EFFECT OF LOW-DOSE L-THYROXINE AND LACIDIPINE AS VASODILATORS ON THE MICROCIRCULATION IN SYSTEMIC LUPUS ERYTHEMATOSUS

Thesis

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LIST OF ABBREVIATIONS

ANA	: Antinuclear antibody
Anti-CL	: Anti-cardiolipin antibody
Anti-ds-DNA	: Anti-double-stranded DNA
C_3	: Complement 3
C_4	: Complement 4
CTD	: Connective tissue disease
L	: Lacidipine
LDF	: Laser Doppler flowmetry
NFC	: Nailfold capillarosocpy
PAOD	: Peripheral arterial occlusive disease
RP	: Raynaud's phenomenon
SLE	: Systemic lupus erythematosus
SS	: Systemic sclerosis
T	: Thyroxine

CONTENTS

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ABSTRACT

The effect of L-thyroxine (25 μg) and lacidipine (2 mg) on the microcirculation in SLE patients was studied by comparing pre- and post-treatment laser Doppler flow (LDF) parameters. We found that the drugs caused impairment of LDF measures. This can be attributed to endothelial dysfunction, platelet activation, or a "steal phenomenon". A significant negative correlation of platelet count and LDF parameters was observed.

Key Words: SLE, Laser, Doppler, Thyroxine, Lacidipine.

INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by multisystem involvement ***(Conaway, 1994).*** It has a considerable potential for morbidity and mortality. Vasculopathy in SLE can affect large vessels as well as small vessels. Vasculitic skin lesions include nail fold infarcts, ulcers and gangrene of the digits ***(Hahn, 1994).*** Raynaud's phenomenon in SLE is present in about 20% of patients ***(Lahita, 1997).*** Whereas duplex scanning of defined vessels has opened new horizons for the non-invasive evaluation of vascular disease, the recent development of laser Doppler flowmetry (LDF) has provided us with a direct modality to study the microcirculation and to assess response to treatment ***(Wollersheim and Thien, 1994).*** Conventional nail fold capillaroscopy (NFC) was applied to study capillary morphology of patients with collagen vascular disease. It was the merit of Maricq and co-workers to introduce the technique of dynamic capillaroscopy and to establish well-accepted criteria for diagnosing microangiopathy ***(Maricq et al., 1993).*** In the treatment of Raynaud's phenomenon, calcium channel blockers, especially nifedipine, have been used and found to be effective ***(Wollersheim et al., 1987).***

Hypothesis: Based on its ability to induce thermogulatory reflex cutaneous vasodilatation, Liothyronine was investigated as a potentially beneficial drug in Raynaud's phenomenon ***(Kontos, 1996).***

Lacidipine and low-dose L-thyroxine may be of value in the treatment of Raynaud's phenomenon and vasculopathy affecting the digits in SLE and scleroderma.

AIM OF THE WORK

To study and compare the effect of some vasodilators; low-dose L-thyroxine and lacidipine on the microcirculation of patients with systemic lupus erythematosus.

SYSTEMIC LUPUS ERYTHEMATOSUS

SLE is an autoimmune disease that affects many organ systems. Damage is mediated by tissue-binding autoantibodies and immune complexes. Female gender is permissive for SLE; 90% of patients are women in child-bearing age ***(Kotzin, 2002).***

Pathogenesis:

Interplay between genetic susceptibility, gender and environmental stimuli may result in autoimmunity. The abnormal immune responses include hyper-reactivity and hypersensitivity of T- and B-lymphocytes and inadequate regulatory mechanisms ***(Hahn, 1991).***

Susceptibility to SLE depends on multiple genes. Predisposing genes include HLA class II DR and DQ, and Class III genes encoding C2 and C4. C4QO, a defective class III allele that fails to encode a functional C4A protein is a common genetic marker. B8.DR3.DQW2, C4AQO is an example of extended haplotypes that predispose to SLE. Non-HLA genes include T-cell receptor gene associated with anti-Ro/SSA antibodies ***(Hahn, 1997).***

Environmental factors include exposure to ultraviolet light (UV), viruses, some drugs and chemicals. Exposure to UV causes flares in most patients. Possible mechanisms include increased apoptosis in keratinocytes and alteration in DNA and intracellular proteins rendering them antigenic.

- Epstein-Barr virus and retrovirus infection may play a role in expanding the abnormal immune response ***(Hahn et al., 2005).***

- Drugs that are most frequently responsible for SLE are procainamide, isoniazid and hydralazine ***(Lahita, 1997).***
- Femaleness is clearly a susceptibility factor. Estradiol binds to receptors on T- and B-lymphocytes increasing their activity and survival, thus favoring a prolonged immune response. Sex hormones also influence immune tolerance. Elevated serum prolactin levels was found in some SLE patients ***(Hahn, 1998).***

Diagnosis:

This is based on characteristic clinical features (Table 1), and autoantibodies (Table 2).

Classification Criteria for SLE

1.	*Malar* rash	
2.	*Discoid* rash	
3.	*Photosensitivity*	
4.	Oral *ulcers*	
5.	*Arthritis*	; non-erosive arthritis
6.	*Serositis*	; Pleuritis or pericarditis
7.	*Renal* disorder	; Proteinuria < 0.5 g per day. or cellular casts
8.	*Neurologic* disorder	; seizures or psychosis
9.	*Haematolgoic* disorder	; haemolytic anaemia, leukopenia, Lymphopenia or thrombocytopenia
10.	*Immunologic* disorder	; Anti-dsDNA, Anti-Sm or Antiphospholipid antibodies
11.	*Antinuclear* antibodies	; an abnormal titer of ANA

Table (1):

If 4 or more of these criteria are present, SLE diagnosis is likely ***(Edworthy, 2005)***

Autoantibodies of SLE

Antibody	Prevalence,%	Clinical utility
1. Antinuclear antibodies	98	Best screening test
2. Anti-ds DNA	70	SLE-specific, correlates with nephritis and vasculitis
3. Anti-Sm	25	SLE-specific
4. Anti-RNP	40	Associated with overlap syndromes
5. Anti-Ro (SS-A)	30	Associated with sicca syndrome, subacute cutaneous lupus and neonatal lupus
6. Anti-La (SS-B)	10	Associated with anti-Ro
7. Anti-histone	70	Drug-induced lupus
8. Anti-phospholipid	50	Predispose to clotting, foetal loss, thrombocytopenia. ELISA tests for cardiolipin and β2GP-1 antibodies, and DRVVT*
9. Anti-erythrocyte	60	Positive direct Coombs' test
10. Anti-platelet	30	Thrombocytopenia
11. Ant-neuronal	60	may correlate with CNS lupus
12. Anti-ribosomal	20	may correlate with depression or psychosis

Table (2)

* DRVVT, dilute Russell viper venom time

(Hahn, 2005)

Clinical manifestations:

- **Systemic** manifestations include fatigue, myalgia, arthralgia, fever and weight loss ***(Conaway, 1994).***

- **Musculo-skeletal features:** non-erosive arthritis affecting knees, wrists and hands are found. Myositis and ischaemic necrosis of bone can occur. Muscle weakness may result from systemic effects of cytokines (IL-1, IL-6, TNF) or side effects of therapy (steroids, chloroquine). Features of idiopathic inflammatory myopathy may dominate the clinical picture of some patients ***(Wortmann, 2005).***

- **Renal manifestations:** Nephritis is the most serious manifestation of SLE. Nephritis and infection are leading causes of death. Clinical renal involvement affects from 35 to more than 90% of patients ***(Glassock and Brenner, 1991).***

Table (3):WHO Pathological classification of Lupus Nephritis

Class	Description
I	Normal
II	Mesangial nephritis
III	Focal proliferative glomerulonephritis
IV	Diffuse proliferative glomerulonephritis
V	Membranous glomerulonephritis
VI	Advanced sclerosing glomerulonephritis

Proteinuria, nephrotic syndrome, hypertension and end-stage renal disease are the sequelae. Aggressive immunosuppression is

indicated, unless a high chronicity index (sclerosis) is obtained on renal biopsy ***(Kotzin, 2002).***

- **Cardiovascular features:**

Pericarditis is frequent. Myocarditis and Libman-Sacks endocarditis with potential valvular incompetence and thromboembolic events are serious manifestations. Lupus patients have accelerated atherosclerosis and are at increased risk for coronary artery disease ***(Hahn, 1998).***

Conduction defects and cardiomyopathy may occur. Vasculitis is common and may be reflected by the presence of splinter haemorrhages or digital infarcts. Vasculitis of the coronary or mesenteric vessels may be life-threatening. Raynaud's phenomenon occurs in about 20% of patients ***(Lahita, 1997).***

- **Pulmonary features:**

Pleurisy and pleural effusion are common. Lupus pneumonitis causes pulmonary infiltrates and plate-like atelectasis. However, the most common cause of infiltrates is infection. Interstitial lung disease, pulmonary hypertension and fibrosis occur occasionally. Infrequent but potentially fatal complications are acute respiratory distress syndrome (ARDS) and intra-alveolar haemorrhage ***(Hahn, 2005).***

- **Gastrointestinal manifestations:**

Nausea, diarrhea and vague discomfort are common manifestations, due to lupus peritonitis. Vasculitis of the intestine, presenting with vomiting, diarrhea and acute abdominal pain, may

be life-threatening, because of perforation, bleeding or sepsis. Pseudo-obstruction and acute pancreatitis are other recognized features ***(Conaway, 1994).***

● **Haematologic features:**

Normocytic anaemia of chronic illness is very frequent in SLE. Positive Coombs' tests, leucopenia, lymphopenia and thrombocytopenia are common ***(Edworthy, 2005).***

● **Neuro-psychiatric lupus:**

Any region of the CNS can be involved. Headaches, sleepiness, seizures, depression and psychosis are common. Other recognized neurologic manifestations include focal infarcts, pyramidal, extra-pyramidal disorders, cerebellar, hypothalamic dysfunction, aseptic meningitis, transverse myelitis, optic neuritis, cranial nerve palsies and peripheral neuropathy ***(Lahita, 1997).***

● **Cutaneous manifestations:**

Skin changes are present in about 80% of patients ***(Soter, 2005).*** These are many and include: butterfly rash, discoid rash, photosensitivity, alopecia, mouth ulcers, digital ulcers, vasculitic lesions, purpura, telangiectasias, livedo reticularis, paniculitis and sub-cutaneous nodules ***(Wallace, 1993).***

Lesions of subacute cutaneous lupus (SCLE) are annular or serpiginous and heal without scarring, but can leave areas of hypo-pigmentation. They are frequently associated with SS-A and SS-B antibodies, and may resemble psoriasis ***(Soter and Franks, 2005).*** Dermal vasculitis was found in 18 to 70% of patients ***(Wallace,***

1993). Raynaud's phenomenon (RP) occurs in 20% of patients, and is characterized by episodes of skin colour changes on exposure to cold ***(Cohen, 2002).*** Periungual telangiectasias are pathognomonic signs of the three major connective tissue diseases-SLE, scleroderma, and dermatomyositis ***(Bolognia and Braverman, 1998).***

- **Thrombo-embolic complications:**

Anti-phospholipid antibody syndrome (APS) can be associated with SLE. Recurrent deep vein thromboses, vascular occlusions and pregnancy losses can occur. IgG or IgM anticardiolipin antibodies (rarely IgA only) are found. Tests for antibody to β_2GP-1 may supplant anticardiolipin as a defining antibody ***(Lockshin, 2005).***

Disease activity indices:

These include 5 formal measures of disease activity:

- SLAM — Systemic lupus activity measure.
- SLEDAI — SLE disease activity index.
- SIS — SLE Index Score.
- BILAG — British Isles Lupus Assessment Group.
- ECLAM — European Consensus Lupus Activity Measurement

(Edworthy, 2005)