



# **Role of Vitamins and Trace Elements In Autoimmunity**

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# What is Autoimmune Disorders?

- A group of disorders with **attacks of immune system to healthy tissue.**
- Autoimmunity is a problem of **self/non-self** discrimination.
- Failure of antibodies and T cells to recognize own cells, so launch **attack against own cells.**



# Etiology of Autoimmune Disorders

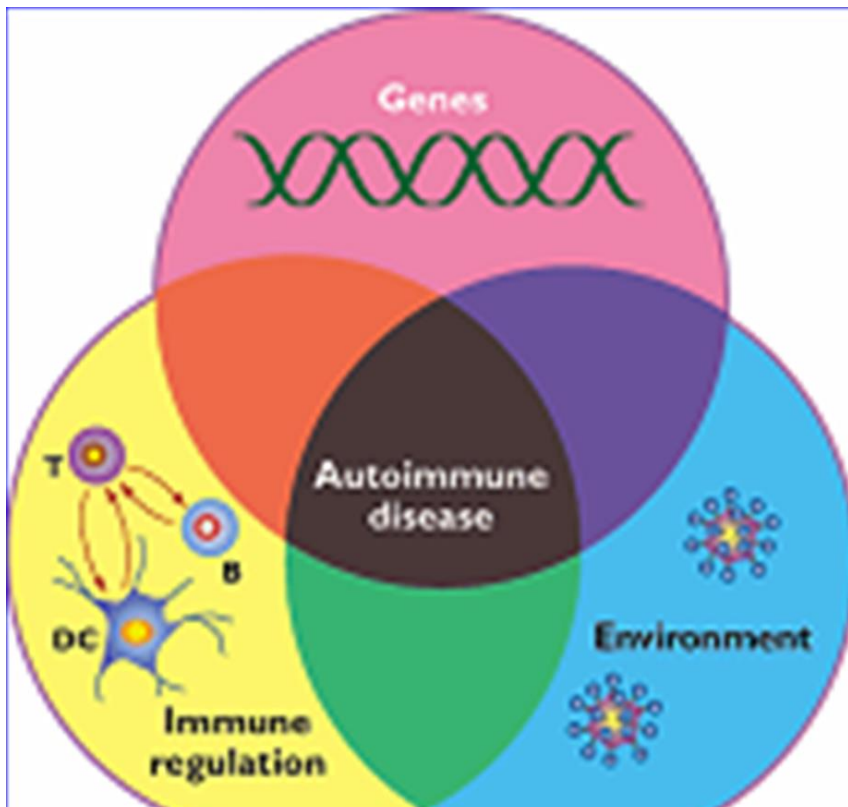
- Etiology is unknown.
- Trigger factors:
  - Immunological factors (Infection)
  - Genetic factors
  - Environmental factors (Chemical, UV, Infection)
  - Physiologic factors (hormonal effect)
- Multi-organ involvement (**non organ specific**) (Blood vessels, Connective tissues, Skin, Endocrine glands, Joints, Muscles, Red blood cells)
- **Organ specific**

# Examples of Autoimmune Diseases

- **Multi-organ involvement:**
  - Systemic lupus erythematosus
  - Rheumatoid arthritis
  - Dermatomyositis
  - Scleroderma
- **Organ specific:**
  - Multiple sclerosis
  - Myasthenia gravis
  - Crohn's disease
  - Grave's disease
  - Type 1 Diabetes mellitus

# Pathophysiology

- Inefficient **lymphocyte** programming
- Reactions between self-antigens and antibody production against foreign antigens



# Mechanism of Autoimmunity

- Tissue destruction (Diabetes)
- Antibodies block normal function (Myasthenia gravis)
- Antibodies stimulate inappropriate function (Graves' disease)
- Antigen-antibody complexes affect function (Rheumatoid arthritis)

# The role of Unknown Factors

- Vit. D
- Trace Elements
- Oxidative stress



# Biologic Effect of Vit. D

- Vit. D (1,25(OH) vit. D) is in fact a pleiotropic steroid hormone similar to other steroid hormones
- Regulation of calcium homeostasis and bone turnover
- **Antiproliferative** and pro-differentiation (anti-tumor)
- Anti-bacterial
- Immunomodulatory
- **Anti-inflammatory**

# Role of Vit. D in Immune System

- 1,25(OH)D, locally produced in the tissues, exerts its effects on several immune cells (macrophages, dendritic cells, T and B cells).
- Presence of **VDRs** on immune system cells.
- Innate immunity:
  - Effect of vit. D on **macrophage** killing of **M. TB** (lower levels of vit. D are **more susceptible to M. TB** infection)
  - Induces **monocyte proliferation** and production of IL-1 and cathelicidin (an antimicrobial peptide) by macrophages.

# Role of Vit. D in Immune System

- Adaptive immunity:
  - Vit. D blocks B cell proliferation, plasma-cell differentiation and immunoglobulin production.
  - Cell Mediated: Calcitriol suppress cytokine production by **Th1** cells.
  - Humoral mediated: Calcitriol enhance cytokine production by **Th2** cells.
  - **IL-17**: vitamin D and calcitriol suppress IL-17 production
- T-regulatory cells (Tregs): Vit. D increase Tregs by directly inducing Treg lymphocyte differentiation and prevention of autoimmunity

- Vit. D has an impact on the **pathophysiological mechanisms** of autoimmunity, although the mechanisms have yet to be elucidated.
- Vitamin D enhances the **innate immune** system and regulates the **adaptive immune** system in a way that appears to **promote immune tolerance** and thus acts to **decrease** the likelihood of developing autoimmune disease.
- Vit. D supplementation, particularly with the use of targeted drug delivery systems that are **absorbed locally in the GI system** act as an important immunomodulatory medium.

# Vit. D in Autoimmune disorders

- In early childhood decreased the incidence of **Type 1 Diabetes M.**
- **Decreased risk of RA** with higher UV-B exposure (especially between birth and 15 y)
- Vit. D deficiency to be common in pediatric SLE and associated with an **increased cardiovascular disease** risk.
- Low vit. D levels among coeliac patients was a **predictor of other autoimmune diseases.**
- Low vit. D levels to be associated with an increased number of **thrombotic events** in Anti Phospholipid Syn.

# Clinical evidence of vit. D and autoimmunity

| Disease                            | Relevance to vitamin D  | Relevance to disease severity   |
|------------------------------------|---|---|
| Type 1 diabetes mellitus (T1DM)    | Supplementing vitamin D (High)  | Questionable decreased likelihood of developing disease   |
| Rheumatoid arthritis (RA)          | Low   | <u>Low vitamin D intake associated with increased risk of developing disease (36–38)</u>  |
| Systemic lupus erythematosus (SLE) | Low   | <u>Increased disease severity and increased flares of disease</u>   |
| Systemic sclerosis (SSc)           | Low   | Increased severity  |
| Multiple sclerosis (MS)            | Lower serum 25(OH)D concentrations in June to September compared with controls (45) | <p>Serum vitamin D levels in the high range of normal correlate with <u>decreased likelihood of relapses and decreased disease activity on MRI studies</u></p> <p>MS relapses associated with lower vitamin D in comparison to <u>periods of remission (45)</u></p> |

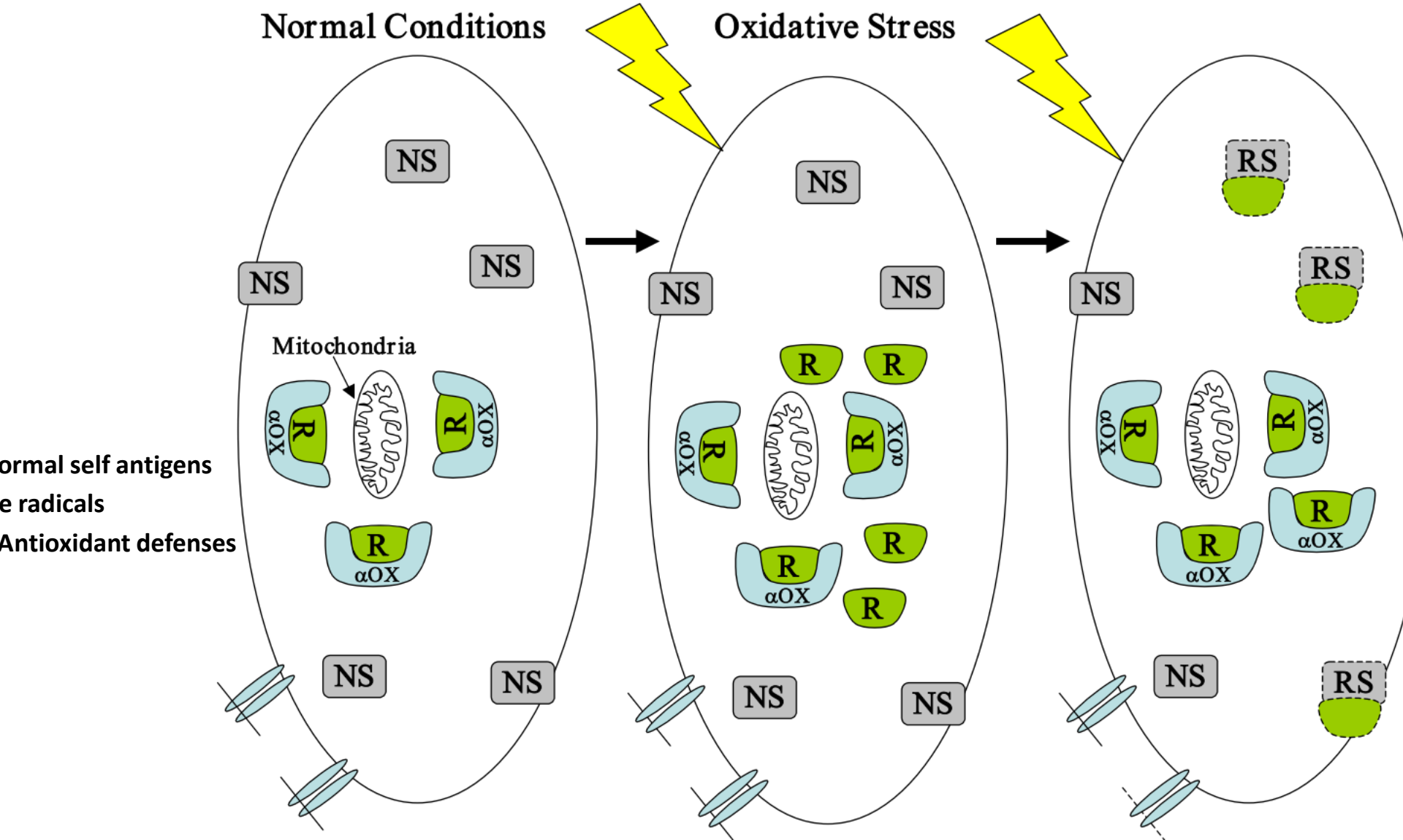
# The role of Oxidative Stress on Autoimmunity

- The reactive oxygen species (such as superoxyde, hydrogen peroxide and nitric oxide) are **physiologic activators for pro-inflammatory cytokines** (TNFa, IL8, IL9, IL3, IFNg).
- Role of antioxidant as an **immunomodulatory** agent.
- Production of ROS has a central role in the pathogenesis of two major complications (early **atherosclerosis** and **osteoporosis**).

# The effect of Oxidative stress on cells

- An **imbalance** between the production and manifestation of reactive species and the ability to detoxify the reactive intermediates
  - Increase in **oxidant generation**
  - Decrease in **antioxidant protection**
  - Failure to **repair** oxidative damage





# Some Evidence on Oxidative Stress

- Patients with autoimmune disorders showed a **reduced antioxidant condition** (reduction of vitamins A, C and E).
- Vegetarian diet and or derivatives of fish oil can provide clinical benefits on RA, JIA, HSP (in SLE?).
- Serum values of vitamins with anti-oxidant activity (alpha-tocopherol, carotene and rretinol), measured in samples stored in a serum **bank from blood donors** who developed after 2–15 years RA or SLE, were lower than for the controls.

# Some Evidence on Oxidative Stress

- Oxidative stress as a **biomarker** for determining disease activity in patients with RA.
- **Decrease of oxidative stress** after disease control.
- High vitamin-E doses administered to **RA** patients were effective in **reducing pain symptomatology**

# Vitamin E

- Antioxidants effects in immune system.
- Deficiency of vit. E increase susceptibility to infection.
- Deficiency of vit. E is accompanied to damage of **lysosomes membranes** and this damage initiate **inflammation**.

# Omega 3 and 6

- Essential fatty acids
- **Suppress cell mediated** immune responses
- **Reducing inflammation**
- **Decrease in the levels of pro-inflammatory chemokines and cytokines**
- **Imbalance in the omega-6/omega-3** ratio may be related to the increased production of proinflammatory cytokines
- Omega-3 fatty acids **modulate prostaglandin** metabolism

# Vit. A

- Known role in immune system
- Deficiency of vit. A increase the risk of infectious diseases.
- Deficiency of vit. A has a **negative effect** on T-cell subpopulations, cytokines and antibody subclasses.

# Selenium

- Antioxidants agent
- Decrease the rate of viral infection
- Improve T-cell function
- Increase natural killer cell activity
- Selenium deficiency: loss of immune competence (cell-mediated and B cell function)
- Decrease inflammatory activity in Autoimmune thyroiditis
- Decrease pain in RA

# Zinc

- Small evidence.
- Protective role in inflammation and prevent from immunopathologic process.



# Dosage

- Vit D: 1000-2000 IU/Daily
- Selenium: 200  $\mu\text{g}$  (or even 500-1000  $\mu\text{g}$ )
- omega-6/omega-3 ratio about 1-4/1
- Decrease the intake of omega-6 fatty acids from vegetable oils and increase the intake of omega-3 fatty acids by using intake of fish to 2-3 times per week.

# Conclusion

- The **evaluation of oxidative stress and of nutritional intake** in all autoimmune disorders.
- Consider developing therapies that decrease oxidative stress in the **target tissue (new strategy in treatment)**
- Both for **prevention** and **early treatment** of the diseases
- The clinical use for **reducing clinical symptoms** (such as vitamin E for reducing of pain in RA).
- Recommendation for all autoimmune disorders:
  - Vit D, Micronutrient antioxidants (selenium, Beta-carotene, Vitamin C, Vitamin E, Methionine)



