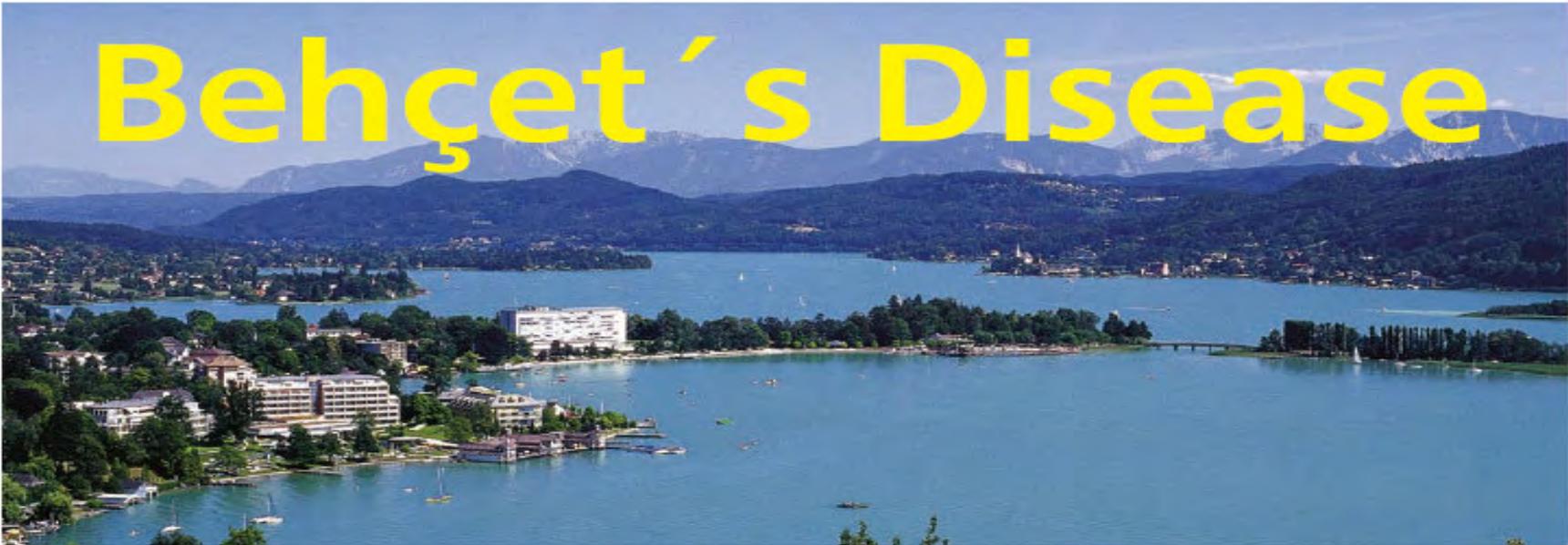




13th International Conference for

Behçet's Disease



Epidemiology • Pathogenesis • Clinical Findings • Management • Prognosis

May 24-27, 2008

Pörtschach / Klagenfurt (Austria)



How to reach Pörtschach / Klagenfurt

By plane you may reach Klagenfurt Airport directly from Berlin, Cologne, Düsseldorf, Frankfurt, Hamburg, Hannover, Leipzig, London, and Vienna



Venue:
Congress Center Wörthersee
Hauptstraße 203, 9210 Pörtschach am Wörthersee, Austria











13th ICBD

May 24~27, 2008
Congress Center Worthersee
Pörtschach / Klagenfurt Austria

***140papers**

- * Oral presentation-Scientific sessions (26)
- * Poster presentation (94)
- * Keynote lecture/ Plenary lecture (5)
- * Update study group (15)

***Meet the professor**

- dermatology, neurology, rheumatology

***Controversial discussion, Open for discussion**



Main Topic

- * **Epidemiology (14)**
- * **Pathophysiology and basic research (32)**
- * **Clinical manifestations (28)**
- * **Disease assessment, laboratory tests and imaging (14)**
- * **Clinical studies and treatment strategies (11)**
- * **Pediatric manifestations (5)**
- * **Oral, genital, and skin manifestations (12)**
- * **Ocular manifestations (13)**
- * **Manifestations of the central nervous system (8)**
- * **Patients' education (1)**

Presentations

Country	No. of abstract
Turkey	31
Iran	22
Korea	13
Tunisia	13
Japan	12
Germany	9
UK	7
Moroco	7
Greece	6
USA	5
France	4
Portugal	4
Spain	3
Netherlands	3
Russia, Austria, Iraq, Israel, Egypt	2
China, Jordan	1



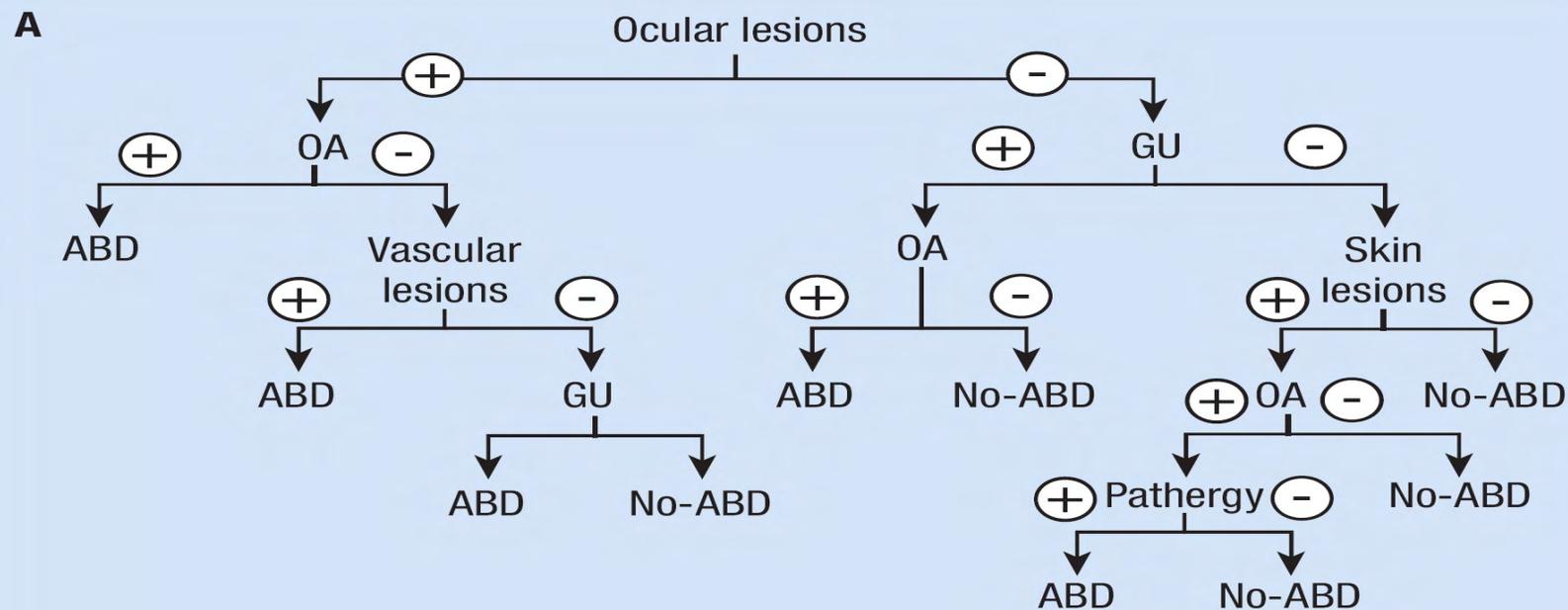
Plenary Lectures

1. Infections and immunosuppression (W. Graninger)
2. BD and central nervous system (A. Al-Araji)
3. Endothelium and thrombophilia (F. Espana)
4. BD at the pediatric age (I. Kone-Paut)
5. New perspectives for BD (H. Yazici)



Epidemiology-1

- * Validation of the International Criteria for BD in Germany, China, Iran, Spain (sensitivity, specificity, accuracy)



B

Diagnosis of Adamantiades-Behçet Disease is made with a score of 3 points:

- 1 point Oral aphthosis
- 1 point Skin manifestations (pseudo-folliculitis, skin aphthosis)
- 1 point Vascular lesions (phlebitis, superficial phlebitis, large vein thrombosis, aneurysm, arterial thrombosis)
- 1 point Positive pathergy test
- 2 points Genital aphthosis
- 2 points Ocular lesions

▲ **FIGURE 167-2** Revised International Criteria for Behçet's Disease (International Team for the Revision of ICB; coordinator: F. Davatchi) according to **(A)** the classification tree format, and **(B)** the traditional format. ABD = Adamantiades-Behçet disease; GU = genital ulcer; OA = oral aphthous ulcer. (From Zouboulis CC et al: Evaluation and revision of the International Criteria for Behçet's Disease (ICBD). Abstracts of the 21st World Congress of Dermatology, Buenos Aires, Argentina, 2007, in press, with permission.)



Epidemiology-2

- * Change in incidence of pathergy phenomenon in Behcet's disease over the time
- * HLA-B5(1) and risk of Behcet's disease: A meta-analysis of genetic association studies



Epidemiology-3

- * **HLA-B27 in BD, 5567 patients in Iran**

- Positive: 481 patients (8.6%)

- Odds ratio compared to the normal (3.69)

- Ankylosing spondylitis, chronic diarrhea, false positive VDRL, Type III and IV WHO glomerulonephritis

- * **HLA-B51 in BD, 1164 patients in Iran**

- Positive: 540 patients (46.4%)

- Favored some manifestations

- : Pathergy reaction, EN, joint manifestations, myocardial infarction, arterial thrombosis

- Not clinically as important to use it for any decision making



Pathophysiology and Basic Research-1

* Gene

* HLA Class I phenotype

- * Positive correlation: HLA-A2, B5, Bw4, Bw6
- * Negative correlation: HLA-A1, A3, A9, A10, A28, A29
- * HLA-B51: a prognostic indicator for a possible severe eye involvement, esp in male Behcet's disease patients

* HLA-A2/B51 combination related to genital lesion

- * Significant relationship between HLA-A26 locus and ocular lesions

* IL-18 promoter polymorphism

- * Susceptibility to Behcet's disease, esp to mucocutaneous form

- * **NODs single nucleotide polymorphisms**

- * **NOD** (nucleotide-binding oligomerization domain)

- : related with the innate immunity and inflammatory control

- * Two of three NOD2 variant alleles associated with Crohn's disease are significantly less present in BD compared to healthy controls.

- > The variant alleles might protect BD.

- * **P Selectin glycoprotein ligand-1 (PSGL-1) variable number of tandem repeats (VNTR) polymorphism**

- * **PSGL-1**: important adhesion molecule involved in lymphocyte recruitment

- * Increased risk of thrombosis in patients with anti-phospholipid antibody syndrome

- * Contribute to the thrombotic tendency observed in patients with BD

- * **IFNAR1 and IFNAR2 polymorphisms in patients with BD**
 - * IFNAR1, IFNAR2 polymorphisms were disclosed to confer susceptibility to multiple sclerosis characterized by **Th1 polarization**
 - * BD patients had a significantly higher frequencies of the genotypic combinations of IFNAR1 and IFNAR2 polymorphisms
-> **jointly but not individually**, may confer susceptibility to BD

- * **CTLA-4 gene polymorphisms**
 - * **CTLA4**
 - Co-stimulatory molecule expressed on activated T cells
 - Plays a key role of inhibitory regulator of the T lymphocyte activation
 - * **SNPs of promoter region on CTLA4 gene** have a candidate predisposing to BD
 - * **The CTLA4-1722T>C** polymorphism may contribute to the clinical useful marker of BD with **ocular lesion**



Pathophysiology and Basic Research-2

* Cell

* **Endothelial progenitor cells (EPCs)**

- * A subtype of BM-derived progenitor cells expressing surface antigens of both hematopoietic stem cells and endothelial cells: maintenance of vascular integrity and neoangiogenesis
- * **Severe reduction of circulating EPCs** in BD -> **impaired endothelial recovery** -> vascular damage

* **RBCs**

- * EM changes in RBCs of BD patients
 - : increased proportions of non-discocytic erythrocytes
 - > reduced deformability -> impair blood flow, endothelial dysfunction, tissue hypoxia

* **PMN cells**

- * Elevated serum MPO in BD -> increased activation of PMN, increased production of free radicals, LDL oxidation-> oxidative stress
- * Decreased serum lactoferrin -> impaired antioxidant defense



Pathophysiology and Basic Research-3

* Cytokine

- * IL-12, IL-6, IL-8, IL-17
- * IL-6 siRNA injected symptomatic BD mice
 - * Downregulate IL-6, decreased severity score, upregulated Foxp3+ Treg cells
- * Impaired interferon-beta production from plasmacytoid dendritic cells in patients with BD after CPG-ODN stimulation

* Infections

- * **Oral streptococci**
 - * Bes-1 DNA and HSP-65 derived from *S. sanguinis* (previously called as *S.sanguis*) in mucocutaneous lesions of BD patients
 - * Bes-1 gene: highly homologous with the peptides of human HSP-60
 - * HSP-65 and HSP-60: high homologies to T cell epitope
 - > proinflammatory Th1 type cytokine production



Pathophysiology and Basic Research-4

* Antimicrobial peptides

* CSA-13

- * Antimicrobial cationic steroid mimic
 - : functions against harmful bacterial infections
 - : suppressive effect to vascular morphogenesis
 - > treatment of hyper-progressive ocular vasculitis

* Human neutrophilic peptide (HNP) 1-3, LL37, S100

- * Salivary HNP 1-3 levels were significantly higher in patients with BD
 - : associated with severe organ involvement
- * Salivary LL37 and S100 levels seemed to be higher in BD
 - : correlated with the frequency of oral ulcers and plaque index score reflecting microbial plaque accumulation
- * Salivary levels of **HNP 1-3, LL-37 and S100** might be related to **disease severity, oral ulcer activity and oral infection focuses** in BD.



Pathophysiology and Basic Research-5

* Toll-like receptor (TLR)

- * TLR expression (TLR 1, TLR2, TLR3, TLR4, TLR9) at rest and after stimulation, in T cells and monocytes from patients with BD **did not differ** from that of healthy individuals
- * TLR signaling is **not impaired** in patients with BD

* TLR and VitD

- * Higher expression of TLR2 and TLR4 in the monocytes of active BD
- * Serum 25(OH)VitD was lower in active BD.
- * VitD3 dose-dependently suppressed the expressions of TLR2 and TLR4.
-> VitD: may be a therapeutic option in BD

* TLR and Heme oxygenase (HO)-1

- * Reduced expression of HO-1 in PBMC from active BD
- * Increased expression of TLR4 in PBMC from BD
-> Microbial pathogen stimulate the innate immune system through TLR4 in PBMC
-> **Defective HO-1 expression contribute to augmentation of inflammation**



Pathophysiology and Basic Research-6

- * **EGFR and its ligands in buccal swabs**
 - * Not increased secretion of EGF and TGF- α in BD patients with active oral ulcers
 - * High expression of EGFR during remission
 - * Downregulated expression of EGFR during active ulcerations
- * **Killer immunoglobulin-like receptor (KIR)**
 - * HLA-B51 express the Bw4 epitope that can bind to a group of polymorphic receptors (KIR) expressed on NK cells and cytotoxic T cells.
 - * KIR3DL1/S1 allelic association with BD
 - > **HLA-KIR interaction is involved in the development of BD.**
- * **Soluble endothelial protein C receptor (EPCR)**
 - * EPCR was discovered at the surface of endothelial cells, binds protein C, and enhances its activation.
 - * Soluble EPCR was also detected in plasma.
 - * Plasma sEPCR was significantly higher in patients with BD



Pathophysiology and Basic Research-7

* Disease activity marker

* Adiponectin

- * Adiponectin from adipose tissue: **antiinflammatory effect**
 - Decreases expression of adhesion molecules
 - Inhibits attachment of active macrophage to endothelial surface
- * Serum adiponecin levels **were high during both active and inactive stage** in patients with BD.

* B-cell activating factor of the TNF family (BAFF)

- * Polarization of T lymphocytes toward the Th1-type
- * Serum BAFF was associated with increased disease activity in BD.
 - > useful marker for the disease activity and potential therapeutic target

* Homocysteine

- * Independent risk factor for venous or arterial thrombosis in Iranian patients with BD
- * Negative correlation between HLA-B51 and serum homocysteine



Treatment Strategies-1

- * **Rebamipide (Mucosta[®])**
 - * Improve the efficacy of colchicine for the herpes simplex virus-induced inflammation in a BD mouse model
- * **Rituximab (anti-CD20 monoclonal antibody)**
 - * Reduce macular edema on fluorescein angiography and optical coherence tomography
- * **N-acetyl cysteine** as an adjuvant therapy
 - * No additional benefit on disease activity
- * **The effect of immunosuppressive treatment on skin pathergy reaction**
 - * Colchicine, azathioprine, cyclosporine, or interferon-alpha 2b does not affect the skin pathergy reaction.



Treatment Strategies-2

- * **Treatment of sight-threatening panuveitis**
 - * Single infliximab infusion has a faster beneficial effect than intravitreal triamcinolone or high dose intravenous methylprednisolone.
- * **Combination therapy** of pulse cyclophosphamide, azathioprine, and prednisolone is **the best choice in ocular BD**
 - * 1000mg cyclophosphamide in 500 ml serum saline 5% once monthly, 2-3mg/kg azathioprine daily orally, 0.5mg/kg prednisolone daily orally
- * **Mycophenolate sodium (case report)**
 - * A good therapy before using biologicals or chemotherapeutics in therapy-refractory BD patients with severe ileo-colitis.



Oral, Genital and Skin manifestations

* Clinical feature

- * **Pemphigus vulgaris misdiagnosed as aphthae**
- * **BD mimickers**
: recurrent aphthous stomatitis, pemphigus vulgaris, erosive lichen planus, bullous pemphigoid, herpes simplex, erythema multiforme, fixed drug eruption, drug eruption, candidiasis, mechanical ulceration, psoriasis, SLE, vasculitic ulceration
- * **Index for oral ulcer activity** : VAS pain score
- * **Oral ulcer activation after dental and periodontal treatment**
- * **Case report**: EM, Cutaneous PAN

* Therapy

- * **Sublingual IFN-a tablet**: effective
- * **Topical tacrolimus** for mucosal lesion: effective
- * **Tropical Nigella sativa 100% oil**: safe and effective for RAS
- * **Zinc sulphate 5% mouthwash**: effective, prophylactic for RAS
- * **Bifidobacterim lactis DN-173 010 strain**: effective



Eye involvement and treatment-1

* Clinical feature

- * **Pathergy reaction on conjunctiva after intravitreal TA injection**
- * **A specific finding of Behcet's uveitis:** inferior peripheral pearl-like precipitates
- * **The risk factors of blindness in Behcet's disease:** higher frequency of uveitis, longer duration of uveitis, retinal vasculitis, initial low vision

* Therapy

- * **Intravitreal TA injection:** effective for the suppression of recurrent ocular inflammation, but high frequency of complications
- * **Interferon-alfa vs cyclosporine in ocular BD:** long-term remission and better final visual acuity in IFNa compared to CyA
- * **Cyclophosphamide pulse therapy:** effective for treatment of severe ocular involvement like posterior segment uveitis or panuveitis in BD
- * **N-acetyl cysteine as anti-oxidant therapy:** effective as alternative therapy, but not conclusive



Eye involvement and treatment-2

- * **Chemokine environment of intraocular lymphocytes in BD uveitis**
 - * **Aqueous humor of non-BD:** CD4+ cells-> high expression of CXCR3
 - * **Aqueous humor of BD:** CD8+ cells, high expression of IL-8, IP-10
- * **TNF-alpha level in BD patients with and without ocular involvement**
 - * Serum TNF-alpha level is higher in BD patients with ocular involvement
- * **Osteopontin (OPN)**
 - * Acidic phosphoglycoprotein, contains arginine-glycine-aspartic acid cell-binding sequence in extracellular matrix
 - * Act as a cytokine contributing to the development of Th1 immunity
 - * Experimental autoimmune uveoretinitis (EAU): a model for human intraocular inflammation such as BD
 - > EAU was ameliorated in OPN-deficient mice and wild type mice treated with OPN neutralizing antibody or OPN-siRNA



Neurologic involvement and treatment

* Clinical feature

- * **Recurrent meningitis, pseudotumor cerebri**
- * **Neurologic manifestation of BD** in USA, Japan, Turkey
- * **Symptom Check List 90-Revised in BD:** SCL 90-R was unable to detect major psychological symptoms in BD.

* Therapy

- * **Infliximab for chronic progressive neuro-BD:** effective treatment by reducing CSF IL-6 levels, smoking might be one of resistance factors to treatment.
- * **Interferon-alpha 2a:** effective in refractory juvenile BD with CNS involvement



Vascular involvement

- * **Large vessel involvement**

- Aortic and peripheral arterial involvement at an older age compared to pulmonary artery aneurysm and venous involvement, not associated with venous lesions

- * **Intracardiac thrombosis**

- * **Pulmonary artery aneurysm**

- * **Coronary artery aneurysm**

- * **Vascular involvement of the intra-abdominal organs**

- SVC obstruction, IVC obstruction, Budd-Chiari syndrome, mesenteric artery aneurysm, splenic artery thrombosis, mesenteric artery occlusion, pulmonary embolism



Other involvement

- * **Sacroilitis and HLA B27**
 - not increased in BD
- * **Thyroid disorders**
 - Graves' disease, Hashimoto's thyroiditis, thyroid nodule, diffuse goiter
- * **Renal involvement**
 - Renal lithiasis, amyolodosis, CRF, hematuria, arterial hypertension, renal TB
- * **Chylothorax and chylopericardium**
- * **Sjogren's syndrome**
- * **Comorbidities in BD**
 - diabetes mellitus, renal disorder, malignancy
- * **Malignancy**
 - BCC, rectal adenocarcinoma, lung cancer

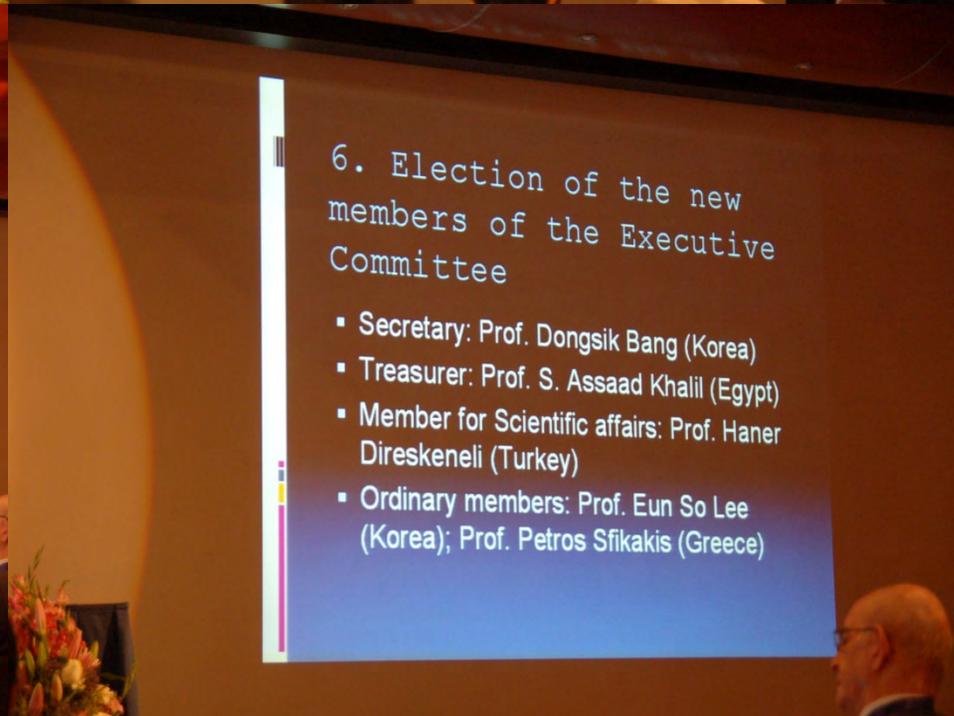
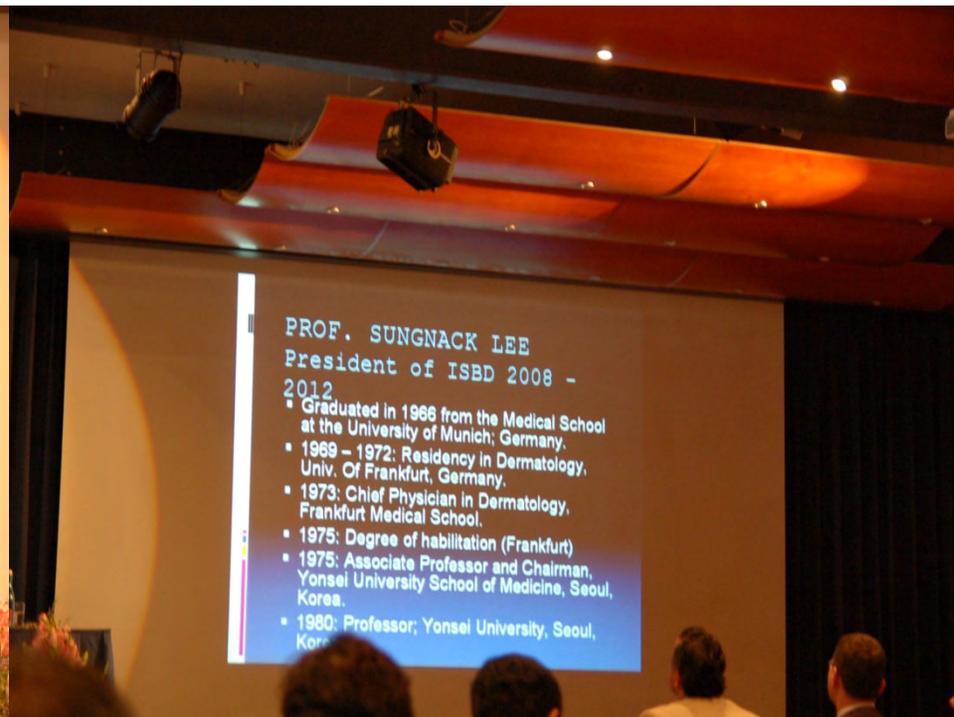


Disease assessment

- * **Intima-media thickness (IMT) of carotid artery in BD**
 - Thinning of IMT: risk factor of aneurysm formation
- * **Increased carotid arterial stiffness (augmentation index: AI) and thickness (IMT) in BD**
 - Independent predictors of elevated cardiovascular risk
- * **Reduced pressure wave reflections (low AI) in active BD**
- * **PPD reaction is not augmented in BD**
 - not affected by the pathergy reaction
- * **Nailfold capillaroscopy In BD**
 - Nail fold abnormality, mainly enlarged capillaries are frequent in BD. These may be related to superficial phlebitis or high blood pressure.

HULUSI BEHCET AWARD







- * **The 14th ICBD**
 - * United Kingdom (London)
 - * July 7-10, 2010
 - * President : Prof. Dorian O Haskard F



Thank You!!