

Gender and autoimmune diseases



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AUTOIMMUNE DISEASES

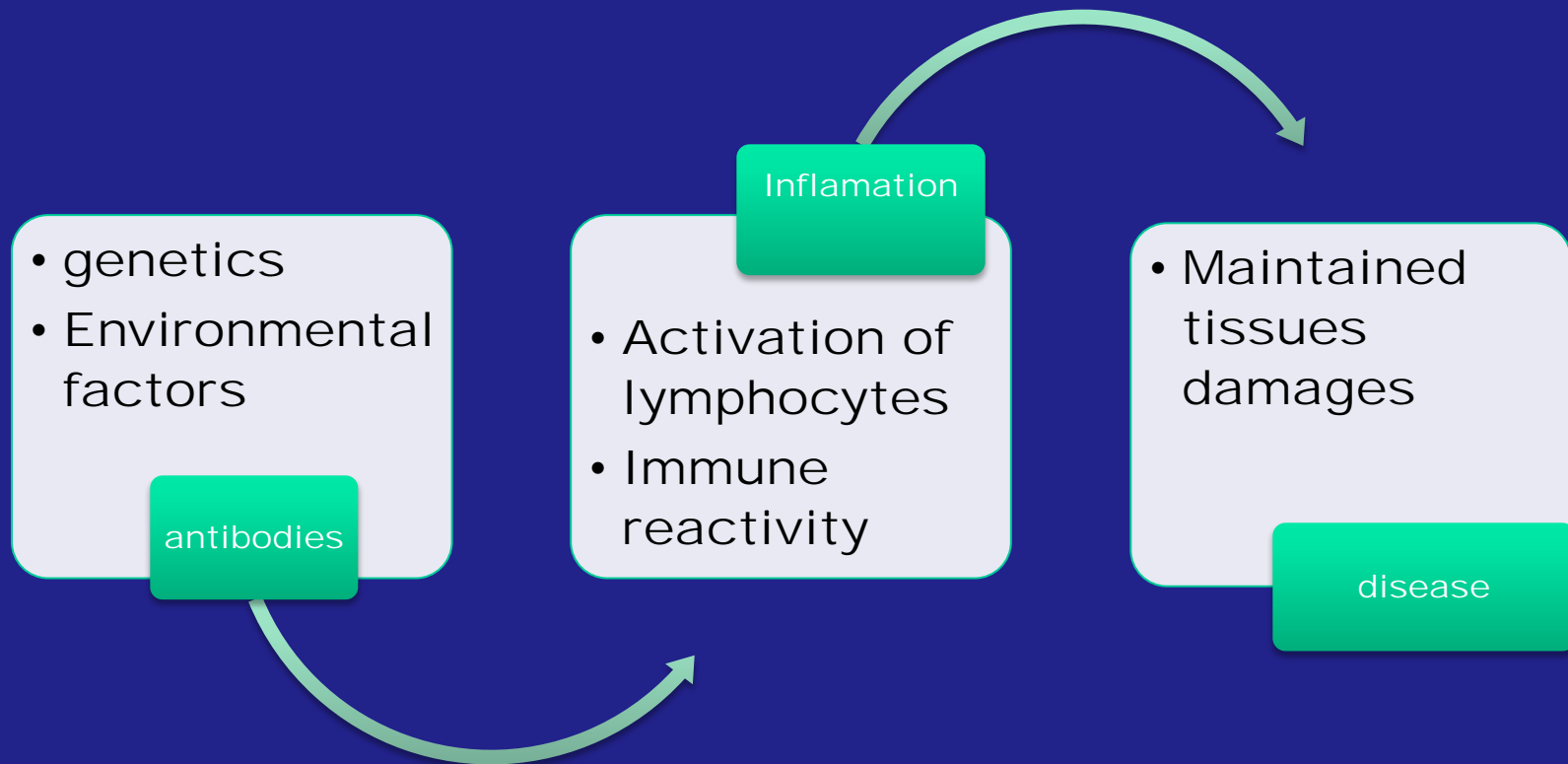
~ 80 disorders 5 % of population

SLE		
SJOGREN S.	STILL DISEASE	HASHIMOTO THYROIDITIS
RHUMATOID ARTHRITIS	AUTOIMMUNE DIABETES	LAMBERT EATON S.
DERMATOMYOSITIS	MULTIPLE SCLEROSIS	MYASTHENIA
POLYMYOSITIS	PRIMARY BILIARY CIRRHOSIS	RELAPSING POLYCHONDRITIS
SYSTEMIC SCLEROSIS	ANTIPHOSPHOLIPIDS S.	





Auto-immunity



Genomics and autoimmune Diseases

- > 200 loci associated to AI Diseases
- Genes on the MHC have the strongest effect
- Mutations seem to act on self reactive B and T cells and modify their reactivity
 - Diabetes melitus
 - Immune Polyendocrinopathy X-linked
- (HLA)- DRB1 locus confers susceptibilty to Rheumatoid Arthritis

(Cho JH. Et al, NEJM, 365 , 2205-19; 2011

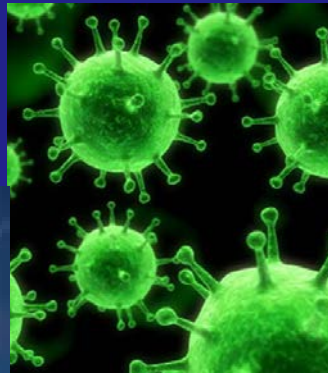
Mclnnes IB, et al, NEJM,365, 1612-23; 2011)

Sex ratio

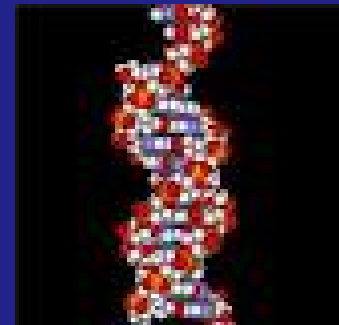
- A majority of autoimmune diseases are more frequent in women
- Lupus SLE 9 women / 1 man
- Sjogren's syndrome 10 women / 1 man
- Hashimoto thyroiditis 10 women / 1 man
- Rheumatoid Arthritis 4 women / 1 man
- Systemic Sclerosis 6 women / 1 man
- Autoimmune diabetes type 1 variable

How to explain female preponderance for autoimmunity?

Environment

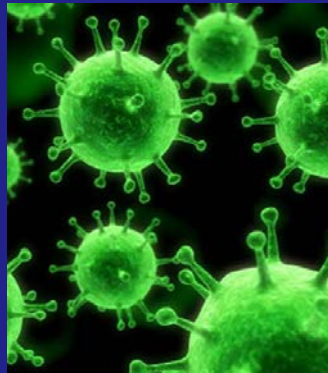


Genetic factors

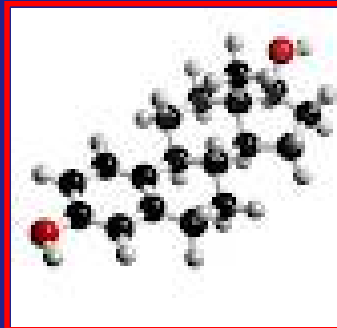


How to explain female preponderance for autoimmunity?

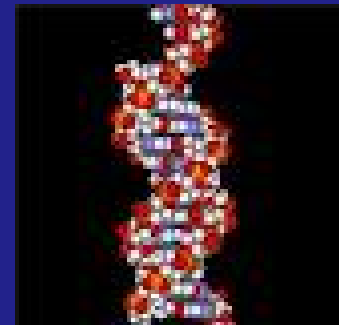
Environment



Hormones



Genetic factors



Hormones and autoimmunity

- Presence of steroids receptors on lymphocytes and other immune cells membrane
 - Estrogens alpha receptors (ER)
- Estrogens
 - enhance Th2 immunological response
 - enhance the programmed death (PD1) pathway and modulates autoimmunity (RK Dinesh et al, Autoimmun.rev. 2010)
 - have a general positive effect on the production of antibodies including pathogenic antibodies (M.Cutolo, arthritis 2007)

Table 1**Expression of steroid receptors by murine immune cells**

Several studies has suggested the expression of progesterone receptors by lymphocytes during pregnancy but it has yet to be proven.

	Estrogen receptors	Androgen receptors	Progesterone receptors
B cells	+	+	-
CD4 T cells	-	-	-
CD8 T cells	+	-	-
Monocytes	+	-	-
Neutrophils	+	-	-
NK cells	+	-	-
Macrophages	-	+	-

Hormones and autoimmunity

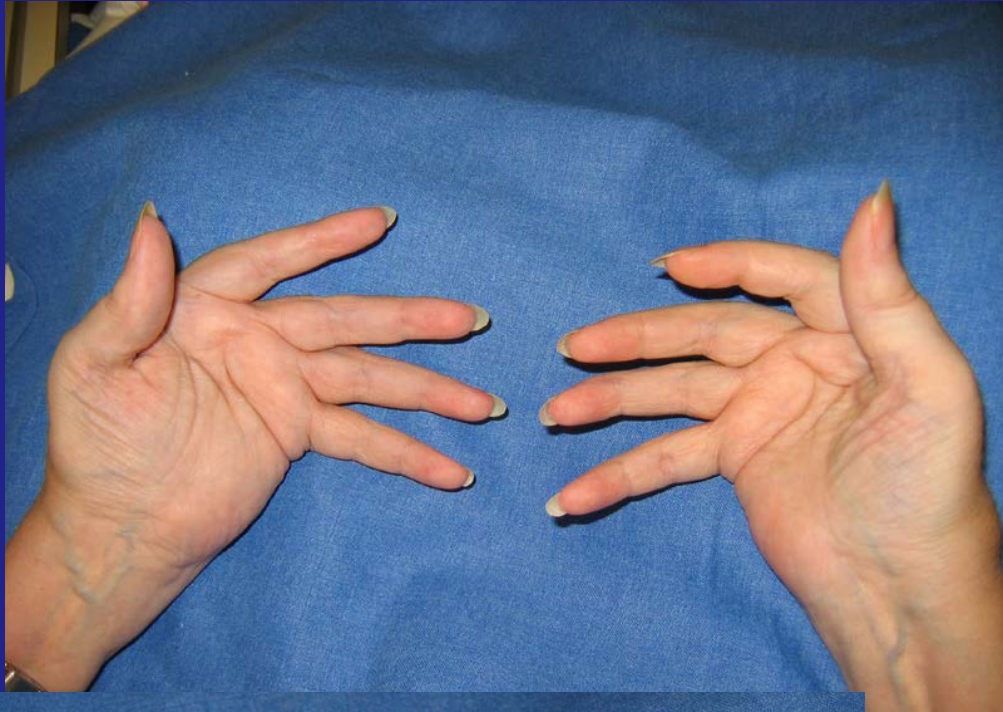
- Progesterone and androgens have a general immunosuppressive effect
- A decrease in DHEA / DHEAS levels could have a facilitating effect on autoimmunity
- Prolactin
 - Secreted by pituitary gland but also by immune cells
 - Accelerates onset of lupus in experimental models
 - High blood levels in SLE, Sjogren's S, RA, Polymyositis, Addison disease, Hashimoto's thyroiditis
- The Hypothalamic-pituitary- adrenal axis is involved in immune regulation and cytokines production

Chromosomes

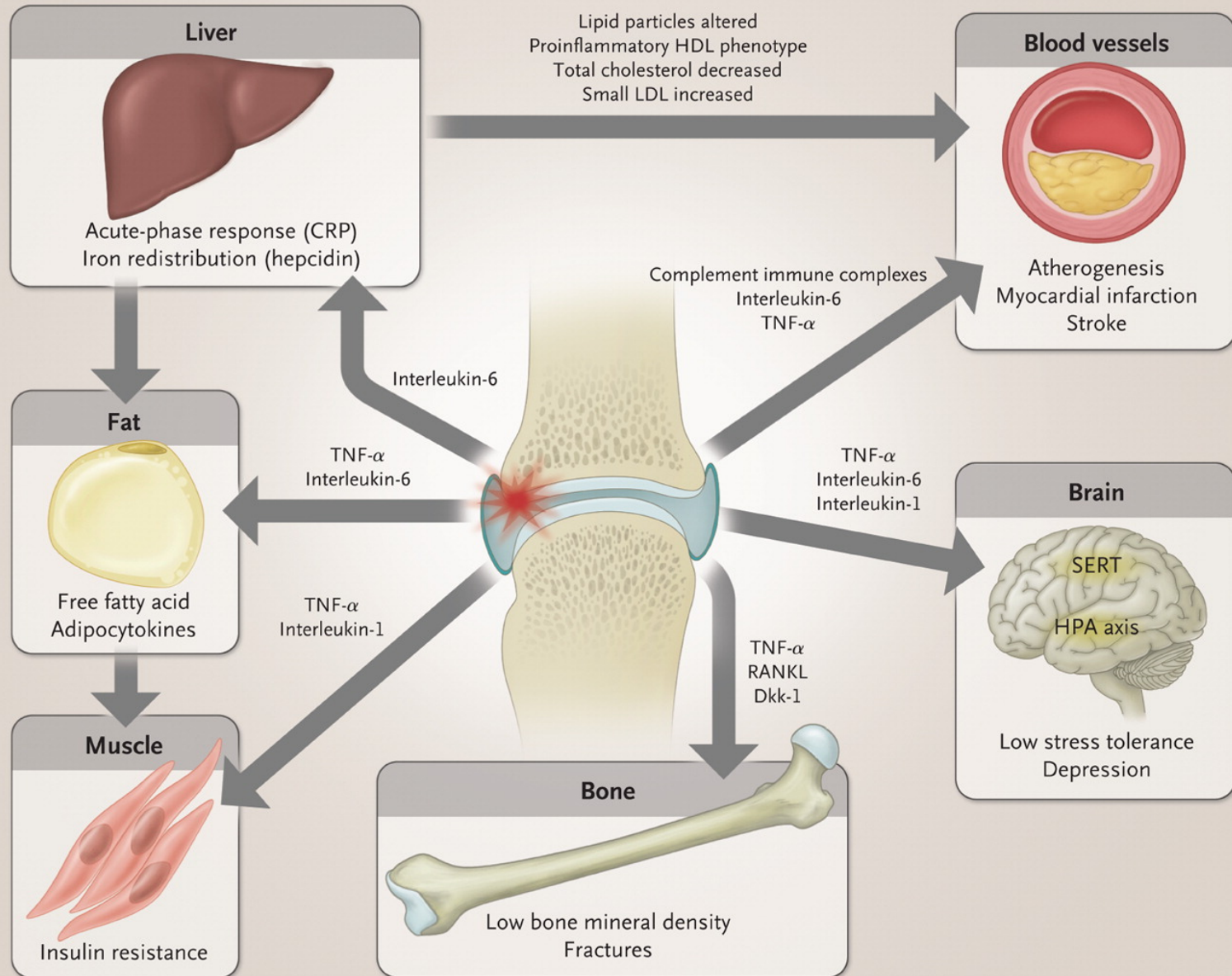
- Sex Chromosomes
 - High rate of circulating leukocytes with a single X chromosome in women with AI diseases.
 - More frequent loss of Y chromosome in men with AI Diseases. (Selmi C. 2008)

Microchimerism

- Fetal microchimerism
 - Long term presence of fetal cells or DNA
 - Scleroderma and Hashimoto Thyroiditis
 - Clinical similarities between GVH disease and AI diseases (
KM Adams Waldorf, JL Nelson, Immunol Invest , 2008)
- Maternal microchimerism
 - Diabetes in children , neo – natal SLE



Rhumatoid Arthritis



Hormones and Rheumatoid Arthritis

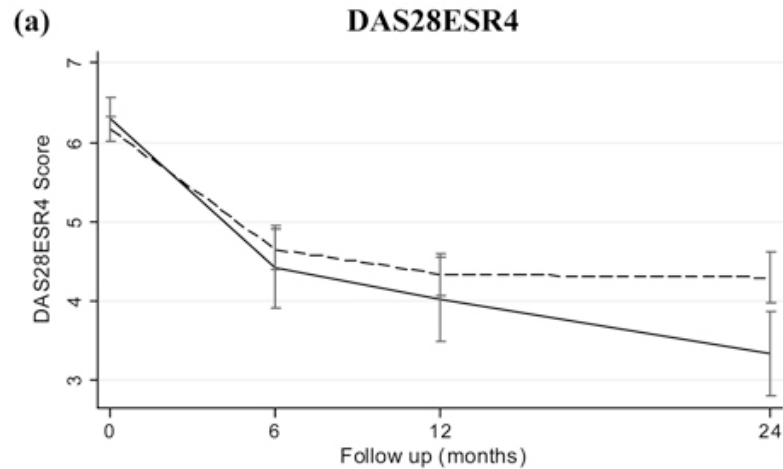
- Men with RA have androgens levels below normal range .
- In synovial fluid of RA joints, estrogens levels are above normal range, whereas androgens are lower. These abnormalities could play a role in synoviocytes proliferation
- women with RA experience a clinical improvement during pregnancy.
- On the opposite there is an increase risk of clinical flare after delivery.
- Hench 's isolation of cortisone was based on observation of RA improvement during pregnancy

Pathogenic role of hormones in RA

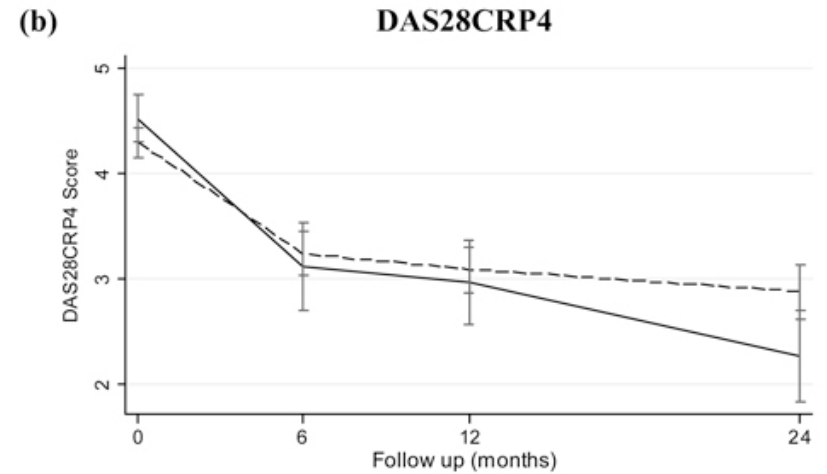
- Normal pregnancy is associated with a shift in cytokines
 - from Th1 : INF-gamma, TNF –alpha, IL- 12
 - To Th2 : IL 10, IL 4, IL 1 receptor antagonist
- In RA patients,
 - the increase in cortisol, estradiol and progesterone during the 3rd trimester
 - Is associated with a drop in IL -12 and TNF-alpha levels
 - In parallel with a frequent clinical improvement

(Golding et al, Rheum Dis Clin , 2007)

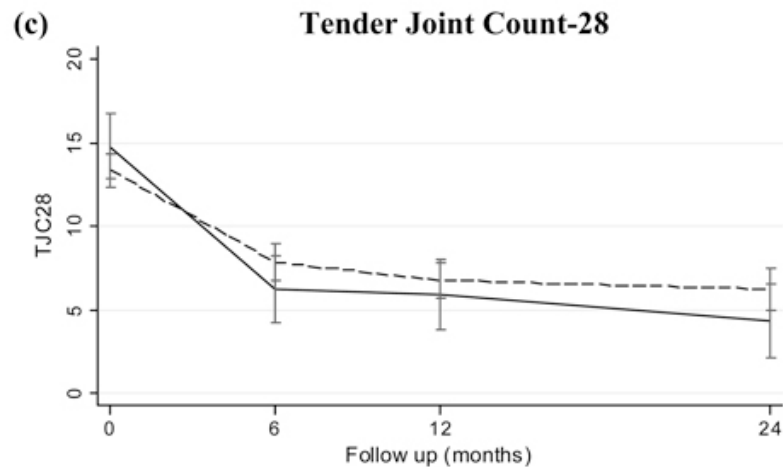
Observed Mean Values for Different Outcome Measures Over Time in Men and Women



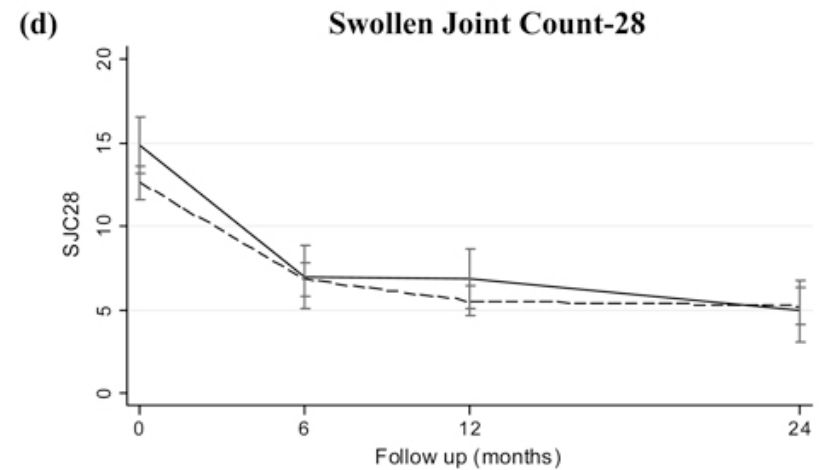
Men:	61	41	40	32
Women:	206	155	142	104



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Women:	206	155	142	104

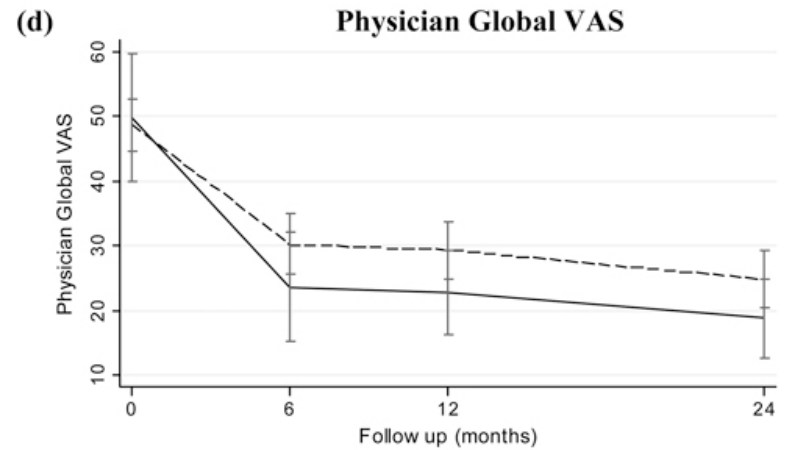
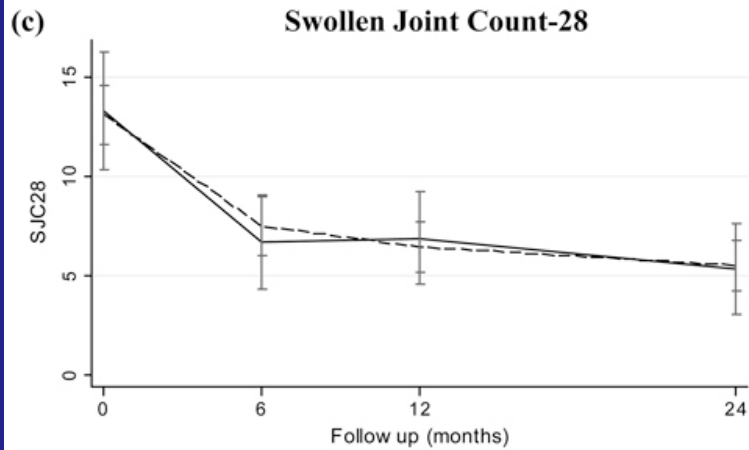
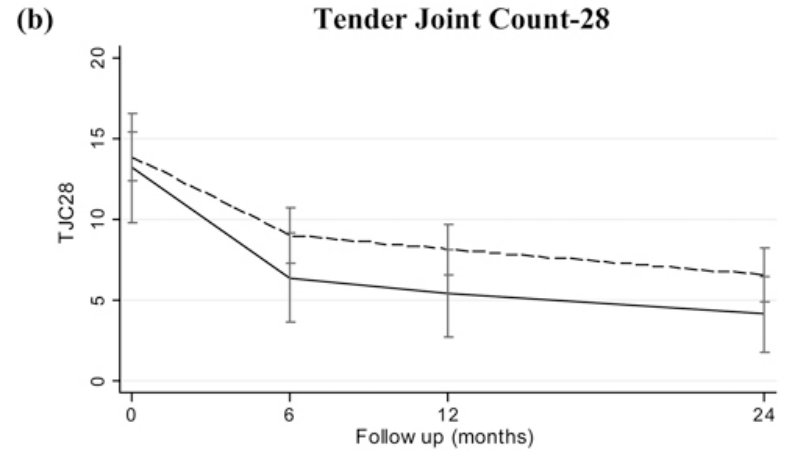
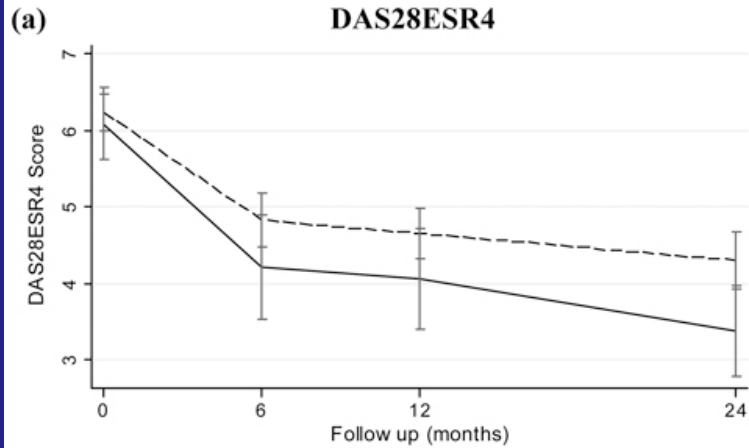


Men:	64	47	47	33
Women:	215	172	150	113

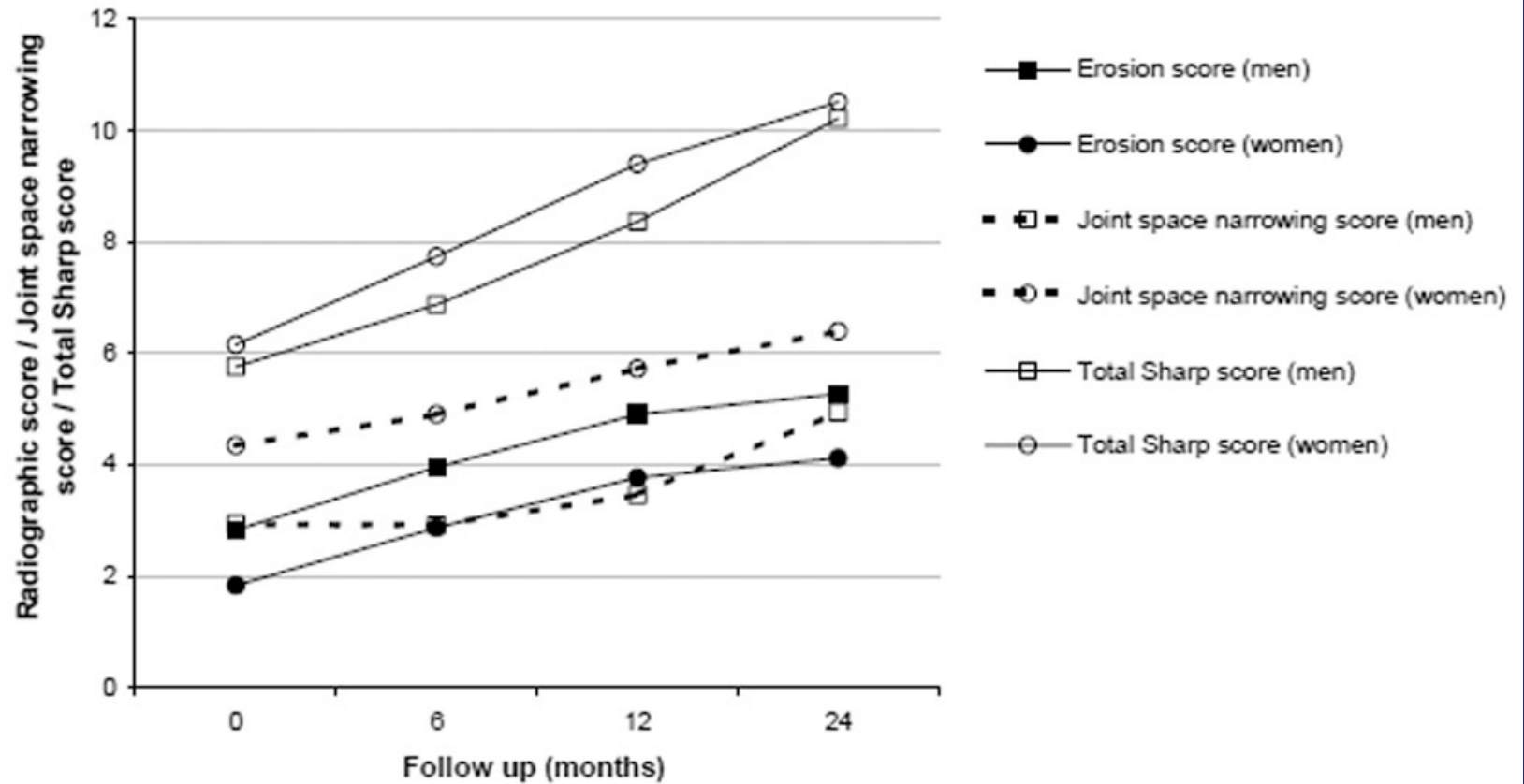


Men:	64	47	47	33
Women:	215	172	150	113

**Observed Mean Values for Different Outcome Measures over Time among Patients with Complete DAS28ESR4
Data at all Time Points (26 men and 80 women)**

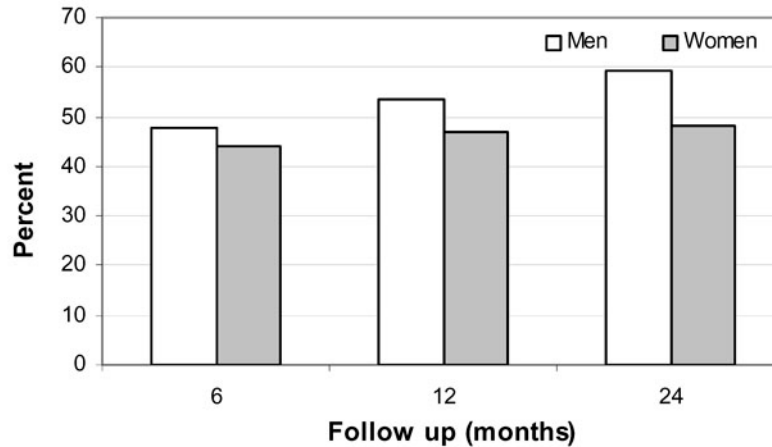


Radiographic Damage



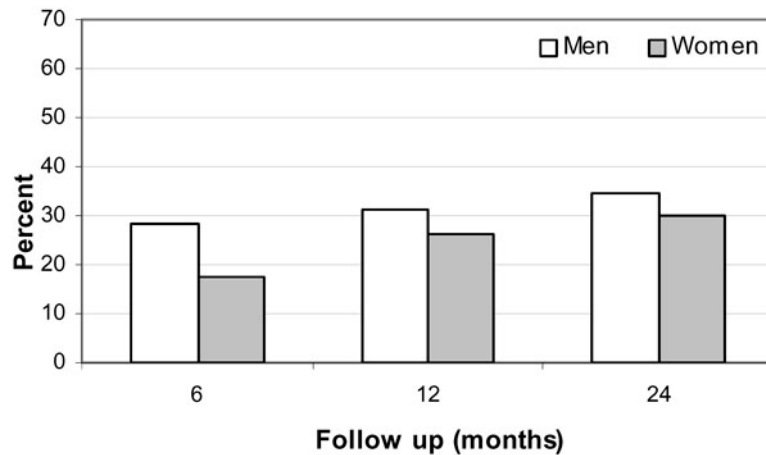
Men:	59	42	38	32
Women:	200	135	121	97

(a) ACR20 Improvement



Men:	46	45	32
Women:	170	149	114

(b) ACR50 Improvement



Men:	46	45	32
Women:	170	149	114

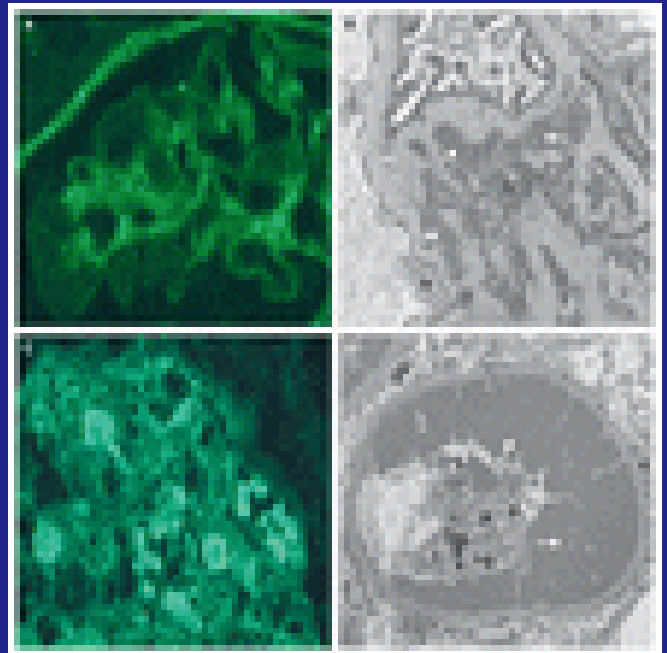
Sjogren's Syndrome

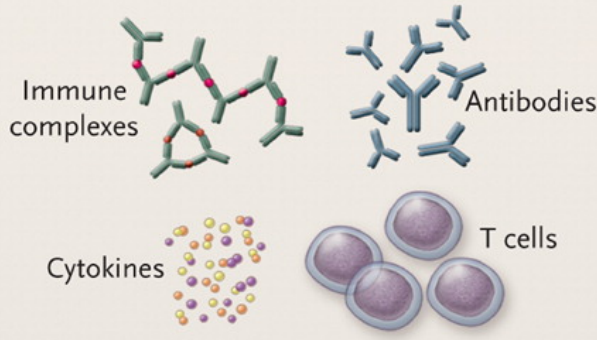
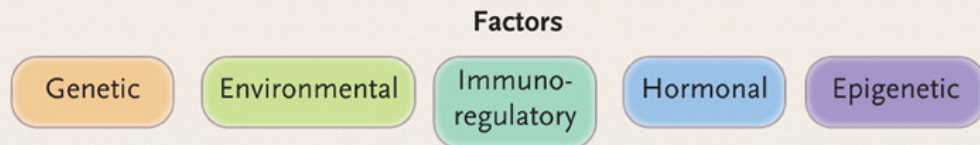


- Correlation between lower estrogens and testosterone and importance of tissular inflammation
- DHEAS blood levels lower than normal
- Possible pathogenic effect of estrogens deficiency on exocrine glands.
- In mice estrogen deficiency initiates tissue specific apoptosis (Arakaki,R et al;Immunotherapy, 2010, 2; 339- 46)

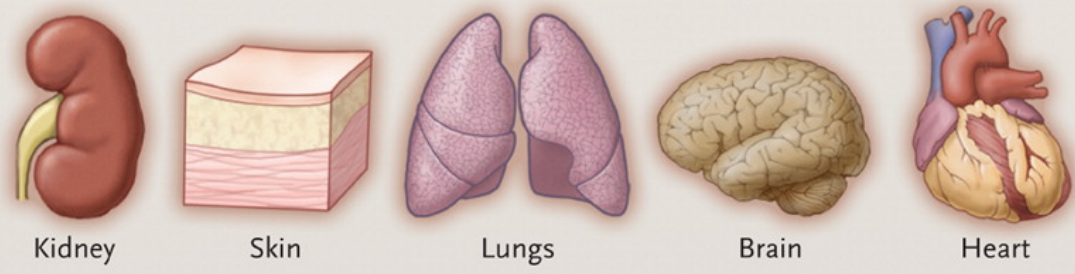


SLE





Organ damage



Systemic Lupus Erythematosus

- In most experimental models, the disease is more frequent and more severe in females
- In majority of cases clinical onset occurs between puberty and menopause
- Pregnancy and exogenous estrogens administration can increase autoantibodies levels and trigger clinical flares
- Men with lupus have an androgens / estrogens ratio lower than normal
- ANA in healthy individuals more prevalent in females (29%) than males (17%) ([Quan Zen Li et al, Arthr Res Ther, 2011, 13; R38](#))
- In men, cardiovascular and renal comorbidities are more frequent. ([Crosslin KL. Gend Med, 2011](#))



SLE and Pregnancy

- Risks for the patient
 - Flares are more frequent (Clowse et al, Obstet. Gynecol, 2006)
 - Arterial hypertension
 - Preeclampsia
 - HELLP syndrome
- Risks for the newborn
 - overall 20% miscarriages or stillbirths (Clark et al, J. Rheumatol. 2006)
 - Presence of Antiphospholipids antibodies increases risks of stillbirths
 - neonatal lupus –cardiomyopathy- congenital heart block-
 - maternal anti Ro/SSA activity



**1979
onset
Multisystem
Lupus**

**Disease
inactive
2
Successful
pregnancies**

**1985 2d
relapse**

**1997 3rd
relapse**

**2006 4th
relapse**

**2009
kidney
transplantation**

Rhumatoid Arthritis and pregnancy

- A prospective study of 140 women with RA
 - during pregnancy
 - 16% had complete remission
 - 66% improved
 - 16% worsened
 - After delivery
 - 77% had more swelling and pain than during pregnancy
(Barret et al, JAMA, 1999)
- Preeclampsia may be more frequent in women with RA
- Prematurity and lower birth rates in active RA (Wallenius et al, Arthr Rheum, 2011)
- Pregnancy may have a protective effect due to persisting microchimerism (Guthrie et al, Arthr Rheum, 2010)



Systemic Scleroderma

Risks during pregnancy

- renal crisis
- cardio-pulmonary complications
- miscarriages
- premature and small infants

immunosuppressive drugs during pregnancy

- Corticosteroids no risk
- Hydroxychloroquine no risk
- Sulfasalazin low risk
- Ciclosporin low risk
- Azathioprine low risk
- IV Immunoglobulins low risk

TO BE AVOIDED

- NSAIDs
- CYCLOPHOSPHAMID
- METHOTREXATE
- LEFLUNOMIDE
- MYCOPHENOLATE MOFETYL
- ANTI TNF ALPHA
- RITUXIMAB

Estrogens use and autoimmune diseases

- Estrogens must be used with caution in patients at risk for vascular thrombosis
 - SLE, SAPL
- Estrogens use for oral contaception in RA patients
 - Is associated with beneficial functional outcome in women with RA
 - (Camacho et al, Arthr. Rheum, 2011)
 - May have a protective effect on the onset of RA
 - (Jorgensen et al, Ann Rhem Dis, 1996)

Conclusions

- Care of patients with autoimmune diseases during pregnancy
 - Information and planning highly recommended
 - Pregnancy followed by an experienced obstetrician
 - Close followup during and after pregnancy by the internist
- Many immunosuppressive drugs have teratogenic effects
- The use of estrogens as contraceptive or post menopause
 - is possible in RA
 - must be discussed in a case by case approach in other diseases

Conclusions

- Gender differences in prevalence and severity of autoimmune diseases seem related to the interactions between hormonal balance and the immune system.
- The impact of the hormonal factor on immunity is complex and different in each autoimmune disease.
- To date, changes in hormonal status by therapeutical interventions have not shown substantial efficacy in clinical trials.
- Fetal microchimerism may be important in modulating the immune response
- A better knowledge of the physiopathological pathways involved in gender differences would benefit to all patients.
- Gender may be an important criteria for a tailored therapeutic approach.