

Lupus, You and Primary Health Care.

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Objectives

- Learning how and when to suspect lupus.
- Appreciating the ongoing role of the Primary Care Provider in Lupus.
- Understanding the importance of non-autoimmune immune mediated aspects of lupus

Nomenclature

- The term *lupus*, was first used as a medical term
 - In 1230 by Rogerius Frugardi
 - In 1611 by Sennert
- *Lupus érythémateux* as a medical condition was coined in
 - 1833 by Pierre Cazenave
- The term *systemic lupus erythematosus* (SLE) was first used between 1895 and 1903.

Importance of Primary Care

- Lupus is the great imitator and masquerader.
- Patients have limited access to specialists.
- Many times specialist rely on their Primary Care Physicians (PCP's) to care out plans.
- Patients survive longer and have an increased risk of chronic illnesses.
 - Hypertension
 - Hyperlipidemia
 - Cardiovascular disease

The Great Imitator

- Multiple sclerosis
- Interstitial lung disease
- Inflammatory bowel disease
- Type I Diabetes
- Autoimmune thyroid disease
- Idiopathic thrombocytopenia
- Antibody negative vasculitis

Common Symptoms

- 60% or more of patients have skin and/or joint manifestations at presentation.
 - Facial rash or sensitivity to sun
 - Lupus arthritis (not just joint pain)
- Proteinuria
- Cytopenia
- Recurrent/unusually severe thrombosis.
- Pleurisy or pneumonitis of unclear etiology.
- Pericarditis, congestive heart failure.

Commonest Findings In Lupus

Frequency (%) of clinical symptoms in new onset lupus


| System | Frequency (%) |
|-------------------|---------------|
| Musculoskeletal | 57.1 |
| Constitutional | 50 |
| Mucocutaneous | 50 |
| Hematology | 38.9 |
| Renal | 28.6 |
| Cardiorespiratory | 17.8 |
| Neuropsychiatry | 14.3 |

Frequency (%) of serological findings in new onset lupus

| Immunology | Frequency (%) |
|---------------------|---------------|
| ANA | 100 |
| ds-DNA | 83.6 |
| Low C3 | 51.8 |
| Low C4 | 49.5 |
| SSA | 28 |
| aCL/ β 2GP/LA | 24/17.2/16.3 |
| Sm | 16 |

Causes of a Positive ANA?

- Pre-clinical disease
- Non-rheumatologic ANA related disease
 - Autoimmune liver disease
 - Autoimmune thyroid disease
- Transiently Positive ANA
 - Post viral: HIV, Hep C, EBV
 - Drugs: Tetracycline
- Lab variability
- Non-pathogenic ANA (Fibro ANA)
 - Antibody to Dense Fine Speckled 70 Anti-gene



Primary Care

Primary Care practices serve the medical needs of your family and are able to provide care that is continuous, comprehensive and coordinated.

Undifferentiated Connective Tissue Disease (UCTD)

- UCTD is the preferred term for people not meeting the SLE criteria.
- Many of these patients never develop lupus.
- The ACR criteria can be used reliably to make a presumptive diagnosis of SLE.
- A negative ANA IF test essentially rules out SLE.
- If lupus is clinically suspected in an ANA negative patient, an SSA test may be helpful.

Education

- SLE management requires a physician-patient relationship
 - PCP
 - Rheumatologist
- Denial of their illness.
- Non-adherence with medications.
- Insurance problems
 - Uninsured
 - Underinsured
 - Patient support and resources.

Cardiovascular Disease (CAD)

- SLE patients have
 - A higher rate of atherosclerosis
 - A higher rates of progression atherosclerosis
 - A higher rate of subclinical atherosclerosis
- At least 13% of SLE patients have symptomatic atherosclerotic lesions
- Major cardiovascular complications in SLE
 - Myocarditis (heart disease)
 - Valvular disease
 - Endocarditis (infections)
 - Arrhythmias (rate and rhythm)

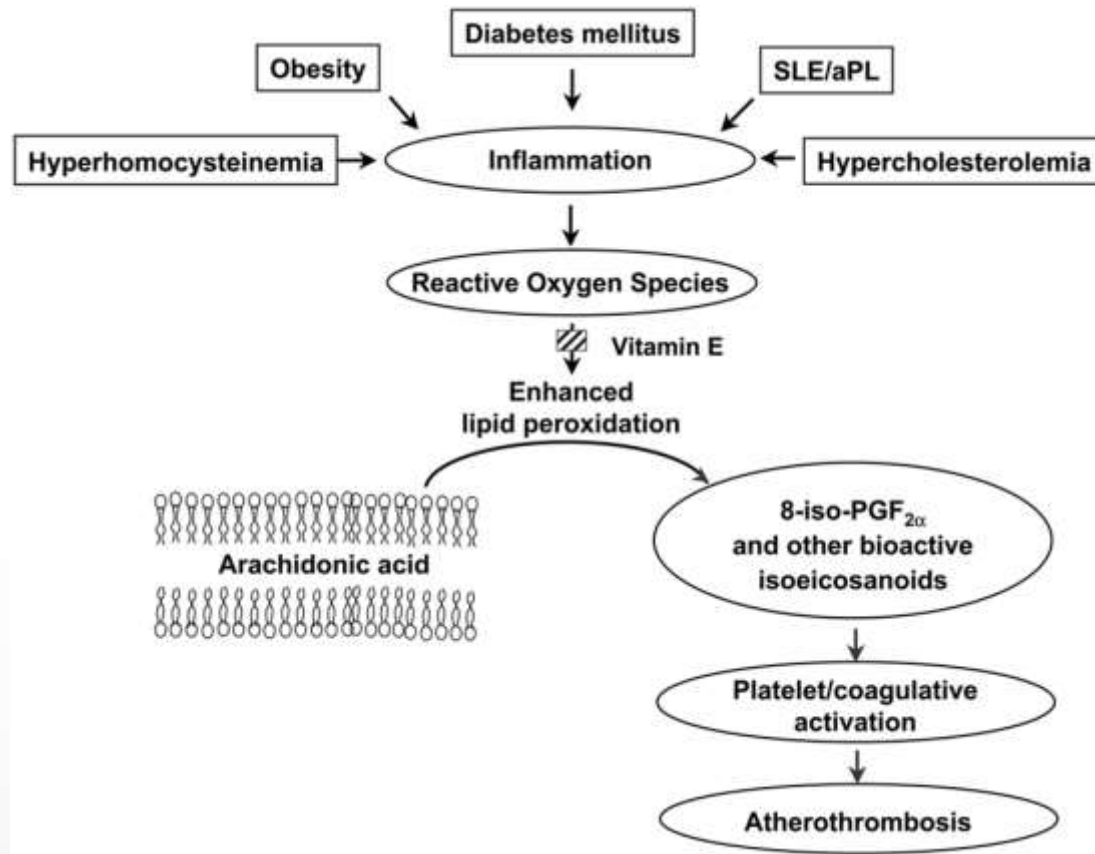
CAD and the Immune System

- Atherosclerosis has a significant immune and inflammatory component.
- Elevated C3 & White Blood Cell count (WBC) is seen in SLE with atherosclerosis.
- Things associated with cardiovascular events
 - Low-grade inflammation
 - Oxidative stress
 - Lipid peroxidation

Atherosclerosis

- Adaptive immunity is involved in atherosclerosis.
- T cells have a pathogenic role to atherosclerosis.
- T-helper (T_H)-1 cells contribute to atherosclerosis.
- T regulatory cells play a protective role against atherosclerosis and inflammation.
- B cells produce protective antibodies against oxidized LDL cholesterol.

Inflammation and CAD



Fat Cells & Immunity

- Fat cells produce cytokines
 - TNF- α
 - IL 1 and 6
- TNF- α
 - Increases IL-6 and IFN- α over-expression
 - Hypertriglyceridemia/Dyslipidemia
 - Inflammation related to atherosclerosis
- Inflammatory is seen in SLE and the following
 - Obesity
 - Hypercholesterolemia
 - Type 2 diabetes mellitus
 - Homozygous homocystinuria

Other Risk Factors

- SLE causes complications that also cause heart disease.
- Extra-cardiac risk
 - Kidney disease (lupus nephritis)
 - Strokes
 - Pulmonary artery hypertension (PAH)
 - Peripheral artery disease (PAD)
 - Pericarditis
- Lupus also causes abnormal tests that are related to heart disease.
 - C-reactive protein (CRP)

Preventive Strategies

- Smoking cessation
- Regular physical activity
- Managing metabolic abnormalities
 - Dyslipidemia
 - Insulin resistance, and diabetes
 - Persistent disease activity
 - Minimizing exposure to corticosteroids
- Vitamin D supplementation
- Anti-malarials
- Low-dose aspirin
- Angiotensin-converting enzyme(ACE) inhibitors



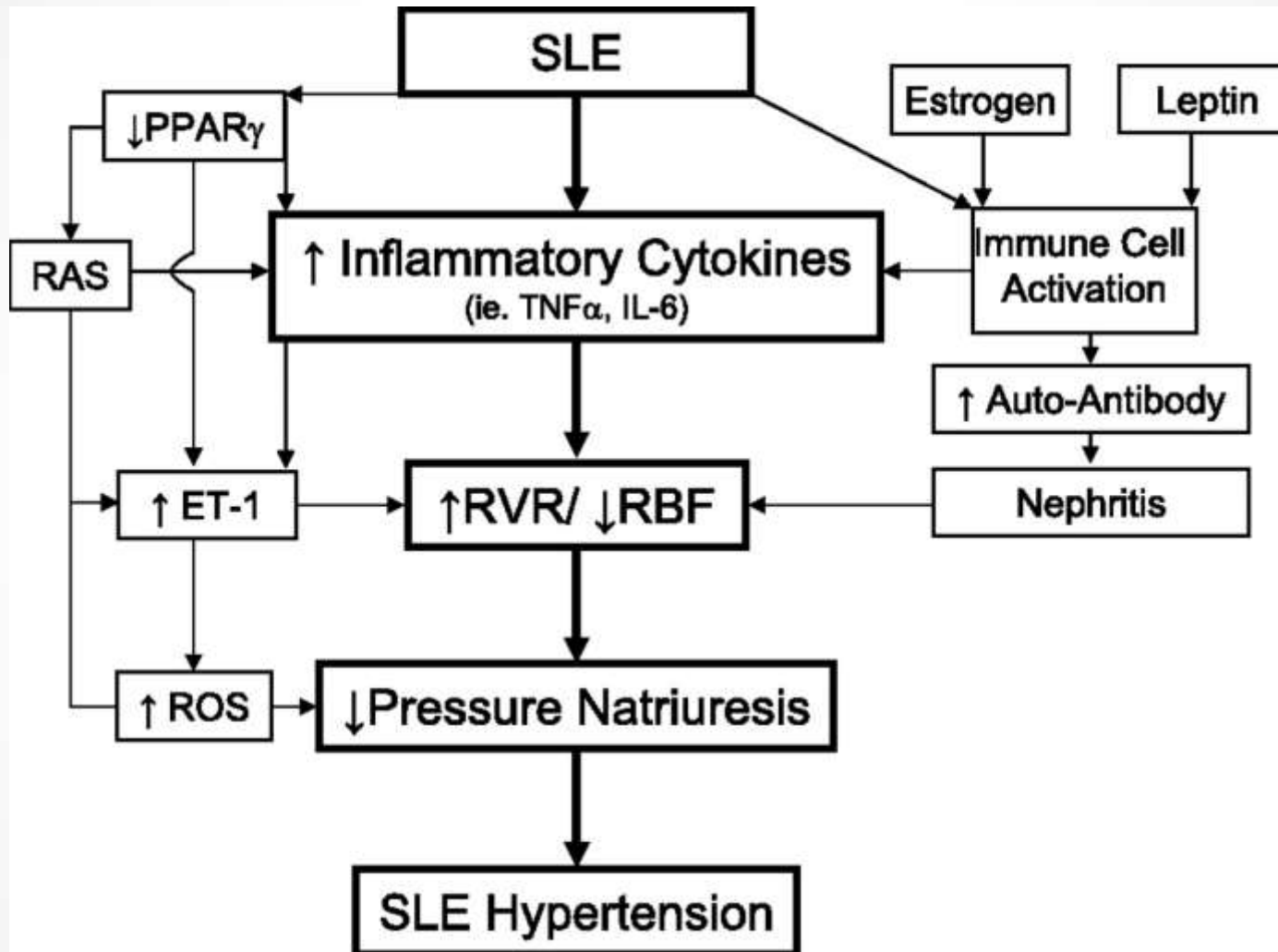
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Hypertension (HTN)

- Hypertension has an immune-mediated causes.
- Chronic immune activation causes
 - Generation of oxygen free radicals
 - Resulting in oxidative stress
- Renal oxidative stress
 - Plays a role in immune-mediated hypertension.
 - Has hypertensive actions on renal vascular and tubular function.
- HTN is seen in Lupus knockout mice
 - Develop hypertension associated with renal oxidative stress.

Flow Diagram Depicting Possible Pathways That Promote SLE Hypertension



Am J Physiol Regul Integr Comp Physiol 2009;296:R1258-R1267

HTN In SLE

- Even patients with active non-kidney SLE have a higher rates of HTN.
- HTN is associated with serologically active SLE
- Active SLE has a higher interleukin (IL)-12/IL-4 ratio.
- Protein oxidation is higher in patients with active SLE.
- HTN is associated with an increased T_H1/T_H2 ratio and oxidative stress.
- There is an association between HTN and levels of
 - Glucose
 - Insulin
 - Hydroperoxides
 - IFN- γ
 - IL-17
 - IL-12/IL-10
 - Adiponectin

Dyslipidemia

- High prevalence of dyslipidemia noted in LN.
- Dyslipidemia is more common in renal impairment
- Even in inactive SLE, dyslipidemia is more severe.
- Steroid use is associated with higher cholesterol levels.

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Pregnancy In Lupus

- Mother
 - Lupus activity
- Placenta
 - Pre-eclampsia/eclampsia/HELLP syndrome
 - Antiphospholipid syndrome
- Baby
 - Neonatal lupus
 - Risk of ANA positivity
 - Learning difficulties
 - Risk of development of lupus

Pregnancy and Lupus

- Pregnancy is least likely to be associated with a flare if
 - Mother has been in a remission for 6 months or greater
 - With HCQ use
- Pregnancy is most likely to be associated with a flare if
 - Active renal disease
- Pregnancy increases the risk of lupus exacerbations in the third trimester and postpartum period.

Antibodies in Pregnancy

- Antibodies that cross the placenta
 - SSA
 - SSB
 - U1RNP.
- Antiphospholipid antibodies (APS).
 - 40% of patients with SLE have these antibodies
 - 50% of those patients experience thromboembolism
 - Increase risk of fetal loss

Neonatal Lupus (NLS)

- NLS symptoms
 - Skin rash (with 2 months of birth)
 - Hematological symptoms
 - Liver or Cardiac symptoms
- Skin rash is seen in 15% and are transient.
- Complete heart block (CHB) rate is 1-2%.
- CHB is irreversible and associated with morbidity and a mortality of 18%.
- A pacemaker are implanted in 2/3 of cases.
- Maternal use of HQC reduces CHB.

Neonatal Lupus Syndrome



Third-degree heart block: P waves (red arrows) independent of the QRS complexes (blue arrows).

Treatment of Cutaneous NLE

- Reduced sun exposure
- Use protective clothing
- Use sunscreen
- Topic hydrocortisone
- Time heals all wounds (by 6 months)

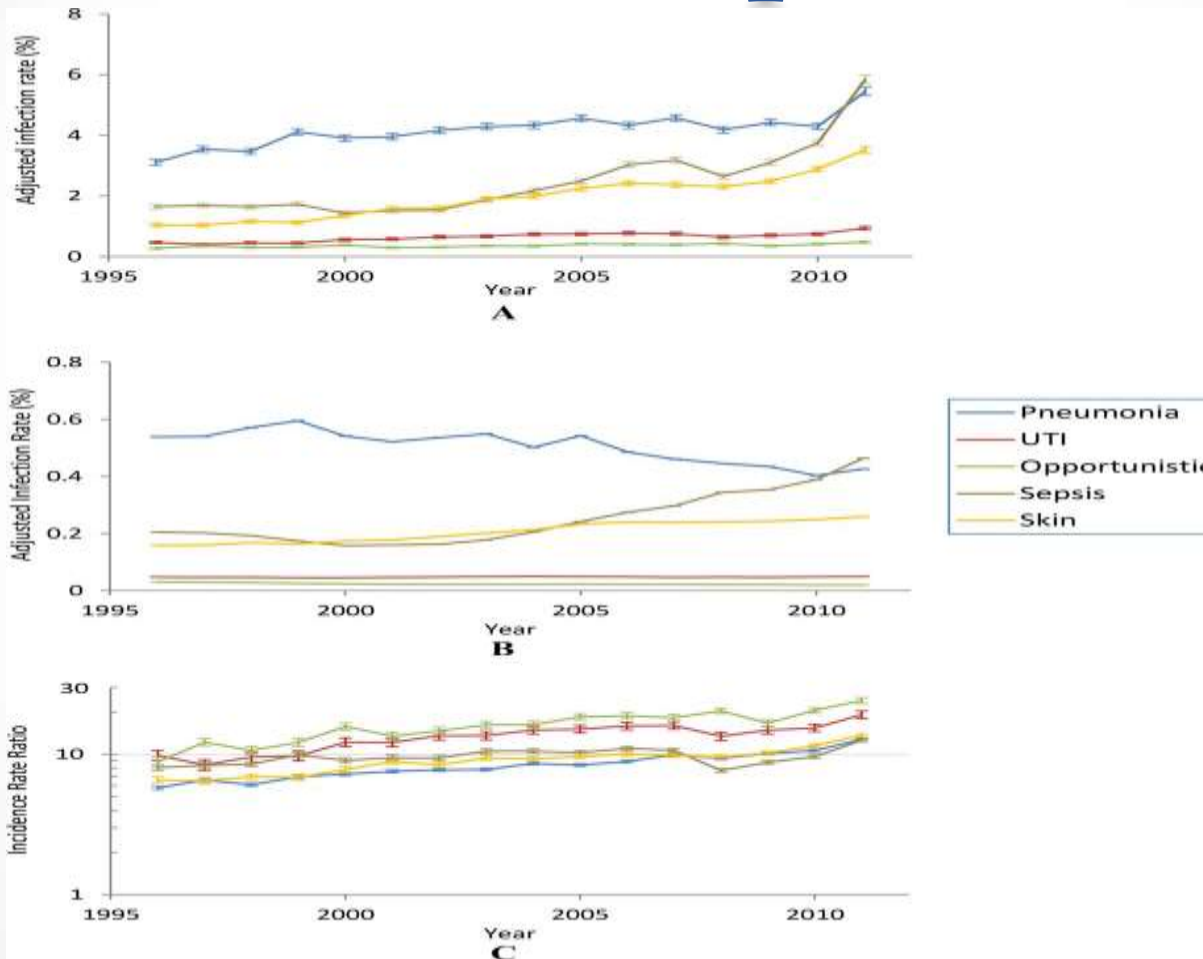
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Lupus and Infections

- Lupus patients have a higher risk of infections
- Steroids increase the risk of infections
- Immunosuppressive medications used in SLE increases the risk of infections
- Infections increase the risk of SLE flares.
- SLE flares increase the risk of infections.

Infectious Hospitalization



Tektonidou et al A. C & R 67: 8, 2015, pp 1078–1085

Immunizations

- Vaccination should be avoided in active disease
- Vaccines are effective and safe in SLE
- Vaccines are best given prior to immunosuppressive therapy is started.
- Anti-malarials are known to be protective against infection

Immunizations

| | Pneumococcal | Influenza | Hepatitis B | Human Pap. | Herpes Zoster |
|--------------------|---------------|-------------------|------------------|------------------|---------------|
| | Before | initiating | treatment | | |
| DMARD Monotherapy | ✓ | ✓ | ✓ | ✓ | ✓ |
| Combination DMARDs | ✓ | ✓ | ✓ | ✓ | ✓ |
| Biologics | ✓ | ✓ | ✓ | ✓ | ✗ |
| | While | already | taking | treatment | |
| DMARD Monotherapy | ✓ | ✓ | ✓ | ✓ | ✓ |
| DMARDs & biologics | ✓ | ✓ | ✓ | ✓ | ✗ |

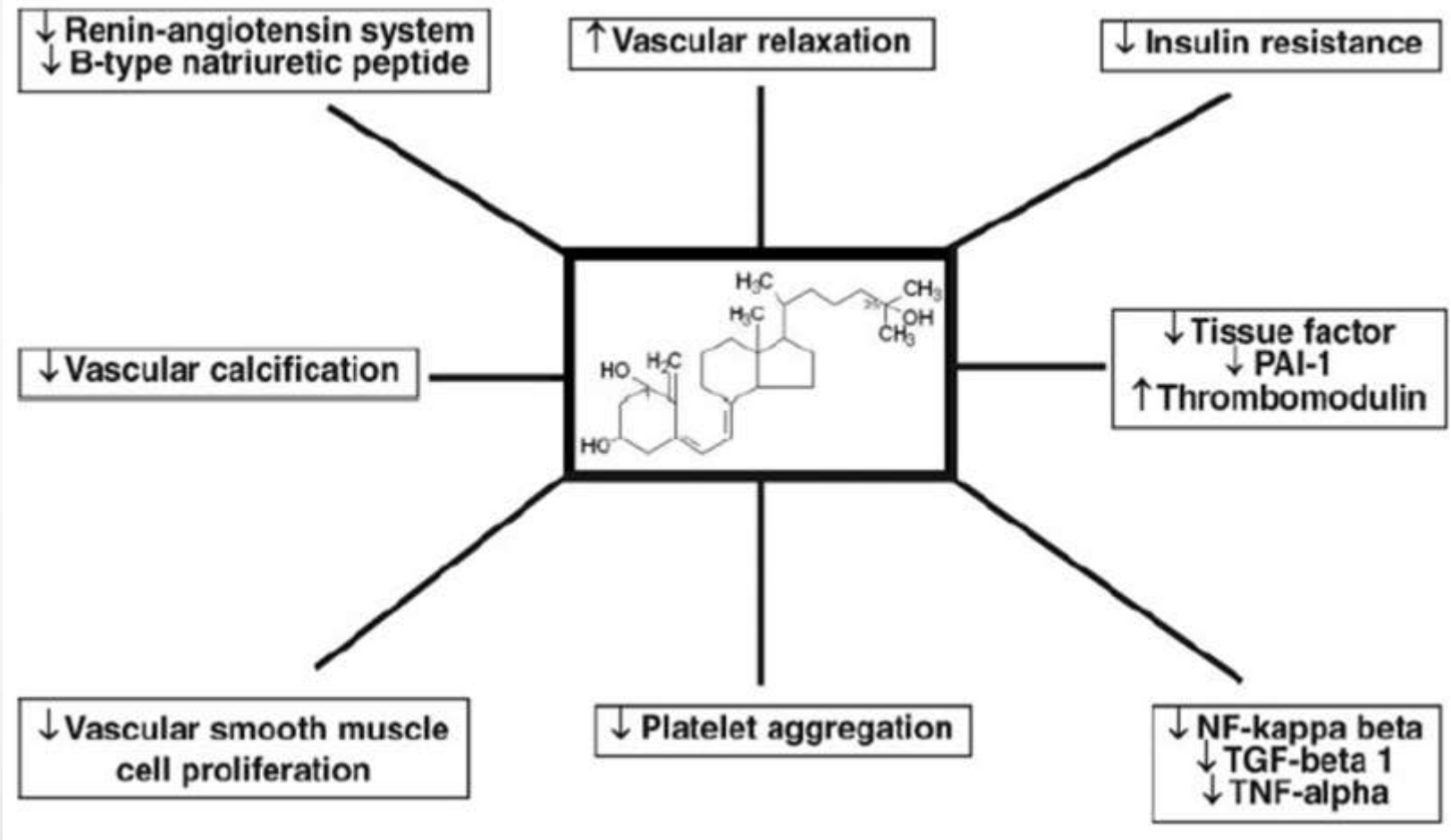
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Vitamin D

- It is a steroid hormone.
- Vitamin D has immune benefits.
- Vitamin D deficiency is more common in active SLE.
- Vitamin D deficiency is association with dyslipidemia, so may be related to heart disease.
- Vitamin D levels are inversely related with atherosclerotic plaque size so may be related to heart disease.

Actions of Vitamin D



Vitamin D and SLE

- Vitamin D has an inhibitory effect on abnormalities seen with SLE.
- Vitamin D values of < 20 ng/mL is associated with higher serum IFN- α & higher levels of activated B-cell.
- Replacement of Vitamin D decreases levels of memory B cells and anti-DNA antibodies.
- Vitamin D inhibit expression of SLE related inducible genes.

Vitamin D and SLE

- 29% of African American African patients have serum vitamin D levels < 10 ng/mL.
 - Photosensitive rash
 - Renal disease
- “Immuno-nutrition” is plagued with difficulties
 - Race
 - Ubiquitous in nature
 - Nutrition
 - Environmental
 - Medication induced: corticosteroid and phenytoin

Vitamin D & Osteoporosis

- Corticosteroid and osteoporosis
- Bisphosphonates and corticosteroids
- Vitamin D and Osteoporosis

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Mood Disorder (MD)

- Mood disorders are the second most frequent neuropsychiatric event in patients with SLE.
- Mood disorders have a negative impact on health-related quality of life.
- There is no relationship between MD and SLE activity, organ damage and lupus autoantibodies.

Antibodies and MD

- Serum IL1 and TNF α levels are associated with SLE mood disorders
- Serum antibodies to *N*-methyl-D-aspartate (NMDA) receptor (anti-NR2) are associated with depression
- 1/3 of lupus patients have fibromyalgia

Fatigue

- Seen in 50-80% of patients with SLE
- Fatigue does not correlate with SLE serological or clinical activity.
- Fatigue highly correlated with the fibromyalgia
 - Pain
 - Depression
 - Sleep abnormalities
 - Poor quality of life²⁻⁵
- Fatigue is also associated with reduced physical fitness

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Cancer

- The data shows an association between SLE and malignancy
- There is an increased risk for the following
 - Hodgkin's lymphoma (HL)
 - Leukemia
 - Laryngeal carcinoma
 - Lung carcinoma
 - Some liver, vaginal/vulvar, and thyroid malignancies
- There is a reduced risk of the following in SLE
 - Skin melanoma

In Summary

- Communication
 - Between doctors
 - Between doctor and patient
- Early diagnosis and early referral
- Infection
 - Early detection, treatment and prevention
- Metabolic syndrome
 - Monitoring
 - Side effects from prednisone
 - Early onset CADx
- Cancer surveillance

