the development of rheumatoid arthritis thank to their function of oxygen radical scavenger [26] but there are not enough epidemiological studies to prove the protective effect on the disease.

3.2 Dietary fiber

Dietary fiber is a natural compound consisting in a soluble and an insoluble components, present in food that is fermented by gut microbiota with the production of SCFA, in particular the three main are propionate, butyrate and acetate, important for the nourishing, modulator effect for intestinal bacteria [27]. A dysbiosis was found in patient with RA and it is associated with an increase in pro-inflammatory markers level [27]. The higher intake of fiber in the diet were made by the introduction of a single bar high-fiber to not modify the dietary habit and it showed a beneficial effect on arthritis and related bone loss [27], the anti-inflammatory properties have a positive effect in the reduction of pro-inflammatory cytokines including TNF-α and IL-6 [28]. The assay gut microbiota-arthritis can be of interest for the positive effect of the bacteria on inflammation and in the reduction of join-bone destruction.

3.3 Vitamin D

RA disease progression is associated with hypovitaminosis of vitamin D, studies show that the activity of the disease has an inversely association with vitamin D [29] and a vitamin D supplementation in patient with RA showed a positive effect on pain levels and bone preservation [22].

3.4 Fats

Fats are important constituent of the phospholipid membrane and are responsible for the modulation of inflammatory mediators. The modulatory effect is made by omega-3 and omega-6 metabolites called eicosanoids, omega-3 metabolite is the EPA (eicosapentaenoic acid) while the omega-6 metabolite is DHA (docosahexaenoic acid) [30, 31]. DHA has shown a more potent capacity in the inhibition of pro-inflammatory cytokine secretion, IL-1, IL-6, while

EPA showed a more potent inhibitory effect on TNF-α [30]; these mediators are the most important in RA pathogenesis and progression, the inhibition of macrophage cytokine production has an important role in immune cells proliferation, inflammation and joint destruction. EPA and DHA affect the NF-kB signalling system [30], a new potential opportunity where diet can help in the modulation of inflammation with the reduction on the severity of the disease but more studies should be made to understand what happens upstream of the system.

Olive oil, rich in the monounsaturated fatty acid called oleic acid, is consumed in the Mediterranean diet and it has shown a positive effect on gene expression and cytokine production [32], the oral administration of oleic acid decrease the production of pro-inflammatory mediators IL-1, IL-6 and macrophages cytokines production [31].

3.5 Gut microbiota health

Gut microbiota in the last years is associated with the systemic health of humans, the complexity of the biota has not yet let scientist to understand the full effects on the human system and more research are made to understand it. The SCFA produced in the gut are distributed through the circulation and have shown an anti-inflammatory influence on macrophages and dendritic cells [28, 33]. Butyrate producing species such as *Clostridia, Faecalibacteria* and *Lachnospiraceae* have demonstrated an anti-inflammatory effect in the context of rheumatic diseases and they play a crucial role in the integrity of intestinal epithelia [33, 34]; subjects with RA has shown an alteration in the microbiota composition that is partially restored after DMARD (disease modifying antirheumatic drugs) intake [33] but the alteration continues as the disease became severe.

The anti-inflammatory diet, based on Mediterranean model, thanks to its dietary pattern rich in fruits and vegetables, fiber intake, whole grains, SCFA from olive oil, legumes, low quantity meat and moderate consumption of fish rich in omega-3 fatty acids has shown a lowering effect in RA disease activity [32, 33]; Mediterranean dietary pattern can be considered of importance for the microbial gut health and as consequence for the subjects affected by chronic inflammatory diseases.

3.6 Alcohol and non-alcoholic beverages

Consumption of moderate intake of alcohol beverages is indicated having a protective effect on a numerous disease such as cardiovascular disease, neurodegenerative disease and even some diseases related with inflammation, the positive effect is thanks to the compounds present in the beverages like resveratrol, polyphenols and antioxidants compounds, red wine is the beverage considered as most effective thanks to its high concentration of these molecules. Resveratrol, present in red wine, inhibits NF-kB system and blocks COX-2 [35] with a positive effect on gene expression and a reduction in pro-inflammatory mediators, even if the positive effect of resveratrol the moderate intake is the key up to a maximum of 1 glass per day or even less up to 2-3 drinks per week. Alcohol is very discussed since the toxic effect of ethylic alcohol can't be denied and people with RA usually take medication and the interaction with alcohol can increase the hepatotoxic effect.

The most important non alcoholic beverage rich in polyphenols is tea, tea is obtained from the infusion of the *Camelia sinensis* leaves in hot water. The polyphenolic compounds of major importance are the catechins in particular the most potent one is called EGCG (epigallocatechin gallate) that has been sown to induce cell-growth arrest, apoptosis probably through NF-kB inhibition and downregulates the infiltration of CD8 T cells in the site of inflammation [35]. The principal effect of tea polyphenols is associated, as just seen, with signalling pathways and not with the antioxidant effect since the concentration of catechins once inside the human body is 100-1000 times lower than the concentration of others potent antioxidant compounds such as vitamin C or glutathione [35]. Consumption of tea polyphenols showed effect on the attenuation of arthritis symptoms and at molecular level showed an inhibition on osteoclastogenesis and T-helper 17 cells [34] with an inhibition of IL-1 and IL-6 produced by synovial fibroblast and a preservation of joint damage [22].

3.7 Herbs and spices

Herbs and spices are usually not considered ingredients but are normally used to enhance the flavour of a plate, the enhancing capacity is not the only one because there is another one and it is the anti-inflammatory capacity of these compounds. Ginger and turmeric are two herbs with an important impact on inflammation thanks to their inhibitory effect on IL-2, TNF-α and IL-8 and they are also able to inhibit prostaglandins and leukotriene synthesis [21].

Curcumin is a polyphenols based compound wide spread in various *Curcuma* species in particular *C. longa* and it is recognized as one of the most potent treatment for inflammatory condition. Clinical trials on healthy volunteers have shown a non-toxic effect even at high dose [23], high dose important for the low absorption of the compounds in the gastrointestinal tract, the daily intake of curcumin should be about 0-3 mg/kg body weight to have a significant pharmacological effect [23]. The ability in the modulation of inflammation is correlated with its multiple action on different modulatory pathways in particular on NF-kB and MAPK, both of them are associated with a pro-inflammatory stimulus. Curcumin is able to inhibit the two system increasing the apoptosis of the cells and at suppress cell proliferation [23], it was also reported that curcumin is able to down regulate TNF-α, chemokines and cell surface adhesion molecules [35].

4 Conclusions

As today diet is not considered effective in the treatment of Rheumatoid arthritis even if in the last years diet can be considered as a "supplementary" treatment especially for the prevention of the disease or to reduce the severity of the disease. The major treatment of the disease is the use of DMARDs that act as IL-1, IL-6, IL-17, TNF-α inhibitors, the principal molecules used are methotrexate and glucocorticoids [6, 10]. The optimal way to reduce the severity of the disease is the early diagnosis with DMARD drugs and the "supplementary" diet treatment, the anti-inflammatory diet pattern is not considered enough to treat Rheumatoid arthritis even though some studies proved the importance of diet as a preventive measure for RA [32, 34]. The control of the diet, based on the Mediterranean model, can have a big influence in the management and control of arthritis and can help subject with the disease to reduce the swelling and pain of the joints but it must be considered another method to improve the general health condition and a way to lower the possibility of becoming an invalid person.

Rheumatoid arthritis is correlated with inflammation and the interaction with other inflammatory diseases is not clear yet, there is a possibility that the presence of one disease increase the risk of developing another one and the lifestyle of the person must be evaluated precisely to lower the probability of developing them. Insulin resistance and obesity are just two examples of metabolic syndrome that can increase the mortality of RA because all of them are related with an alteration in the inflammatory state of the body and with a progressive overload on human health.

Physical activity is recognized as a crucial factor in the prevention of diseases and in the general improvement of human health. It can help in the early stage of different metabolic syndrome but there are not specific studies about the interaction between RA and physical activity, in which way RA is influenced? Could there be a reduction of joint damage and bone loss thanks to physical activity? Could physical activity be considered as a prevention form as diet, or could it be considered as a real treatment to improve the health condition of subject with RA? More scientific evidence should be evaluated to understand better the disease and possible alternatives way to treat RA.

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