

Endothelial dysfunction and extra-articular neurological manifestations in Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease that affects about 1% of the global population, with a female-male ratio of 3:1. To date, genetic predisposition, the involvement of a deficient immune system and lifestyle are known to be the major responsible for the onset of the disease.

RA preferably affects the joints, with consequent joint swelling and deformities followed by ankylosis. Patients suffering from rheumatoid arthritis can also develop extra-articular manifestations, which mainly affect the cardiovascular system, the nervous system, the skin, the eye, the respiratory system, the kidney and the gastrointestinal system.

It has been shown that about 20% of RA patients can develop neuropathies, multiple mononeuritis, distal sensory neuropathies and sense motor neuropathies. Neurological involvement occurs as a consequence of vasculitis of the nerve vessels leading to vascular ischaemia, axonal degeneration and neuronal demyelination. In RA, the risk of developing cardiovascular disease is very high and depends, most probably, on vascular damage resulting from endothelial dysfunction. Hence, it is reasonable to assume that the integrity of the endothelium is also involved in the neurological disorders resulting from RA.

This review aims to highlight the main characteristics of the extra-articular manifestations at the nervous level resulting from rheumatoid arthritis. To this end, the literature main results on these pathological manifestations have been collected with particular focus on the involvement of endothelial dysfunction. In fact, the endothelium could be considered a valuable target for minimizing the incidence of extra-articular neurological manifestations in RA.

Keywords: Rheumatoid arthritis, inflammation, neurological extra-articular manifestations, endothelial dysfunction, polyphenols.

1. Introduction

Rheumatoid Arthritis (RA) is a chronic systemic inflammatory autoimmune disease, which affects approximately 1% of the global population. The disease usually includes two major subtypes: the "seropositive" subtype (SPRA) and the "seronegative" (SNRA) subtype [1]. The first subtype is characterized by the production of two auto-antibodies, Rheumatoid Factor (RF), used as a fundamental factor in the diagnosis of RA, and Anti-Cycliccitrullinated Peptide Antibody (ACPA) which has recently attracted particular attention since is a predictive marker of RA, even in the early stages of the disease. The second subtype does not develop these autoantibodies and has been described as a less aggressive form than SRPA [2]. RA occurs preferably in females, with a female-to-male ratio of 3: 1; also, the onset of the disease occurs between the ages of 25 and 50. However, in recent years there has been a progressive increase in the incidence rate with the advancement of the average age of onset from 50 to 55 years. In this case, RA affects both sexes with the same incidence [3]. The disease can begin slowly and gradually with mainly nonspecific symptoms such as fatigue, low-grade fever, general malaise, and joint pain; later, more defined symptoms such as intense pain, morning stiffness, and swelling of the joints appear [4]. In some cases, RA begins in an acute form, and in this case joint involvement with distinctive signs of inflammation occurs [5]. In general, the joints most frequently affected are those of the hands and wrists, followed by those of the feet, knees, elbows, ankles, up to involving the wider joints of the shoulders, hips, jaws, and cervical spine [6]. With overt disease, joint swelling occurs, caused by synovial effusion, and the onset of joint deformities and ankylosis [7]. It is known that RA patients can also develop extra-articular manifestations, which mainly affect the skin, the eye, the nervous system, the respiratory system, the gastrointestinal system, the cardiovascular system, and the kidney [8]. The main components responsible for the onset of the disease are three: genetic predisposition, immune system, and environmental factors. To date, it is assumed that these three mechanisms are involved simultaneously [9]. This review deepens the involvement of the endothelium and its integrity in the extra articular nervous manifestations that occur in patients suffering from rheumatoid arthritis.

1.1 Rheumatoid arthritis, genetic factors and immune involvement

The first important genetic factor is family predisposition: individuals with specific cases of RA in the family have a 40-50% chance of developing the disease [10]. In addition to a family predisposition, the presence of a set of alleles is known that carry information for the formation of some amino acid sequences which are related to the risk of developing RA [11]. Recent scientific research has also highlighted the presence of some polymorphisms directly associated with RA in

non-DNA coding regions, capable of indirectly acting on the hyper activation of immune response cells, such as T lymphocytes. Other polymorphisms implicated with RA were found to be directly related to cellular inflammatory pathways, such as STAT4 [12] and NF-kB [13]. Extensive genetic studies have shown that the presence of HLA-DR alleles (HLA-DRB1, HLA-DR4, HLA-DR10), is correlated with RA. These alleles consist of a common structural portion, called "shared epitope" (SE), whose amino acid sequence is made up of glutamine, lysine, arginine, alanine, alanine (QKRAA) or glutamine, arginine, arginine, alanine, alanine (QRRAA) [14]. SE contributes to the development of RA and two different pathways have been hypothesized to explain this correlation: 1) SE can directly present the antigen to T-lymphocytes; 2) SE is involved in selecting specific T cells from existing ones. In both pathways in the synovial membrane, there is abnormal activation of T-Helper cells, which proliferate and produce soluble factors, such as interleukins and cytokines. These factors regulate the function of B-lymphocytes, monocytes, cytotoxic lymphocytes, and immunosuppressive lymphocytes. Furthermore, B-lymphocytes are responsible for the production of autoantibodies and consequently, the complete immune response directed towards the antigen is activated [15]. This massive immune response due to IL-6 and IL-1-mediated osteoclastic activation leads to synovial inflammation associated with multiple proteolytic enzymes that destroy the joint cartilage, slow alteration of bone, tendons, ligaments, and capsule joint, ultimately causing joint dislocations, deformities, and ankylosis [16]. HLA-DR4 is particularly present in white subjects, while HLA-DR1, DR10 and DRw6 are increased in the non-Caucasian race [17]. Another genetic correlation with RA is given by gender and specifically affects sex hormones: the immune cells, in fact, widely express the receptors of sex hormones such as estrogen, progesterone, prolactin and androgens. In general, 17- β estradiol and prolactin act as a humoral immunity enhancer, while testosterone and progesterone act as natural immunosuppressants. These data can explain the different clinical patterns of RA at different stages of women's sexual life:

- higher incidence of RA in women, during the fertile sexual period, compared to men (ratio 3:1);
- menopausal remissions in women with RA [18].
- improvements in the course of the disease in approximately 75% of women during pregnancy. It is important to underline the shift that 17- β estradiol undergoes during pregnancy. In this circumstance, the function of the sex hormone is mainly anti-inflammatory with marked inhibition of pro-inflammatory cytokines, such as Tumor Necrosis Factor, IL-1 β , IL-6, and Natural Killer cells [19].

The main characteristics of RA are summarized in Figure 1.

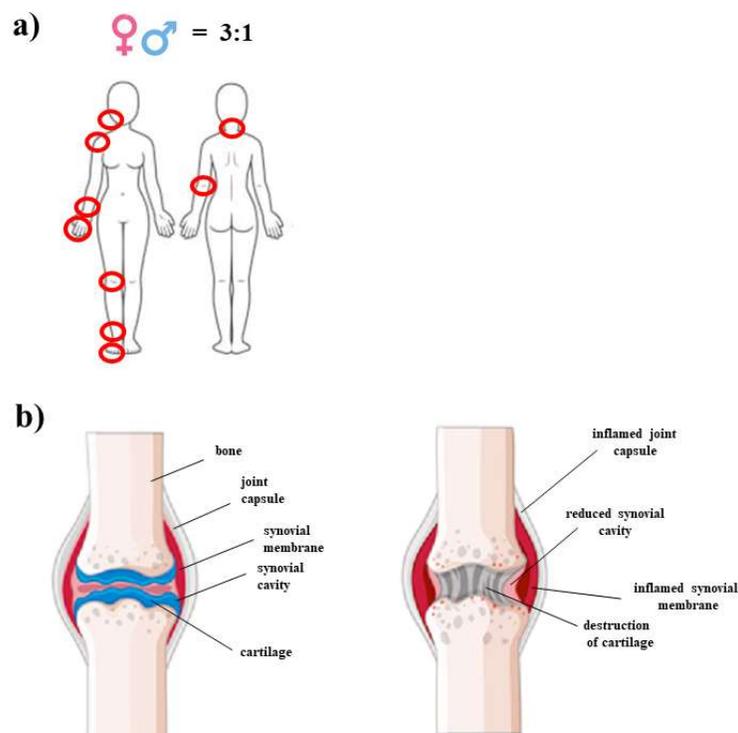


Figure 1. Main characteristics of RA. Panel a) shows the joints involved in RA. The morphological differences between normal and RA involved bones are represented in panel b).

2. Rheumatoid arthritis and endothelial dysfunction

In the scientific literature, there are innumerable data that reports how RA patients have a high risk of developing cardiovascular disease (CVD) and that this predisposition is the cause of premature mortality and/or a reduced life expectancy in 40-50% of these patients [20, 21]. The reasons for this risk are related to an increase in atherosclerosis induced by inflammation [22]. Vascular damage resulting in atherosclerosis and the development of atherosclerotic plaque certainly begins following early damage to the endothelial function: in fact, there is a change in the phenotype of endothelial cells, which leads to a functional and reversible alteration of these cells. The endothelium is defined as a selectively permeable barrier located between the blood flow and the vascular wall of specific organs; in physiological conditions, the endothelium is responsible for maintaining blood fluidity, regulating blood flow and permeability of the vascular wall. Furthermore, the endothelium acts as a real barrier capable of selectively regulating the communication between blood and tissues. Endothelial balance is maintained thanks to its property of releasing soluble mediators, such as nitric oxide (NO), the main regulator of vascular homeostasis, which is released in response to physiological stimuli and is the main component for proper maintenance of the endothelium [23, 24]. NO is preferably located near the cells that produce it, acting as an autocrine/paracrine factor. Many

agonists are involved in the production and release of NO from the endothelium; among these, acetylcholine, histamine, thrombin, serotonin, bradykinin, substance P, isoproterenol, and norepinephrine. Altered production of NO induces reduced vasodilation, a pro-inflammatory state, an increase in the migration of blood cells, the local release of cytokines, and pro-thrombotic properties. From this point of view, endothelial dysfunction is recognized as the Primum Movens of atherogenesis. These processes, if concomitant with RA, lead to platelet activation, abnormal fibrinolytic activity, increased oxidative stress, and a state of hyper-coagulability [25]. In RA, endothelial dysfunction is responsible for the alteration of small vessels of the microcirculation, essential for supplying oxygen and nutrients to the surrounding tissues, as well as for the exchange of fluids and repair processes [26]. Endothelial involvement in RA was also demonstrated by the study based on the count of the number of altered endothelial cells, which under the microscope appear visibly morphologically altered. Furthermore, the vascular endothelial adhesion molecule type 1 (sVCAM-1) and the endothelins were found to be modulated [27]. A clinical evaluation of endothelial dysfunction in RA patients was performed in a prospective study involving 44 patients who had been suffering from RA for more than 12 months [28]. In order to estimate the endothelial function, the brachial artery method was adopted, measuring the percentage change in diameter, mediated by blood flow, and the results obtained were compared to those of healthy subjects. Only 6 out of 44 patients showed normal endothelial function. This study confirmed, in clinical practice, the endothelial function as an early predictor of atherosclerosis in patients with RA. Another clinical study conducted on 68 patients with RA has shown that a sedentary lifestyle worsens microvascular endothelial dysfunction [29]. Early endothelial dysfunction in RA involves impaired angiogenesis that leads to cardiovascular comorbidity. In particular, recent data have highlighted the blockade of tumor necrosis factor-alpha (TNF α), which in RA can modify the vascular condition. Angiogenesis is an important feature of rheumatoid synovitis; although the new blood vessels supply oxygen to the increased inflammatory cell mass, the neo-vascular network, being dysfunctional, cannot restore oxygen homeostasis in the tissues, and therefore the rheumatoid joint remains in an extremely hypoxic environment. Furthermore, the increase in oxidative stress contributes greatly to tissue damage [30]. Glucocorticoids (GCs) were the first drugs used to pharmacologically treat RA. The studies conducted on the effects of GC on endothelial dysfunction, in patients with RA, have proved complex and contradictory, with results difficult to interpret due to the great heterogeneity in RA disease, the dosages of GC used, the duration of drug treatment, or concomitant therapies with GCs [31]. An interesting study has recently been conducted on the effects of prednisolone treatment on endothelial function in an *in vivo* model in which RA was induced. The results demonstrated the pleiotropic effects of GC on endothelial pathways suggesting that GCs act on an endothelial target. The main

candidate could be the mitogen p38, involved in the signaling pathway of protein kinases (MAPK), which would be activated by inflammation [32]. Based on what has been stated so far, the endothelium could be considered as an important target. It appears of crucial therapeutic outcome acting in the early stages of the pathology, and restoring its proper functions could reduce the risk of CVD and, probably, other extra-articular manifestations of RA. Figure 2 shows the involvement of the endothelium in RA.

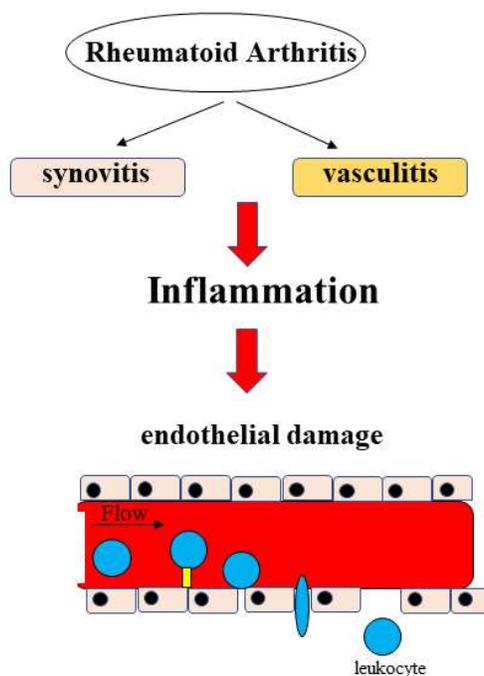


Figure 2. Involvement of the endothelium in RA.

3. Extra-articular manifestations in Rheumatoid arthritis: neurological involvement

Patients with RA can develop a wide range of neuronal damage; in particular, it has been highlighted that about 20% of patients can develop neuropathies, multiple mononeuritis, distal sensory neuropathies, and sensorimotor neuropathies: in all these disorders neurological involvement occurs as a consequence of vasculitis of the nerve vessels leading to vascular ischemia, axonal degeneration, and neuronal demyelination [8]. In patients with RA, drug-induced toxicity is also involved in neuronal damage [33]. Many neuropathies develop due to nerve compression, as in the case of carpal tunnel syndrome, generating not only pain but also paresthesia and neuronal damage. It has been

shown that chronic synovitis, at the foot level, is associated with the development of Morton Neuroma and tarsal tunnel syndrome, two pathologies responsible for pain in patients with RA [34].

In addition to the carpal tunnel syndrome, central nervous system involvement in RA patients includes multiple manifestations such as meningitis, optical atrophy, cerebral vasculitis, and rheumatoid nodule formation [35, 36]. Among these alterations, cervical myelopathy is the most common in patients with RA for more than 15 years and is associated with significant morbidity and mortality [37]. The frequency with which cervical myelopathy occurs is 2.5% and the main symptoms are neck pain, occipital headache, sensory deficits, lower cranial nerve palsy, and transient ischemic attacks. These symptoms are caused by compression of the spinal cord and brain stem [38]. The cervical vertebrae C1 and C2 are the typical targets of the pathology and the involvement of the cervical spine can present various forms including erosions of the vertebral endplates, erosions of the spinous process, changes in the apophyseal joint followed by osteoporosis [39]. These inflammatory lesions of the cervical spine, associated with frequent subluxations, occur within the first ten years after the diagnosis of RA, although many patients remain completely asymptomatic [40]. Diagnosis of cervical myelopathy is carried out by X-rays, through which it is possible to assess the parameters of the craniocervical junction. MRI also provides more detailed information on ligament structures [41].

Rheumatoid meningitis is a neurological manifestation of RA, affecting the central nervous system, which can occur during a remission phase of the autoimmune disease [42]. The main symptoms include headache, seizures, deafness, speech disturbances, and stroke-like symptoms, eg hemiparesis and cognitive impairment. Since these symptoms can be misinterpreted, it is necessary to make a correct diagnosis through the combination of numerous data including the objective clinical presentation, analysis of the cerebrospinal fluid obtained by lumbar puncture, MRI of the brain, and a biopsy that can exclude other etiologies. Furthermore, to rule out possible infections, the cerebrospinal fluid should be negative [43]. The analysis of the pathological manifestations describes the chronic inflammation of the meninges, the concomitant presence of vasculitis, and necrotizing granulomas [44]. In some cases, but not all, the presence of ACPA and RF autoantibodies can be detected [45].

Rheumatoid nodules are nodular lesions found in the subcutaneous area normally subjected to pressure or mechanical stress, such as the joint of the fingers or forearm. They are usually present in about 20-40% of patients with more aggressive RA and the SPSA form; RF is, normally, present in patients with autoimmune disease who develop rheumatoid nodules. If, on the other hand, RF is absent it may be that the patients develop the other pathological forms [46]. Rheumatoid nodules are characterized by specific histological peculiarities: there are numerous macrophages and multinucleated cells arranged around a central necrotic area [47]. The presence of rheumatoid nodules

reduces the functional capacity of the patient who is affected and a rehabilitation program is recommended. Sometimes, pharmacological and rehabilitative treatment is replaced by surgery, but this option has not always proved to be decisive [48]. To date, the scientific literature has highlighted that many extra-articular neurological manifestations present in RA could be due to adverse reactions of the common drugs taken for this autoimmune disease: among these, it seems that prolonged use or at high doses of GCs, can cause manifestations psychiatric and cognitive impairment [49]. The use of Methotrexate, a drug widely used in RA, can cause peripheral neuropathies, retinal damage, and ear alterations. [50] Finally, more than 40% of patients with RA can generate psychiatric symptoms as a consequence of the drugs taken such as anxiety and depression [51]. Extra-articular neurological manifestations in RA also include the ophthalmological field; these pathological processes, often, occur early and are among the first signs of the disease. These inflammatory ophthalmological conditions include episcleritis, scleritis, and peripheral ulcerative keratitis and can greatly exacerbate ocular prognosis as they aggravate RA conditions and increase the risk of developing systemic vasculitis [52]. For this reason, at the time of the diagnosis of RA there should be a close collaboration between the rheumatologist and the ophthalmologist. Scleritis, for example, when associated with RA, can lead to severe ocular complications and is thought to be caused by the deposition of the immune complex found in the necrotizing collagen associated with the sclera [53]. Most cases of scleritis are treated with immunosuppressive drugs and have a good resolution, although some refractory cases are more aggressive and resistant to steroid therapies [54].

Current scientific knowledge offers an interesting link between the extra-articular neurological manifestations due to RA and the endothelium: in fact, it is widely known that an inflammatory condition activates endothelial cells [55-57]. At the level of the nervous system, there are two important barriers: the first separates the Central Nervous System from the systemic circulation: it is the Blood-Brain Barrier (BBB) [58]; the second, at the level of the Peripheral Nervous System, separates the blood from the peripheral nerves and constitutes the Blood Nerve Barrier (BNB) [59]. BBB and BNB have been extensively studied in the case of neurodegenerative diseases or peripheral phenomena of neurodegeneration [59, 60]. Endothelial cells play a fundamental role during the inflammatory process, from the early stages, and throughout its duration: in fact, they are activated by promoting: 1) rapid and transient activation, through which the interaction between endothelium and leukocytes occurs due to reduction of the main intercellular junctions; 2) slow but persistent activation capable of increasing the expression of many pro-inflammatory cytokines and adhesion molecules. The main cytokines are expressed as a consequence of activated leukocytes and are mainly represented by tumor necrosis factor- α (TNF- α) and interleukin-1 [61]. Activation of the endothelium causes an increase in vascular permeability, adhesion molecules, and nuclear transcription factor

NFκB [62]. Numerous studies have shown that patients with RA present with early endothelial dysfunction at the microvascular and macrovascular levels [63]. In these cases, biomarkers are available that highlight endothelial damage, predictive of the extra-articular manifestations of RA, even if the physio-pathological mechanisms involved are not yet fully understood; the accumulation of ROS and the reduction of NO are two characteristic endothelial responses that express a state of dysfunction [64]. In RA conditions, the endothelium is subject to stress and an increase in the inflammatory state; in particular, the activated endothelial cells stimulate angiogenesis, promote cell proliferation and migration; induce the expression of TNF- α , IL-6, IL-8, inducing an increase in cell permeability and leukocyte infiltration [65]. To date, it is well known that TNF- α and IL-1 are responsible for the bone damage found in patients with RA. Furthermore, the maintenance of the inflammatory process is also due to the overexpression of IL-6, which has been abundantly found in the synovial fluids [66, 67]. In RA, this cytokine actively participates in the destruction of the joints, in the increase of endothelial permeability, in the recruitment of T lymphocytes and monocytes, and the overall aggravation of the disease [68, 69].

Numerous studies have shown a possible relationship between neuronal endothelium and neurological manifestations in RA patients [70, 71]. For example, increased levels of circulating adhesion molecules, such as vascular cellular adhesion molecule and E-selectin, were found in patients with RA associated with peripheral neuropathies compared to RA patients without neurological complications [72]. Furthermore, in the same experimental groups, higher levels of anti-endothelial cell antibodies and neurological alterations were found in patients with RA associated with peripheral neuropathies than in patients with RA alone [73]. Endothelial dysfunction at the blood-nerve interface is involved in the onset of many disease states through three mechanisms which include:

- a reduction of NO;
- a greater expression of pro-inflammatory factors;
- a modification of the permeability of the endothelium [59].

The first mechanism is associated with reduced production of NO which results, in pro-inflammatory situations, from an increase in the accumulation of ROS and from the induction of endoplasmic reticulum stress in endothelial cells [74-77]. Under physiological conditions in each cell, there is a balance between the endogenous production of free radicals and their neutralization by antioxidant systems [78, 79]. However, when the accumulation of ROS becomes massive, there is a drastic reduction in the endogenous antioxidant capacity and these reactive species react with organic and inorganic molecules thus producing other radicals with a series of chain reactions. The modification of the redox state results in a reduced eNOS activity, with consequent inhibition of NO formation.

Among the ROS the most dangerous species is the superoxide anion (O_2^-) which can react with O_2 to generate peroxynitrite ($ONOO^-$). $ONOO^-$ is a powerful oxidizing molecule capable of altering the structure of biological macromolecules, including those involved in the synthesis of NO [80-82]. At the same time, the involvement of the endoplasmic reticulum leads to an increased expression of endothelin-1 and a reduction in the expression of one of the enzymes responsible for the synthesis of NO, the Endothelial Nitric Oxide improved eNOS activity and greater vascular relaxation were observed. If the endoplasmic reticulum stress is not resolvable and shows too high ROS levels and altered homeostasis of the calcium ion, the endothelial cells activate pro-apoptotic signals (JNK, p38, and caspase-9) which lead to cell death [83, 76].

The second mechanism is activated as a direct consequence of the first: in fact, the endothelial alterations previously mentioned are accompanied by the increase of various pro-inflammatory factors. It has been shown that there is an increase in C reactive protein, IL-1 β , IL-6, and tumor necrosis factor (TNF- α). Finally, an increase in pro-inflammatory molecules is associated with an increase in the permeability of the endothelium, with consequent leukocyte adhesion and migration of monocytes. Up-regulation of expression of cell adhesion molecules (CAM) occurs, such as intercellular adhesion molecule 1 (ICAM-1), vascular cell adhesion molecule (VCAM-1), and selectin E [84]. These molecules are expressed on the plasma membrane of endothelial cells and increase the affinity of the leukocytes and the weakening of the barrier, thus causing diapedesis of leukocytes in the peripheral tissues. Ultimately, the breakdown of the integrity of the BNB, as a consequence of the endothelial alteration, occurs as a result of reduced expression of the proteins of the tight junctions and the adherent junctions [59].

During the inflammatory process, a significant role is also played by estrogens and this consideration is very important due to the the female population prevalence to develop RA. As previously reported, estrogen acts as a humoral immunity enhancer, but it is equally important to emphasize that, at the nervous level, estrogens provide a protective response [85, 86]. It was highlighted, in particular, that treatment with estrogen attenuates the recruitment of adhesion molecules, monocytes, and leukocytes in the endothelium of patients suffering from neurological diseases. This evidence could explain the protective effect of estrogens in the neurological field, even if it would be advisable to carry out further and more updated studies [87]. Maintaining the integrity of the endothelium, at the level of the BBB and BNB, could reduce the development of those pathologies accompanied by central and peripheral nerve dysfunctions. It is also necessary to conduct further studies on the mechanisms involved in endothelial alteration and extra-articular neurological manifestations associated with RA, to improve current knowledge on the involvement of the central nervous system in patients with RA,

to precisely delineate the cellular mechanisms involved and to implement, consequently, the success of the treatments.

4. Rheumatoid arthritis and nutrition

In recent decades, a correlation between eating habits and the onset of inflammatory or autoimmune diseases has been increasingly highlighted [88]. This association was confirmed following the discovery that certain foods promote pro-inflammatory reactions, while other foods have been shown to have anti-inflammatory properties. Therefore, the RA trend can easily be correlated to dietary choices. A very interesting clinical study has been conducted on 300 subjects suffering from RA, whose main information (personal data, drugs taken, any comorbidities present and disease activity) were entered in a six-monthly register. The patients were questioned about the main effects caused by the intake of an established group of foods and whether, following the intake, the symptoms of RA had improved or worsened. The 20 foods considered belonged to two categories: a) "potentially inflammatory" such as milk, cheese, red meat, tomato, eggplant, white potatoes, hot peppers, diet soft drinks, beer; b) "potentially anti-inflammatory" such as fish, spinach, blueberries, strawberries, chocolate. The results obtained showed that in subjects suffering from RA, the intake of blueberries and fish had led to a reduction in RA symptoms, while the intake of cheese, red meat, sugar and desserts had fueled the inflammation [89]. All the clinical studies conducted in this direction have been found to agree that a Mediterranean diet can slow down the inflammatory based disease such as RA [90-92]. The Mediterranean diet includes the consumption of high amounts of fruit, vegetables, unrefined cereals, legumes, nuts, a moderate intake of white meats, fish, dairy products, yogurt and a reduced consumption of red meat and sugar, olive oil it is the main source of edible fats and wine is consumed regularly, but moderately. This type of diet also provides a high ratio between monounsaturated and saturated fats [93]. It is important to emphasize that fish consumption is mainly based on those containing long-chain polyunsaturated fatty acids (omega 3) and that this extremely balanced diet is related to a reduction in the risk of RA [94]. The Mediterranean diet, therefore, has anti-inflammatory potential effect and for this reasons, it is well correlated as a protective tool in all those inflammatory pathologies [95, 91, 92]. Food molecules can interact with the gastro-intestinal barrier and induce an alteration of the intestinal microbial flora, causing local and/or systemic changes [96]. Man is colonized by a multitude of microorganisms, defined as a whole "microbiota", which can establish various forms of relationship with the host organism, proving to be symbionts, commensals, or pathogens. The gut microbiota has shown a symbiotic correlation with the host organism that has been described as mutually beneficial: the host organism provides suitable nutrients

and habitat for the microbiota, while the gut microbiota supports the intestinal development and maturation of the host organism providing beneficial nutrients. Therefore, a co-metabolism is generated between the microbiota and the host system [97]. The intestinal microflora carries out fermentation reactions associated with the production of short-chain fatty acids (SCFA), including acetate, propionate and butyrate that can be found in the intestinal tract and peripheral blood. These compounds participate in promoting the development of intestinal immunity, and protecting against colonization by pathogenic microbes [98]. A growing number of scientific evidence has shown that the alteration of the composition of the intestinal microbiota was responsible for the onset of many chronic inflammatory disorders [99, 100]. An alteration of the intestinal microbial composition creates a "dysbiosis" that promotes a pro-inflammatory phenotype through immune modulation. The onset of RA has also been shown to correlate with intestinal dysbiosis [101]. In particular, some studies, conducted on animal models and patients, have shown that the dysbiosis of the intestinal microbiota induces progression of the RA disease: patients with RA have shown a reduction in the beneficial component of the microbiota, with a decrease in the gastrointestinal bifidobacteria (Bifidobacteria) and an increase in pathogenic species such as Enterobacteria and Staphylococcus [40]. Other lifestyle factors that are related to RA are daily physical activity, mainly aerobic and with a gradual increase in physical endurance [102], optimal sleep hygiene [103], adequate supplemental intake of Vitamin D [104], moderate consumption of alcohol [105, 106].

5. Therapeutic interventions in Rheumatoid arthritis

Currently, the treatment of RA is still inadequate since there is no full knowledge of the development and evolution of this pathology. The usually employed drugs are non-steroidal anti-inflammatory drugs, immunosuppressants, antirheumatic drugs, and corticosteroids, which together or separately, reduce pain, swelling, and suppress various adverse factors of the disease [107]. Gene therapy is also currently taking into account and this constitutes a major advance in the management of RA. A greater interest in compounds capable of interacting with the loci of the suppressor genes of inflammation mediators is constantly evident. These compounds are used to reduce the progression of the disease [108, 109]. In the last two decades, there has been a constant increase in the use of biological agents with contradictory and often adverse results [110, 111]. Neurological manifestations of RA have also been treated with these pharmacological agents [112]. The management and treatment of RA and its pathological manifestations from an economic point of view, as well as the side effects resulting from drug therapies, have pushed the current medical science to increasingly use of phytochemicals and drugs of natural origin with documented anti-arthritic effect, to reduce or eliminate adverse effects [113]. A protective role of natural compounds has also been demonstrated towards RA [114] and,

among these, the class of polyphenols has proved particularly effective. Polyphenols represent the most studied phytochemical compounds in the last two decades since they have shown a high positive impact on health; in particular, they have shown a protective role in many degenerative pathologies of the nervous and cardiovascular systems, in cancer, inflammatory diseases and pain of different etiologies [115-118]. Particular focus to the lifestyle of patients has been rapidly increasing for the pain therapy with a special role of nutrition in pain development and its management [91, 92]. Many foods, such as fruit, vegetables, virgin olive oil, wine, cereals, spices, and dried fruit contain high amounts of polyphenols; the common chemical characteristic of polyphenols is an aromatic ring to which hydroxyl groups and other substituents are linked, although about 8000 compounds are known which differ precisely for the different substituents linked to the aromatic ring. The main function of polyphenols is to have strong antioxidant properties [119]. As already mentioned, numerous evidence have shown a close correlation between RA and oxidative stress [120, 121]. Polyphenolic antioxidants neutralize reactive species and enhance the activity of antioxidant enzymes [122, 116-118]. Resveratrol, a non-flavonoid phenol, is a substance that is naturally produced by various plants, such as vines, blackberries, and cocoa, and is endowed with protective activity against pathogens such as bacteria or fungi. It has been shown that resveratrol produces protective effects in RA, reducing the accumulation of ROS, suppressing the inflammatory response and cell proliferation, and consequently decreasing cell apoptosis in synovial tissues [123-125]. The active polyphenols contained in extra virgin olive oil (oleuropein, tyrosol, and hydroxytyrosol) also have strong anti-inflammatory, anti-oxidant, anti-proliferative activity [126-130]. In particular, the oleuropein of olive oil [131] and hydroxytyrosol [132] have shown important protective activities in RA, through the down-regulation of many inflammatory cytokines, including TNF- α , IL-1 β , and IL-6. They also reduce the expression of molecules related to inflammation pathways, such as p38, JNK, p65, and I κ B- α [133, 134]. Precisely for these properties, numerous chemical strategies have been developed to improve the stability and efficacy of these polyphenolic compounds [135].

Scientific data show that other substances of natural origin have protective functions against RA. Among these, we mention the cranberry and the curcumin [136]. Curcumin, in particular, has been shown to reduce inflammation and synovial hyperplasia (synovial hyperplasia) in rats with induced RA [137]. In addition to these compounds, there are many other polyphenols whose antioxidant and anti-inflammatory properties are known, but which have not been directly tested in RA. One of these is represented by the polyphenolic fraction of bergamot. Bergamot (*Citrus bergamia*) is an endemic plant that grows in Calabria (Southern Italy) that has a wide range of flavonoids and glycosides, such as neoeriocitrin, neohesperidin, naringin, rutin and poncirin. This peculiar composition provides the uniqueness property to the bergamot compared to the other citrus fruits. Due to its peculiarity it is

employed in different formulations such as essential oil, hydro-alcoholic extract and fruit juice. Recent scientific results have identified massive antioxidant and anti-inflammatory effects on the part of the polyphenolic fraction of bergamot, to the point that this fruit is considered a real nutraceutical [138-141]. Following these considerations, bergamot could be a promising candidate for studies of its activity on in vivo models of RA. Furthermore, the polyphenolic fraction of bergamot could also be tested in the neurological manifestations caused by RA, since, to date, no encouraging results are known from phytochemicals and nutraceuticals.

6. Conclusion

In this review we have deepened the knowledge of the extra-articular manifestations of rheumatoid arthritis, giving particular relevance to the involvement of the nervous system. The endothelium could be taken into account as a valuable target for minimizing the incidence of extra-articular neurological manifestations in rheumatoid arthritis also providing an innovative therapeutic goal.

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