Role of Selenium in Pathogenesis and Treatment of the Autoimmune Diseases

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1-PATHOPHYSIOLOGY OF MULTIPLE SCLEROSIS

Neuronal injury, leading to characteristic multifocal plaques apparent on magnetic resonance imaging and a wide variety of neurologic symptoms. The disease pathology is known by multifocal plaques within the central nervous system (CNS), in both the white matter and gray matter, with perivenular inflammatory cell infiltrates, demyelination, axonal transection, neuronal degeneration, and gliosis. MS pathogenesis is complex, as it affects both T- and B-cell processes and is heterogeneous in appearance. Relatively recently, the historical 4 core clinical categories of MS were defined in an effort to improve classification of the clinical course, better detect where a given case is positioned in the disease spectrum, and to guide clinical investigations.

In young and middle-aged subjects, MS is one of the most frequent contributors to neurologic disability, and it acts detrimental effects on a patient's productivity and health-related quality of life. Commonly, cases with MS have a long life span, although healthcare utilization increases over time. Consequently, the disease places a substantial burden on cases and their caregivers/families, as well as employers, and the healthcare system.

Risk Factors

The pathogenesis of MS is complex, as both genetic factors and environmental exposures have role. Both ethnicity and geography affect the prevalence of MS, proposing that heritable factors have role in MS pathogenesis, as well. The relatives of cases with MS have greater risk for the disease; however, the genetic basis of MS is complex and heterogeneous. Multiple genes have cumulatively role in disease risk and disease behavior, and the genes and alleles involved are different from patient to patient. Genes encoded in the class II region of the major histocompatibility complex (MHC) on chromosome, specifically the HLA-DR2 haplotype DRB1*1501-DQB1*0602 have been proposed. It is known that the MHC-disease correlation results from effects on antigen-presenting cells, which change immune reactivity to auto-antigens, possibly myelin-related auto-antigens. A number of epidemiologic investigations have shown unequal

geographic distribution of MS; the disease is relatively rare in the tropics and increases in rate with increasing latitude in both the northern and southern hemispheres. Compared with other ethnic groups residing at the same regions, those with northern European ancestry have higher risk for MS; however, more recently, an increasing incidence of MS has been shown in southern Europe. There is also evidence of tempering of the latitude gradient in MS incidence during the past years. This may be in part be clarified by the increased incidence of MS in geographic regions closer to the equator and to an increase in the female-to-male ratio of MS with time. Migration findings propose that the risk of developing MS is determined at the time of puberty or before.

Other putative risk factors include infectious factors, a diet high in salt and low in long-chain fatty acids, environmental risk factors, and low exposure to sunlight, although none have been definitively correlated. Taken together, 3 major epidemiologic shifts in MS have been found in recent years: (1) an increased rate of MS, mostly because of longer survival; (2) a possible true increase in the incidence of MS in many countries, particularly in women, resulting in higher female-to-male sex ratios; and (3) a lessening of the idea of a latitudinal gradient in Europe and North America regions. The increase in the female-to-male sex ratio proposes an environmental affect on the risk of MS; however,

environmental variants may be exerting at the population level rather than at the individual level.

Clinical Presentations

The broad range of signs and manifestations of MS show multifocal plaques in the CNS, including the afferent visual mechanisms, cerebrum, brainstem, cerebellum, and spinal cord. Taken together, the range and severity of symptoms in a case at a particular time shows the extent of plaques, their location, the severity of tissue injury, and the rate of accumulation. However, the association between plaques (as seen on standard magnetic resonance imaging) and clinical symptoms is only approximate. This may be due to the recovery and neural plasticity compensate for injury, and residual function may not parallel alterations in MRI. Moreover, recent work has approved that there are pathological characteristics in both white and gray matter not visible on standard MRI. MS manifestations caused by interruption of myelinated tracts in the CNS. The initial manifestations often include 1 or more of the following: weakness or reduced dexterity in 1 or more limbs, a sensory disturbance, monocular visual loss (optic neuritis), double vision (diplopia), gait instability, and ataxia. As MS ensues, bladder dysfunction, fatigue, and heat sensitivity are found in many cases.

Additional manifestations include Lhermitte's sign,

facial weakness or pain, vertigo, brief tonic spasms, and other paroxysmal presentations, which are thought to represent discharges along demyelinated axons. Cognitive deficits are frequent, particularly in advanced patients, and include memory loss, impaired attention, problem-solving difficulties, slowed data processing, and difficulties in shifting between cognitive tasks.

Diagnosis

Clinically, MS is known by discrete episodes ("attacks" or "exacerbations" or "relapses") of neurologic dysfunction. The type and severity of manifestations created by these episodes vary significantly between cases and depend upon the site of neurologic involvement. Frequently, cases may experience numbness, tingling, weakness, vision loss, gait impairment, incoordination, imbalance, and bladder disturbances. In between these attacks, at least during the remitting periods of the illness, cases have fairly stable neurologic activity. Nevertheless, residual manifestations may persist and many cases have fatigue or heat sensitivity in the interval between attacks. Over several years to decades, many cases who present with relapsing-remitting MS (RRMS) evolve to the secondary progressive characteristics of illness, in which they show an insidious worsening of function and the accumulation of neurologic disability unrelated to any acute attacks that may or

may not appear. This is especially true in untreated cases.

MS diagnosis is considerably affected by clinical judgement. The diagnosis of MS is primarily clinical and relies on the approval of manifestations and signs attributable to white matter plaques on MRI that are disseminated in time and space, along with the exclusion of other disorders that may mimic MS. There is no single laboratory evaluation diagnostic for MS. In addition to a thorough history and physical evaluation, diagnostic tools needed to diagnose MS and exclude other diagnoses include MRI, CSF analysis, and evoked potential testing. CSF analysis reveals increased immunoglobulin levels and 2 or more oligoclonal bands (OCBs) in more than 90% of cases. Delayed latencies of the visual, somatosensory, and auditory evoked potentials on electrophysiological investigations, as well as prolonged central motor conduction times, are hallmark of demyelination; this may represent clinically silent plaques. Blood tests are commonly used to rule out other disorders that mimic MS.

Differential Diagnosis

Another critical component of MS diagnosis is the exclusion of alternate causes. The list of conditions that mimic MS clinically or radiologically is extensive; however, in clinical practice, there are few causes that truly mimic MS on both fronts. In MS, differential diagnosis

must be guided by clinical manifestation and neurologic evaluation. Some of the diseases that are often mistaken for MS include nonspecific neurologic manifestations (eg, migraine, functional neurologic disorders, fibromyalgia, and small vessel ischemic disease alone or in combination), other demyelinating diseases (eg, neuromyelitis optica, idiopathic transverse myelitis, and acute disseminated encephalomyelitis), systemic inflammatory disorders with CNS presentations (eg, sarcoidosis, CNS commonly includes a vitamin B12 level (for vitamin B12 deficiency causing the syndrome of subacute combined degeneration), treponemal antibody testing (for syphilis), Borrelia serologies (for Lyme disease, depending on geography, local epidemiology, and season), and antiphospholipid antibody syndrome evaluation. Aquaporin-4 antibody evaluation for neuromyelitis optica should be carried out in any case with a longitudinally extensive myelitis, and in all cases who experience a first episode of acute optic neuritis. Although erythrocyte sedimentation rate may provide evidence of a systemic inflammatory cascade, it is extremely nonspecific. Antinuclear antibody evaluation is a pivotal serologic marker of a number of systemic inflammatory (rheumatologic) syndromes, but false positives occur in otherwise healthy subjects at rates of more than 30% at the 1:40 dilution and 5% at the 1:160 dilution (using human epithelial type 2 cells as the antinuclear antibody test substrate). A positive

result for a putative MS “mimic” does not itself exclude the diagnosis of MS (ie, a case with MS can be vitamin-B12 deficient and still have MS).

2- ROLE OF SELENIUM IN MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is a chronic and inflammatory disorder of the central nervous system (CNS) whose rate is clearly increasing in many regions. Symptomatology and patient's disability are outcomes of the presence of demyelinating plaques in the CNS and include weakness, fatigue, incontinence and paralysis. The immunopathogenesis of these plaques is complex and affects the interplay of distinct subsets of T lymphocytes.

Autoreactive T cells specific for myelin peptides, probably triggered in the peripheral lymphoid organs by molecular mimicry or bystander stimulation, migrate toward the CNS and target the myelin sheath-producing oligodendrocytes, stimulating a local inflammatory and injurious mechanism. Classically, Th1 and Th17 cells, locally stimulated by myelin presented by microglia act mainly by releasing pro-inflammatory mediators as IFN-γ, TNF-α, IL-6 and IL-17. Th17 cells have

also being correlated with blood-brain barrier (BBB) disruption, facilitating therefore lymphocyte transmigration to the CNS. Local antigen presentation, that is carried out in the presence of MHCII and co-stimulatory molecules, allows T cell stimulation in the CNS and is viewed as a critical event for disease evolution. Different cell types as peripheral dendritic cells (DCs), infiltrating macrophages, CNS-resident microglia, and T lymphocytes (Th1, Th17, and Tregs) have been extensively assessed concerning their role in this neuroinflammatory mechanism.

This orchestrated cell interplay will, ultimately, produce inflammation and subsequent neurodegeneration. Strong findings show that oxidative stress is a dominant stimulant for inflammation and vice versa and that this cyclical mechanism is implicated in both, demyelination and axonal injury cascade. A close association between the oxidative stress and the stimulation of the inflammasome platform has been reported. CNS reactive species of oxygen (ROS) are mostly synthesized by infiltrating macrophages and stimulated microglia. In addition to direct injury to the BBB and myelin sheath, ROS are also known as the main inflammasome stimulators. The inflammasomes are innate system receptors that perceive inflammatory messages coming from infections or from host derived mediators. Several inflammasomes have been found so far but NOD-like receptor pyrin/domain-containing-3

(NLRP3) inflammasome is currently the best known complex involved in the pathogenesis of chronic inflammatory and autoimmune conditions including MS. Briefly, pathogen-associated molecular patterns (PAMPs) or damage-associated molecular patterns (DAMPs) interaction with Toll-like receptors (TLRs) stimulates NF-κB function, promoting the transcription of NLRP3, pro-IL-1β, and pro-IL-18. Subsequent trigger as presence of ROS, potassium efflux, calcium influx or mitochondrial injury, allows oligomerization of the inflammasome complex and subsequent secretion of active IL-1β and IL-18. In addition of being crucial mediators of innate immunity, IL-1β and IL-18 play critical roles instructing Th1 and Th17-types of polarization.

Although there is no treatment for MS yet, the current treatment, which is essentially based on the usage of immunomodulatory agents, can decrease the intensity and number of disease relapses. Alternative and adjunct treatments have been largely assessed, including compounds derived from helminths, medical cannabis and vitamin D. In the last few years, investigations used experimental autoimmune encephalomyelitis (EAE) to assess alternative or adjunct treatments for MS. EAE is applied worldwide as an investigation method to allow a deeper comprehension of MS immunopathogenesis. C57BL/6 mice develop a chronic type of disease known by only one peak

of CNS inflammation and demyelination, whereas SJL/J mice resembles the relapsing-remitting MS (RRMS), presented by periods of stability in between relapses. Considerably, around 85% of the cases develop this type of disease. Both murine models are largely used to investigate new prophylactic and therapeutic approaches, but SJL/J mice also has role in the development of treatments to decrease the intensity or rate of relapses.

Many of the treatments currently elected for MS treatment were assayed and validated by pre-clinical assessments carried out with the EAE model. Despite the variety of treatments, some cases do not respond to available treatments and the global inhibition of the immune system can stimulate collateral effects as increased susceptibility to infections.

In the view of MS immunopathogenesis, a product with the potential to control ROS synthesis and/or inflammasome stimulation and capable of reaching the CNS are thought logical to be tested. From this perspective, selenium (Se) is a micronutrient crucial for normal physiological mechanisms that is endowed with antioxidant and anti-inflammatory characteristics. It is involved in the mitochondrial dynamics, calcium channels and free radical regulation, that are all mechanisms implicated in MS pathogenesis. Moreover, Se usage can make a regulatory phenotype in Th cells, decrease the expression of adhesion factors as E-

selectin and polarize macrophages to an anti-inflammatory function. Se usage has already been effective in the control of Parkinson and other possible autoimmune disorders. Its positive effects depend mainly on its incorporation into proteins that will mediate the stimulation, proliferation and differentiation of innate and adaptative immune components. Se-containing amino acids, such as selenocysteine and selenium-methionine, can provide direct antioxidant effects and can also be incorporated into the production of antioxidant enzymes, as glutathione peroxidase, thioredoxin reductases and methionine sulfoxide reductases. Synthetic compounds containing organic Se resemble the effects of human selenized proteins, including antioxidant function.

3- PATHOPHYSIOLOGY OF ORAL LICHEN PLANUS

The mouth is a representor of health or disease, a sentinel or early warning system. The oral cavity may well be thought as a window to the body because oral presentations accompany many systemic disorders. In many instances, oral involvement precedes the appearance of other manifestations or plaques at other areas. Most of the oral mucosa is derived embryologically from an assessment of the ectoderm and perhaps not surprisingly, this, like other similar orifices, may become involved in diseases that are primarily correlated with the skin. Lichen planus (LP) is a chronic mucocutaneous disease of the stratified squamous epithelium that involves oral and genital mucous membranes, skin, nails, and scalp. Oral lichen planus (OLP) is known as the mucosal counterpart of cutaneous LP. It is constructed from the Greek word "*leichen*" means tree moss and Latin word "*planus*" means flat.

Historical Background

The designation and description of the pathology were first reported by the English physician Erasmus Wilson in 1866. He reported this to be the same disease as "lichen ruber," previously reported by Hebra and described the disease as "an eruption of pimples remarkable for their color, their figure, their structure, their habits of isolated and aggregated development." In 1892, Kaposi stated the first clinical variant of the disease, lichen ruber pemphigoides. In 1895, Wickham reported the characteristic reticulate white lines on the surface of LP papules, today known as Wickham striae. Darier is credited with the first formal report of the histopathological alterations related to LP.

Epidemiology

The exact incidence and prevalence of LP is unclear. In 1895, Kaposi reported the disease as "rather frequent" with 25 to 30 patients presenting annually. In the United States, the incidence of LP is indicated to be approximately 1% of all new cases seen at health care clinics. The Indian subcontinent has an especially high incidence of disease. LP is estimated to involve 0.5% to 2.0% of the general population, the prevalence being ranging from 0.5% selectively in Japanese people, 1.9% in Swedish population, 2.6% in Indian population and 0.38% in Malaysia (relatively uncommon). The relative risk

is 3.7% in subjects with mixed oral habits, lowest (0.3%) in non-users of tobacco and highest (13.7%) among those who smoked and chewed tobacco. This disease has most often been shown in middle-aged cases with 30-60 years of age and is more frequent in females than in males. OLP is also reported in children, although it is rare. It affects all racial population. However, according to some literature white subjects are five and a half time more likely to develop this disease compared to other races. OLP occurs more commonly than the cutaneous form and tends to be more persistent and more resistant to therapies.

Etiology

Although the exact etiology of this disease is still unclear, but some factors are correlated with it. These are as follows:

Genetic Factors

Familial patients are rare. A correlation has been found with HLA-A3, A11, A26, A28, B3, B5, B7, B8, DR1, and DRW9. In Chinese cases, an increase in HLA-DR9 and Te 22 antigens has also been repotted.

Dental Materials

A great many materials frequently used in restoration managements in the oral cavity have been found as triggering elements for OLP, including silver amalgam, gold, cobalt, palladium, chromium and even non-metals such as epoxy

resins (composite) and prolonged application of denture wear.

Pharmaceutical Factors

Oral lichenoid drug reactions may be stimulated by systemic agents including NSAIDs, beta blockers, sulfonylureas, some angiotensin-converting enzyme (ACE) inhibitors, and some antimalarials, contact allergens including toothpaste flavorings, particularly cinnamates.

Infectious Factors

OLP has been proposed to be associated with bacteria such as a Gram-negative anaerobic bacillus and spirochetes but this has not been approved. Some of the investigations show the role of *Helicobacter pylori* (HP) in the etiology of OLP. However, no evidence of its role has been found in OLP in some recent investigations. Recently, it has been shown in some studies that few periodontopathogenic microorganisms are also correlated with the cases of OLP. Role of candida infection is conflicting in OLP. Several investigations have revealed an increased rate of candida species. However, some investigations show that there is an insignificant correlation between candida infection and OLP. OLP has been shown to be correlated with different viral agents such as human papilloma virus (HPV), Epstein Barr virus (EBV), human herpes virus 6 (HHV-6) and human immunodeficiency virus (HIV). Epidemiological findings from different

investigations worldwide strongly propose that hepatitis C virus (HCV) may be an etiologic factor in OLP. In OLP, HCV replication has been shown in the epithelial cells from mucosa of LP plaques by reverse transcription/polymerase chain reaction or *in-situ* hybridization; also, HCV-specific CD4 and CD8 lymphocytes were shown in the subepithelial band. These probably propose that HCV-specific T lymphocytes may have a role in the pathogenesis of OLP. The putative pathogenetic association between OLP and HCV still remains conflicting and requires a lot of prospective and interventional investigations for a better clarification.

Autoimmunity

OLP may occasionally be correlated with autoimmune diseases such as primary biliary cirrhosis, chronic active hepatitis, ulcerative colitis, myasthenia gravis, and thymoma.

Bowel Disease

Bowel disorders occasionally reported concomitant with OLP include coeliac disease, ulcerative colitis and Crohn's disease.

Food Allergies

Food and some of food additives such as cinnamon aldehyde have been shown to be correlated with OLP.

Stress

One of the most important factors responsible for

the development of OLP is anxiety and stress. Some of the investigations in literature show the role of the psychological stress in the etiology of OLP.

Habits

Although most cases with OLP have no increased rate of cigarette smoking, it has been proposed to be an etiological factor in some Indian populations. Betel nut chewing is also more common in Indian cases with OLP than in those without.

Trauma

Trauma as such has not been reported as an etiological factor in LP, although it may be the mechanism by which other etiological factors act their roles.

Diabetes and Hypertension

Investigations have shown that both diabetes mellitus (DM) and high blood pressure are correlated with OLP.

Malignant Neoplasms

LP has been found on the skin and/or mucosae of cases affected by a range of different neoplasms such as with breast cancer and metastatic adenocarcinoma.

Miscellaneous Correlations

OLP has occasionally been correlated with other disorders such as psoriasis, lichen sclerosis, urolithiasis, agents used to treat gall stones,

Turner's syndrome.

Pathogenesis

OLP is a T-cell mediated autoimmune disorder in which the auto-cytotoxic CD8 + T cells stimulate apoptosis of the basal cells of the oral epithelium.

An early cause in the disease mechanism affects keratinocyte antigen expression or unmasking of an antigen that may be a self-peptide or a heat shock protein. Following this, T cells (mostly CD8+, and some CD4 + cells) migrate into the epithelium either due to random encounter of antigen during common surveillance or a chemokine-mediated migration toward basal keratinocytes. These migrated CD8 + cells are stimulated directly by an antigen binding to major histocompatibility complex (MHC)-1 on keratinocyte or through activated CD4 + lymphocytes. Moreover, the number of Langerhans cells in OLP plaques is enhanced along with upregulation of MHC-II expression; subsequent antigen presentation to CD4 + cells and interleukin (IL)-12 stimulates CD4 + T helper cells which stimulate CD8 + T cells through receptor interaction, interferon γ (INF-γ) and IL-2. The stimulated CD8 + T cells in turn kill the basal keratinocytes through tumor necrosis factor (TNF)-α, Fas-FasL-mediated or granzyme B-stimulated apoptosis.

A Cytokine-Mediated Lymphocyte Homing Mechanism

In OLP, there is enhanced expression of the vascular adhesion molecules (VAM), that is, CD62E, CD54, and CD106, by the endothelial cells of the sub-epithelial vascular plexus. The infiltrating lymphocytes produce reciprocal receptors (CD11a) to these VAM. Some of the mediators that are responsible for the upregulation of the VAM are: TNF-α, IFN-γ and IL-1.

Nonspecific mechanisms like mast cell degranulation and MMP-1 stimulation more aggravate the T-cell accumulation, BM disruption by mast cell proteases and keratinocyte apoptosis. The normal integrity of the BM is conducted by a living basal keratinocyte due to its production of collagen 4 and laminin 5 into the epithelial BM zone. In turn, keratinocytes need a BM-derived cell survival signal to prevent the initiation of its apoptosis. Apoptotic keratinocytes are no longer able to conduct this activity, which leads to disruption of the BM. Again, a non-intact BM cannot send a cell survival message. This sets in a vicious cycle which associates with the chronic nature of the disease.

The matrix metalloproteinase (MMP) have principally role in tissue matrix protein degradation. MMP-9, which cleaves collagen 4, along

with its activators is upregulated in OLP lesional T cells, leading to increased BM disruption.

RANTES (Regulated on Activation, Normal T-cell Expressed and Secreted) is a member of the CC chemokine family which has a crucial role in the recruitment of lymphocytes and mast cells in OLP. The recruited mast cell undergoes degranulation under the influence of RANTES, which secretes chymase and TNF-α. These substances upregulate RANTES release by OLP lesional T cells.

Weak production of transforming growth factor (TGF)-β1 has been shown in OLP. TGF-β1 deficiency may increase the risk of autoimmune lymphocytic inflammation. The balance between TGF-β1 and IFN-γ determines the level of immunological function in OLP plaques. Local overproduction of IFN-γ by CD4 + T cells in OLP plaques reduces the immunosuppressive effect of TGF-β1 and increases keratinocyte MHC class II expression and CD8 + cytotoxic T-cell function.

4- ROLE OF SELENIUM IN ORAL LICHEN PLANUS

Oral lichen planus (OLP), one of the mixed red and white plaques affecting the oral mucosa, is a chronic inflammatory mucocutaneous disorder with immune-mediated pathogenesis that can involve extraoral areas. The overall incidence of OLP was shown to be up to 2.2% worldwide. There are six clinical types of OLP that can occur individually or combined together: reticular, plaque-like, atrophic, erosive/ulcerative, papular, and bullous. Clinical manifestations of OLP range from totally asymptomatic plaques to very painful ones, depending on the clinical variant(s) encountered in each case; cases with non-erosive variants (reticular, papular, and plaque subtypes) are commonly asymptomatic, whereas those suffering from atrophic, erosive, and bullous subtypes of OLP commonly suffer from variable degrees of pain and need treatment. Besides pain and debilitating outcomes on quality of life encountered in OLP cases due to erosions and

ulcerations, the development of oral squamous cell carcinoma is the most important complication of OLP. The management of symptomatic OLP (atrophic, erosive, and ulcerative lesions) is essential, to alleviate pain and improve the quality of life. A state of oxidative stress (OS) has been proposed to have role in the pathogenesis of OLP and its malignant transformation potential risk. However, a cause–effect association between oxidative stress and appearance of OLP has not been well approved till now. OS plays a pivotal role in the appearance of the common histopathologic features of OLP by mediating basal keratinocyte apoptosis and recruitment of T lymphocytes and other inflammatory cells to the OLP plaques. This could be associated with the ability of reactive oxygen species (ROS) to maintain an inflammatory condition in OLP plaques by upregulating pro-inflammatory mediators (tumor necrosis factor α [TNF-α]) which play a critical role in recruitment of T lymphocytes, activating members of the matrix metalloproteinase (MMP) family that degrade the basement membrane, and changing intracellular signaling molecules that are responsible for apoptosis. On the other hand, in OLP, the inflammatory cellular infiltrate, which has mainly CD4+ lymphocytes, is a well-known source of ROS. In high levels, ROS intensify the inflammatory mechanisms in the presence of T lymphocytes and destroy the lipid membrane of keratinocytes, resulting in more local tissue destruction and more

production of ROS, that is, a vicious cycle. Many antioxidants have been assessed for the management of OLP, in order to counteract the increased levels of ROS detected in OLP plaques, introduce a definitive treatment for OLP plaques, and reduce side effects of corticosteroids, which are the 1st line of management for OLP. However, more randomized clinical trials on larger sample sizes of patients should be carried out to investigate clinical efficacy. Selenium (Se), a crucial trace element, is a well-known potent antioxidant that is identified naturally in the human body. Se derives its nutritional health effects from 25 selenoproteins that have selenocysteine (SeC) at their active center, with glutathione peroxidase and thioredoxin being the most common. Through selenoproteins, Se activities against oxidative stress, slows down the aging process, reduces viral infections, plays critical roles in chemoprevention through its involvement in DNA modulation, and has metabolic characteristics in the human body along with thyroid hormone metabolism, and immune system change. An investigation performed in 2011 on Iraqi cases reported that levels of serum Se were negatively associated with OLP disease chronicity and severity.

Selenium has been previously suggested as an alternative therapy for OLP in two clinical trials, but to date its efficacy has never been investigated as a single treatment in the management of OLP cases. In 2011, a study assessed the efficacy

of IMOD, an Iranian immunomodulator drug consisting of selenium, carotene, and flavonoids, in the management of 30 cases suffering from OLP. This Iranian immunomodulator drug was shown to be effective in the management of OLP plaques. Another clinical trial performed on 30 cases with erosive OLP in 2015 assessed the effectiveness of selenium ACE (selenium plus vitamins A, C, and E) as an adjunctive treatment to the conventional management modality of OLP (topical corticosteroids and antifungal). Selenium ACE was shown to be successful as an adjunctive treatment in OLP cases.

5- PATHOPHYSIOLOGY OF PSORIASIS

Psoriasis is a chronic and relapsing disease involving 1–3 % of the world's population. It results from the interaction between genetic factors and a large spectrum of environmental factors that stimulate the development of skin plaques. The role of lifestyle habits, such as smoking, diet, and alcohol usage, has been given significant attention in recent years. Alcohol consumption is proposed to be one of the risk factors for the disease and also may be correlated with the course of psoriasis and affect its treatment. The metabolism of ethanol has role in lipid peroxidation and decrease of natural antioxidants, therefore increasing the toxic effects of free radicals. An impaired antioxidant skin barrier may lead to an increase of free oxygen radicals in psoriatic lesions. Some oxygen metabolites are highly reactive, whereas others, such as hydrogen peroxide, are less reactive and have the potential to diffuse easily across the cell membranes.

They may, therefore, impose oxidative changes upon the membrane. After reaching the inside of the cells, they will stimulate the cellular antioxidant defense barriers. Oxidative stress develops within the cells after its defenses are depleted, and oxidative changes will be evident. Increased reactive oxygen species (ROS) and lipid peroxidation have a critical role in the inflammatory mechanisms. As such, they are reported in many dermatologic diseases, for example, atopic dermatitis, psoriasis, vitiligo, acne vulgaris, pemphigus vulgaris, and alopecia areata. Selenium is considered to have immune-modulating and antiproliferative characteristics. It can affect immune response by altering the expression of mediators and their receptors or making immune cells more resistant to oxidative stress. The antiproliferative characteristics of selenium compounds are related directly to their toxicity. As an integral part of thioredoxin reductases and other antioxidant enzymes, such as glutathione peroxidases, selenium has role in protection of the skin against harmful environmental factors, e.g., in the prevention of ultraviolet-induced cell injury and death. On the other hand, it has been shown that selenite and selenocystamine could trigger apoptosis in keratinocytes because of their prooxidant catalytic function. Current findings about changes of selenium level and activity of selenium-dependent enzymes in blood of cases with psoriasis are conflicting.

Psoriasis and Oxidative Stress

The human body is equipped with a complete arsenal of barriers against external and internal invasions. Those against ROS, such as superoxide, peroxide, and hydroxyl radical, are essential in inflammatory processes, where they participate in physiological mechanisms, such as the arachidonic acid cascade and phagocytosis. The levels of ROS are kept under strict control by the function of a complex defense system including antioxidant enzymes, such as superoxide dismutase and GSH-Px, and by nonenzymatic species such as vitamins C, E, A, or βcarotene. There is a large body of findings that poly- and mononuclear phagocytes are essentially involved in host defense. In addition to removing circulating immune complexes, debris, and necrotic cells, they effectively attack invading microorganisms. Monocytes and macrophages have additional important activities as antigen-presenting and cytokine-releasing cells, whereas polymorphonuclear phagocytes are noted to represent the first line of defense in terms of ingesting and killing potential risk factors. During particle ingestion, granulocytes and macrophages synthesize large amounts of highly reactive molecules, mainly oxygen radicals, therefore resulting in a considerable increase in energy and oxygen usage. The sharp increase in usage of

molecular oxygen during phagocyte stimulation does not reflect an increase in aerobic energy synthesis as primarily assumed (a “respiratory burst”), but is the result of an increased production of highly reactive oxygen species. Neutrophils and other phagocytes manufacture superoxide by the one-electron decrease of oxygen at the expense of NADPH. Most of the superoxide radical reacts with itself to produce hydrogen peroxide. From these factors, a large number of highly reactive antimicrobial oxidants are produced, including hypochlorous acid, which is synthesized by the myeloperoxidase-catalyzed oxidation of Cl− by H2O2; hydroxyl radical (OH·), synthesized by the decrease of H2O2 by Fe2+ or Cu+ ; peroxynitrite (ONOO−), formed by the reaction between O2− and NO− ; and many others. These reactive oxidants are produced for the aim of killing invading microorganisms, but they also inflict injury on nearby tissues and seem to be of pathogenic importance in a large number of disorders including psoriasis. The skin conducts its role as an interface between the human body and its surrounding environment, therefore the skin is constantly exposed to both endo- and exogenous prooxidants, resulting in the production of harmful oxidant species. Oxidative stress and the production of excessive free radicals have been associated with skin inflammation in psoriasis. Cases with this condition have decreased plasma levels of β-carotene and α-tocopherol as well as a decrease in

serum selenium and high levels of malondialdehyde, a marker of lipid peroxidation in the plasma and red blood cells. There are literature results that propose that topical usage or oral consumption of antioxidants, such as vitamin E and selenium, is proposed as preventive treatment for the psoriasis.

6- ROLE OF SELENIUM IN PSORIASIS

Selenium Deficiency and Psoriasis

The selenium level in psoriasis cases is lower than that of healthy subjects, but there are few investigations on its role in the pathogenesis of the disease. An impaired antioxidant barrier in skin may lead to a rise of free oxygen radicals in psoriatic lesions. Thionine may regulate immunologic mechanisms of the disease by increasing the number of CD4+ T cells in reticular dermis within psoriatic lesions. Previously published preliminary findings revealed that selenium level and selenium-dependent GSH-Px function in erythrocytes are higher in males with psoriasis, lasting no longer than 10 years than in those with the disease lasting 3 years or more. Kadry and Rashed, using plasma and tissue samples from 20 cases with psoriasis and 10 healthy subjects, assessed the levels of overexpression of

osteopontin and selenium in psoriasis, and their association with metabolic condition in cases to find a possible association between these markers and comorbidities found. They found that the plasma selenium levels were lower in cases with psoriasis than in healthy subjects and showed that overproduction of osteopontin and low plasma selenium levels are predictable factors for occurrence of psoriasis. Another study evaluated the effect of selenium usage on the efficacy of narrowband ultraviolet B (UVB) management in cases with psoriasis and assessed the association between serum levels of selenium, sTNF-R1, and C-reactive protein (CRP) during management in these cases. They managed 37 cases by administering 200 μg Se/day as thionine or placebo in addition to UVB radiation five times a week. The cases were assessed by evaluating the psoriasis area, severity index, and serum levels of selenium (in micrograms per liter), sTNF-R1 (in nanograms per milliliter), and CRP (in milligrams per liter) at the initiation of treatment and at 2 and 4 weeks of treatment as well as 1 month after the end of management. Their findings approve that the sTNF-R1 and CRP levels were increased in active psoriasis, and that 1-month usage with thionine does not help as adjuvant treatment in cases with psoriasis.

Low serum selenium levels in cases with psoriasis, and that management with thionine for 4 weeks failed to give a positive clinical result to topical treatment in these cases have been recently

reported. There have been findings indicating the association between plasma selenium level acute-phase response marker in cases with different inflammatory diseases, including psoriasis, and malignancies. Ultraviolet B irradiation is a potent trigger of TNF-α synthesis and secretion by human keratinocytes in vitro. However, UVB can reach the upper dermis and stop endothelial cells. Selenium compounds prevent in vitro the secretion of UV-induced proinflammatory mediators (interleukin-6, interleukin-8, and TNF-α) by inhibition of mRNA for these mediators in human keratinocytes. It also has been revealed that preincubation of murine keratinocytes for 24 h with thionine or sodium selenite (thionine is more effective) leads to inhibition of UV-induced interleukin-10 expression in these cells. In contrast, an investigation showed no significant alterations in serum levels of interleukin-10 and TNF-α after three irradiations with narrow-band ultraviolet in five cases with psoriasis. Another investigation showed selenium levels in plasma and whole blood of 64 cases with psoriasis and in agematched healthy subjects and showed no significant differences between these study groups. British investigators found no differences in selenium absorption or atopic dermatitis and healthy subjects, but the exchangeable total body selenium was lower in psoriasis cases than in healthy controls. Findings of case–control investigations showed that low selenium level can be a risk factor for some

types of neoplasm and, therefore, proposed that depressed selenium condition also can be a risk factor for psoriasis, a disease known by cell hyperproliferation. As it was reported above, experiments on selenium usage in psoriatic cases revealed that selenium in inorganic forms, but not as thionine can achieve clinical improvement. Another study assessed the immunological and redox markers in a group of psoriatic cases managed with efalizumab. They showed that the activities of GSH-Px and glutathione-s-transferase in granulocytes were considerably increased, and catalase was reduced exclusively in nonresponders vs complete or partial responders.

Role of Selenium Supplementation on Treatment of Psoriasis

As stated before, TNF-α is a mediator critical for stimulating and maintaining psoriatic plaques. A recent study assessed the effect of selenium consumption on soluble TNF-α receptor type 1 and topical treatment in psoriasis cases. They showed that 4-week consumption of thionine was ineffective in the acceleration of remission of psoriatic plaques. Previous investigations showed no significant differences in selenium absorption or excretion between psoriasis cases and controls after intravenous and oral consumption of SeMet, but the total exchangeable body selenium was lower

in psoriasis cases. Another investigation proposed that insufficient dietary intake of selenium in a Polish population and in psoriasis cases, together with excessive desquamation or poor selenium absorption, may be additional causes for low plasma selen level. Consumption of thionin in a Finnish case with high baseline serum selenium level led to a significant increase in the number of CD4+ T cells and in nonsignificant enhancements in CD11c + and CD1+ cells within the reticular dermis of psoriatic plaques. In an investigation, 69 cases were supplemented daily with either 600 μg of selenium-enriched yeast, 600 μg of selenium-enriched yeast plus 600 IU of vitamin E, or placebo for 12 weeks. They showed that neither supplementation regimen decreased the severity of psoriasis or made side effects. A recent study evaluated the effects of oral selenium (400 μg) on expression of phosphorylated p53, Fas, Bcl-2, Bax, and oxidized guanosine and Langerhans and sunburn cells counts. They showed that oral consumption of sodium selenite did not significantly protect human skin against alterations in marker proteins correlated with ultravioletinduced injury during TL01 phototherapy. Another study showed for the first time that the combination of conventional treatment and consumption of vitamin E, coenzyme Q10, and selenium led to an improvement in the clinical condition of cases with severe psoriasis as well as a decrease in oxidative stress. Supplementation using inorganic forms of selenium

(sodium selenite and selenate) is also shown to result in clinical improvement in cases with psoriasis.

7- PATHOPHYSIOLOGY OF RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is a systemic inflammatory disease that mainly affects articular inflammation. Approximately 0.5% to 1% of the population worldwide is affected by the disease, which may lead to joint damage and disability. Moreover, approximately 40% of cases present with extra-articular presentations, complicating disease progression and mortality. Autoantibodies isolated from patient serum and synovial fluid play important roles in the pathogenesis of RA. According to the literature, 70–80% of cases with RA are positive for autoantibodies (autoAbs), such as rheumatoid factors (RFs) and anti-citrullinated protein antibodies (ACPAs). Although they are not essentially present in all cases, antibodies reacting with self-antigens, including immunoglobulins and posttranslational modified (PTM) protein epitopes, have been shown for over 80 years to exist in RA.

RFs were the first auto-Ab found in RA. They were reported by Waaler in 1940 as factors with hemagglutinating function in the serum of a case with RA and named by Pike in 1949 for their correlations with RA. Subsequent investigations have shown that the presence of RF is correlated with a more severe and erosive RA phenotype. Compellingly, using an analytical ultracentrifuge method, Kunkel and his colleagues later found that RF is an antibody to antigen–antibody complexes. Furthermore, scientists reported that RF targets antigenic epitopes within the crystallizable fragment (Fc) region of immunoglobulin G (IgG) and is found in different isotypes. Although the specificity of RF for RA is only about 60–70% and the conditions needed to break tolerance to IgG are not yet fully known, RF was included in the 1987 ACR classification criteria for RA and noted as the paradigm of auto-Ab clinical importance in RA.

The detection of ACPAs can be traced back to 1964, when Nienhuis and Mandema showed anti-perinuclear factors within the sera of RA cases. Approximately 30 years later, Hoet and colleagues reported them with regard to their reactivity toward citrullinated peptides. Following the discovery of multiple protein candidates eligible for peptidyl arginine deiminase (PAD) citrullination, “RA citrullinome”, referring to the collection of hundreds of citrullinated proteins found in the serum and synovial fluid of RA cases, was

reported to the field of RA investigation in recent decades. With its superb diagnostic specificity, immunopathogenic relevance and excellent clinical associations, ACPAs were considered in the 2010 American College of Rheumatology (ACR)/ European League Against Rheumatism (EULAR) RA classification criteria. Alongside the classical RA auto-Ab RF, ACPA was also noted as a pivotal hallmark of the disease in the past decade.

In recent years, growing studies has approved that proteins resulting from PTMs, other than citrullination, are also capable of stimulating autoimmune reactions important for the development of RA. Indeed, autoantibodies against carbamylated protein (anti-CarP Ab), acetylated proteins, malondialdehyde, malondialdehyde-acetaldehyde and other posttranslated modified epitopes, such as anti-hinge antibodies, have attracted considerations due to their clinical importance and their potential application in refining RA diagnosis and treatment. Among them, anti-CarP Ab, reported in 2011, is maybe one of the best assessed anti-PTM autoantibodies.

Genetic Risk Factors

Genetic background is a critical factor affecting the development of RA. There is an estimated 40–50% familial risk among seropositive RA cases with strong risk noted in first-degree relatives. In addition to the high association for RF reported

among identical twins with RA, a number of investigations have shown differences in genetic components between RA cases positive or negative for RF. However, controversies were reported, as some investigations showed that RA cases, regardless of the presence of RF, may harbor similar human leukocyte antigen (HLA) susceptibility alleles.

A conserved amino acid sequence at positions 70 and 74 within the HLA-DRB1 molecule, namely, the “shared epitope (SE)”, is a pivotal genetic risk factor for ACPA-positive RA. Moreover, a dose effect of SE alleles on risk of RA among ACPA-positive RA cases was also reported in literature. Utilizing paired samples of presymptomatic subjects, Kissel and others recently showed that SE alleles are correlated with ACPA Fab glycosylation in the predisease phase. In addition to SE, the protein tyrosine phosphatase nonreceptor type 22 risk allele shows a synergistic action along with the SE alleles. In addition, single-nucleotide polymorphisms and long noncoding RNAs are correlated with the presence of ACPAs in RA cases. Tumor necrosis factor (TNF) receptor-associated factor 1 C5 region, TNF-α-induced protein, CD40, C-C motif chemokine ligand 2, antisense noncoding RNA in the INK4 locus, and peptidyl arginine-deiminase 4 are some of the well-documented genetic factors associated with ACPA-seropositive RA.

In contrast, the genetic risk for anti-CarP Ab is less

reported in literature. While HLA-DR3 is shown more commonly in subjects with ACPA-negative RA than in the healthy subjects, HLA-DR3 is also correlated with RA patients positive for anti-CarP Ab and negative for ACPA.

Tobacco Smoking

The importance of tobacco smoking as a risk factor for RA has been well established. Interestingly, although smoking has been correlated with all seropositive RA, it is approved to be correlated with the presence of RF, even in the absence of RA. Large population investigations and twin reports have shown the correlation between smoking and ACPA positivity, with a dominant risk being in subjects positive for SE. Aside from the inflammatory alterations in the lungs subsequently causing activation of PADs, in the setting of SE, smoking creates a risk of high ACPA levels and proposes a distinct mechanism of ACPA synthesis different from that of RF.

Furthermore, smoking is known to promote carbamylation in cases with RA. While smoking has been shown to promote MPO-mediated conversion of thiocyanate to cyanate, the level of anti-CarP Ab, however, was not considerably higher. Perhaps critical factors (genetic or environmental exposures) other than carbamylation alone are needed for the stimulation of anti-CarP Ab.

Microbial Triggers

As RF is physiologically critical to increase immune complex clearance, to assist B cell uptake for antigen presentation and to facilitate complement fixation, an increased level of RF has been found in subjects with chronic or indolent infection, including hepatitis B or C virus infection or infective endocarditis. Nonetheless, the synthesis of RF under such conditions commonly stops following resolution of the infection. Due to the action of bacterial pore-forming virulence and calcium ionophores in stimulating calcium influx and producing nontolerized neocitrullinated epitopes, the role of periodontitis-causing bacteria and intestinal microbiota in ACPA-related RA was recently reported. Although infection is likely to stimulate the release of MPO from activated neutrophils during infection episodes, no direct evidence has linked acute infection to anti-CarP Ab-positive RA, and the risk of infection in autoantibody-mediated RA is still under evaluation.

8- ROLE OF SELENIUM IN RHEUMATOID ARTHRITIS

RA is a chronic disease with systemic inflammatory condition that primarily affects the small diarthrodial joints of the hands and feet, which may result in disability. Increased levels of oxidative stress biomarkers and decreased levels of blood antioxidants in cases with RA corroborate the fact that oxidative stress and Reactive Oxygen Species (ROS) play a critical role in the physiopathology of RA. Due to the crucial role of selenium in the endogenous antioxidant enzyme glutathione peroxidase, selenium deficiency is proposed to be critical in the pathogenesis of RA. A low selenium concentration has been shown in RA, which results in increased levels of peroxidation products in serum and synovial fluid.

Investigators assume that reduced levels of selenium in RA may be associated with the redistribution of selenium from plasma into tissues as a defense mechanism in severe inflammatory disorders. Another study reported that the function

of glutathione peroxidase was considerably lower in RA cases compared to that in controls. Therefore, with regard to the crucial role of selenium as a major component of glutathione peroxidase enzyme, the lower function of this enzyme may be due to selenium deficiency. A preliminary investigation revealed that selenium consumption for three months considerably decreased pain and joint involvement in RA. The consumption of sodium selenite for RA cases alleviates some manifestations of the disease and results in the improvement of immunological markers. The decreased inflammatory response in cases who received selenium also improved swelling and stiffness of the joints, as well as the severity of pain. Another investigation suggested the consumption of sodium selenite in the treatment of RA, especially in cases with subclinical hypothyroidism. Evidence proposes that sodium selenite usage could be an effective method for the management of articular syndrome and could decrease inflammation and autoimmune presentations of RA, which is important to prevent RA progression. Although several investigations propose that selenium is an effective nutrient for treatment of RA, some investigations propose that selenium does not considerably affect RA, and alters in rheumatoid severity or disease progression occur independently from selenium level. These conflicting results could be attributed to differences in the investigation design or the chemical form of selenium (e.g.,

selenomethionine, selenite, selenite). Therefore, it is thought that more investigations concerning the effects of selenium consumption on RA activity should be carried out to investigate the exact responses of the disease to different types of supplements.

A low plasma selenium content has been shown amongst cases with any of a variety of disorders, including rheumatoid arthritis, although neither the reason for this anomaly nor its possible functional importance are known. The seleno-enzyme glutathione peroxidase has role in the antioxidant defence by reacting with hydrogen peroxide and related compounds. Different oxygen radicals may have role in the pathogenesis of rheumatoid arthritis, and the accumulation of lipid peroxidation products in synovial fluid has been shown. In mammals, selenium is covalently bound commonly in selenocysteine moieties in proteins, and in human tissue glutathione peroxidase is the only selenoprotein hitherto found. In a previous investigation, most of the selenium in human plasma was shown to be located in selenoproteins other than glutathione peroxidase. Few other investigations on selenium loc a I' Ization in human tissue have been carried out, one reason probably being the difficulty in indicating the low selenium levels present in biological material.

9- PATHOPHYSIOLOGY OF CROHN'S DISEASE

Crohn disease (CD) was first reported by Dr Burrill B. Crohn and colleagues in 1932.1 Along with ulcerative colitis (UC), it is considered under the spectrum of chronic idiopathic inflammatory bowel disease (IBD). A recent estimate proposes that 1.3% (3 million subjects) of the US population has a diagnosis of IBD. Crohn disease is a chronic disorder with an annual incidence ranging from 3 to 20 cases per 100,000. The median initiation of disease is age 30 years and it has 2 peaks, first between age 20 and 30 years and then a smaller peak around age 50 years.

Crohn disease is known by discontinuous skip plaques involving any part of the gastrointestinal tract from the mouth to the anus. The inflammation is commonly transmural and on pathology granulomas may be present on biopsies. Presenting manifestations are variable but can include diarrhea, abdominal pain, weight loss, nausea, vomiting, and sometimes fevers or chills.

The natural process of the disease is one of periods of remission and flares. There are multiple different types of disease including inflammatory, stricturing, and penetrating. Cases can have 1 or more of these disease phenotypes during the process of their disease, and cases often progress from inflammatory to stricturing or penetrating. Unfortunately, there is no treatment for CD and most cases need at least 1 surgical resection. The aim of medical treatment is to achieve a steroid-free clinical and endoscopic remission with the hopes of preventing complications and surgery. Until recently, treatment options were limited to thiopurines, methotrexate (MTX), natalizumab, and antietumor necrosis factor (anti-TNF) agents. Of late, treatments with novel processes of action have been approved including a gut-selective anti-integrin (a4b7) inhibitor and a monoclonal antibody to IL-12/IL-23.

Environmental Risk Factors

Crohn disease seems to be initiated by changes in the gut microbiome or disruption in the intestinal mucosa. Cases with IBD often Crohn disease seems to be stimulated by changes in the gut microbiome or disruption in the intestinal mucosa. Cases with IBD often have a dysbiosis that leads to a decrease in the diversity of the gut microbiome. Although the literature surrounding the specifics is evolving, the exact process by which changes in the gut

microbiome predispose to CD is still not fully known. Gastrointestinal infections, nonsteroidal anti-inflammatory drugs, and antibiotics have all participated in the development of IBD. However, none of these correlations has been substantiated with large epidemiological investigations. In one investigation, cases with enteric infections from salmonella or campylobacter had an increased risk of developing IBD within the first year of their disease. Furthermore, sustained consumption of nonsteroidal anti-inflammatory drugs, especially in women, may increase the risk of IBD. Antibiotic exposure early in life has also been correlated with an increased risk of developing CD. In women, both hormone replacement treatment and oral contraceptives may increase the risk of IBD. The best-assessed environmental risk factor, cigarette smoking, doubles the risk of developing CD. This risk is enhanced in both current and former smokers. Investigations have also proposed that appendectomy may increase the risk of CD but this may be due to exact classification of appendicitis which in truth was actually CD. The role of diet in the development of CD also remains unknown. Some investigations have proposed that diets high in sugar, omega-6 fatty acids, polyunsaturated fatty acids, total fat, oil, and meat increase the risk of CD whereas a diet high in fiber and fruit reduced the risk of CD. However, more investigations are still required to clarify the role of diet and the risk of developing CD.

Genetic Risk Factors

Although family history does portend an increased risk, only 10% to 25% of cases with IBD have a first-degree relative with the disease. In twin investigations, concordance rates for CD in monozygotic twins range from 20% to 50% compared with 10% in dizygotic twins. Crohn disease is more frequent in cases of Ashkenazi Jewish origin than in non-Jews and is less commonly reported in African Americans or Hispanics. Although genetic risk factors are still being clarified, there are more than 200 genes that have been correlated with the development of IBD. The first gene reported was the NOD2 locus on chromosome 16. Homozygotic alterations at NOD2 have a 20 to 40 times higher risk of developing CD, while being heterozygous increases the risk by 2 to 4 times. A number of other genetic foci affecting multiple different mechanisms (eg, autophagy, adaptive immunity, and epithelial activity) have also been correlated with CD.

Laboratory Testing

Although there is no laboratory assessment that definitely rules out CD or is diagnostic of CD, results on serum and stool assessments can assist with making a diagnosis. Stool investigations should be obtained to rule out other diseases of gastrointestinal manifestations and diarrhea.

Laboratory abnormalities are seen more commonly with a longer duration and more severe disease. Cases may have an anemia from iron deficiency anemia, chronic inflammation, and B12 deficiency. Inflammatory mediators including erythrocyte sedimentation rate and/ or c-reactive protein may be assessed, but normal levels do not rule out CD activity. Multiple evaluations have been assessed to investigate inflammation in the gastrointestinal tract including fecal calprotectin or fecal lactoferrin. However, none of these evaluations is unique to IBD and can be assessed with any intestinal infection or inflammatory condition.

10- ROLE OF SELENIUM IN CROHN'S DISEASE

Inflammatory bowel disease (IBD) primarily includes Crohn's disease (CD) and ulcerative colitis (UC), which are known by chronic and relapsing intestinal inflammation. In newly industrialized regions, the prevalence of IBD is continuously increasing. Except for chronic intestinal inflammation, these two disorder present with distinct clinical and histopathological characteristics. The pathogenesis of IBD has not been assessed in depth. Multiple factors, such as genetic mutations, diet, disordered intestinal microbes, and hyperactivation of immunity, have role in initiation of IBD.

Among these factors, dysfunction of the mucosal immune system is the most crucial in the pathogenesis of CD and UC. Some previous studies has shown some obvious differences in the immune microenvironment, particularly in the T cell differentiation mechanisms, between these two types of IBDs. However, the subjects included in

the distinct investigations have been administered various treatments, such as amino salicylates, steroids, immune modulators or biologic agents, which would have affected their pathological immune mechanisms. Therefore, the pathological characteristics of immune responses in naive IBD remain poorly assessed. The increasing prevalence of IBD in newly industrialized regions is likely correlated with the progress of urbanization and structural alterations in the diet. Current investigations have shown that short-chain fatty acids, tryptophan, and bile acids have role in mucosal immune homeostasis and initiation of IBD. Metabolites are crucial mediators in regulating T cell activity. Metabolic mechanisms synthesize abundant intermediate metabolites and byproducts, such as reactive oxygen species (ROS), which have an critical role in modulating T cell activities and metabolic shifts. ROS level is tightly controlled by the antioxidant system, which includes superoxide dismutases (SODs), catalase (CAT), glutathione peroxidases (GPxs), thioredoxin reductases (TrxRs), and glutathione reductase (GR). Considerably, several nonenzymatic molecules, such as reduced glutathione (GSH), uric acid, and ascorbate, can also have reactions with ROS. However, the correlation of ROS and antioxidant molecules with distinct T cell differentiation and the initiation of IBD remains unknown. Selenium is a crucial trace mineral that is incorporated into proteins to form selenoproteins, which have indispensable roles in

ROS scavenging and redox alterations. Among the 25 selenoproteins found in humans, GPxs and TrxRs are well-known antioxidant enzymes, whereas the physiological activities of other selenoproteins (e.g., selenoprotein W [SELW], SelT, and SelH) remain incompletely known. A few investigations have shown selenium deficiency in subjects with IBD, as shown by reduced selenoprotein P (SePP1) in serum. In a mouse colitis models, selenium deficiency exacerbates intestinal damage and promotes inflammatory mechanisms. However, the specific selenoproteins that change T cell activity in IBD remain poorly evaluated.

Dietary Supplementation with Selenite Alleviates Colitis in Animal Models and Individuals with IBD

In vitro investigations have revealed that consumption of selenium can considerably decrease the expression of IFN-g in Th1 cells. To find out whether selenium has role in Th1 differentiation in vivo, an adoptive T cell transfer-induced colitis model was performed that typically shows predominant Th1 and Th17 cell responses. Recipient Rag1–/– mice were fed a selenium-deficient diet for 4 weeks and then adoptively transferred CD45RBhi CD4+ T cells. During colitis establishment, the recipient mice were fed a

common diet, a selenium-deficient diet, or a sodium selenite-supplemented diet (8 ppm). The selenium-deficient diet clearly stimulated more serious colon inflammation correlated with higher body weight loss. The mice in the selenium-supplemented group revealed the least weight loss and longest colon length among the three groups. Consistently, selenium deficiency resulted in epithelial denudation, and this effect could be rescued by selenium usage. Consistent with the in vitro phenotype, reductions in the total colonic CD4+ T cell population were found and rate of IFN-g+ CD4+ T cells in the selenium-supplemented group. Conversely, selenium deficiency aggravated colitis and enhanced the number of infiltrating Th1 cells in the colon. To evaluate the in vivo activity of SELW in inflammatory disorders, WT and Selenow–/– effector T cells were transferred into Rag1–/– mice that were fed a selenium supplement. The transferred Selenow–/– CD4+ T cells clearly stimulated severe body weight loss and reduced the colon length to the same extent as that in the WT controls. Increased rate of Selenow–/– cells and Th1 cells were found in the colon. These findings more showed the importance that selenium alleviated the initiation of T cell-mediated colitis via SELW. Clinical evidence has shown that subjects with CD also show a low serum selenium level. Therefore, a pilot investigation in subjects with CD and low level of serum selenium was carried out. They were orally used sodium selenite at a dose of 360 mg per day for

8–10 weeks and were followed up weekly by telephone visit. As expected, consumption of selenite partially relieved the clinical manifestations of CD, as indicated by a rapid decline and lower scores in disease function compared with the NT control groups. Colonoscopy revealed improvement of the plaque at the same segment of the colon in subjects with CD after selenite management. The endoscopy score and biomarker findings, including the amounts of calprotectin, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), also showed that selenite supplementation clearly improved the clinical manifestations of subjects with CD. CD4+ IFN-g+ cells were also reduced after selenium consumption compared with those in subjects who did not receive sodium selenite. These results revealed that consumption of selenium improved the colitis outcomes in subjects with CD by inhibiting an excessive Th1 cell-mediated immune response in the colon.

11- ROLE OF SELENIUM IN OTHER AUTOIMMUNE DISEASES

Selenium and Systemic Lupus Erythematosus (SLE)

SLE is a multi-organ autoimmune disorder known by general systemic inflammation with specific physical presentations and increased titer of autoantibodies against double-stranded DNA and other nuclear components. High antibody levels and inflammation lead to tissue injury and involvement of the heart, skin, joints, lungs, blood vessels, kidneys, liver, and nervous system. The exact effect of selenium on SLE cases has not yet been explained. Another study proposed that selenium supplementation has significant effects on natural killer cells function in murine SLE. Moreover, serum levels of selenium in SLE cases have been shown to be lower compared to healthy subjects. It has been shown that increased selenium intake may be effective for SLE cases, however, there is no report about its effects on autoantibody synthesis and disease progression. Based on the investigations presented here, it is thought that

a positive association may exist between serum selenium deficiency and higher titers of SLE-specific antibodies. However, due to insufficient evidence about selenium usage in SLE cases, the possible therapeutic role of selenium is unclear. More detailed investigations in the future could show the effect of selenium usage to alleviate SLE presentations.

Selenium and Sjögren Syndrome

Sjögren syndrome is a systemic disease with an autoimmune nature. The lymphocytic infiltration of the exocrine glands is an important presentation of the disease. This results in dryness of the eyes and mouth due to inflammation and resultant pathology of the lacrimal and salivary glands. Investigations about the effect of selenium on Sjögren syndrome reveal that serum selenium value is low in untreated cases, especially in older cases. Moreover, a former investigation showed that the management of Sjögren syndrome cases with selenium in combination with vitamin E halted disease progression for several years in some patients, but not in all cases. Although investigations showed that selenium level is low in these cases, there is insufficient evidence regarding the effect of selenium on this syndrome. Therefore, an exact conclusion cannot be made at the moment. More investigation regarding the probable anti-

inflammatory effect of selenium in preventing the progression of this condition are needed.

Selenium and Behçet's Disease

Behçet's Disease (BD) is a chronic, sever, and inflammatory disorder known by recurrent oral aphthous ulcers, genital ulcers, uveitis, and skin plaques. For the first time, it has been shown that selenium deficiency impedes the humoral immune mechanism in BD. Investigations showed that serum selenium level in BD cases was lower compared to healthy subjects. In contrast, it has been reported that levels of selenium in BD cases with ocular involvement is higher than healthy subjects. A proteomic analysis of autoimmunity in BD revealed that 16% of cases with uveitis were positive for the anti-selenium binding protein (SBP) antibody. It has been reported that autoimmunity reaction against the retinal SBP may have role in the pathogenesis of uveitis in these cases. Therefore, it is thought that higher levels of selenium in BD cases with ocular involvement is associated with autoimmunity against the retinal SBP. Although serum selenium level has been assessed, the effect of selenium administration in the management of BD cases is not clear. More investigations on the effect of selenium supplement in these cases could increase our knowledge about BD treatment strategies.

Selenium and Scleroderma (Systemic Sclerosis)

Scleroderma is a rare connective tissue disease with unclear pathogenesis. It presents by autoimmunity mechanisms and excessive evidence of collagen and extracellular matrix components. The early phase of the disease is known by active inflammation and is potentially reversible. Micronutrient antioxidants' level reveals reduced levels of scleroderma, which is commonly associated with low selenium level. In support of this results, some studies revealed low levels of glutathione peroxidase in cases with scleroderma. In another investigation, treatment of cases with 0.2 mg of selenium as Na2SeO3 and 10 mg of tocopheryl succinate enhanced glutathione peroxidase levels and resulted in desired clinical outcomes. Therefore, investigations propose a positive association between disease activity and serum selenium level. Accordingly, it could be found that sufficient selenium may be effective for the attenuation of scleroderma progression. Low serum levels of selenium in some autoimmune disorders was reported. Selenium supplementation has positive effects in the treatment of RA, and scleroderma. Selenium usage decreases the incidence and severity of certain autoimmune disorders through the maintenance of thyroid activity and the anti-inflammatory effect of selenium. Since this issue is of clinical

significance, it can be noted in potential nutrition interventions and have a positive effect on some autoimmune disorders. One of the main limitations of this investigation was the lack of efficient clinical evidence to evaluate the effect of selenium supplementation on autoimmune disorders. Despite the fact that the included papers were assessed by one reviewer and cross-checked by another investigator, still, publication bias could be another limitation of this investigation. Although there is strong evidence on the effectiveness of selenium usage on RA, more strong clinical findings are needed to establish the effect of this substance on autoimmune musculoskeletal disorders, Sjögren syndrome, Behcet's disease, and scleroderma. On the other hand, no evidence was reported regarding the role of selenium in some autoimmune disorders like vasculitis, seronegative arthritis, and antiphospholipid antibody syndrome. We suggested more investigations evaluating the level of selenium in these cases and addressing the effect of selenium supplementation on their treatment.

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