Inflammation in End-stage Renal Disease
- the fire that burns within

Antalya 14 May 2009

Peter Stenvinkel, MD, PhD
Chronic Kidney Disease - It's More Common Than You Think

462,293 individuals from Taiwan.
National prevalence of CKD 11.9%

CKD - a public health priority

Extremely High Risk for Cardiovascular Complications in CKD

- AIDS + HAART >95% five year survival
- Testicular cancer 95%
- Breast cancer 85%
- Bladder cancer 75%
- Kidney transplant 75%
- Rectal cancer 62%
- Cervix cancer 60%
- Colonic cancer 54%
- Dialysis 46% (10 yr survival <15%)
- Ovarian cancer 44%
- Stomach cancer 20%
- Lung cancer

Sources:
- Cancer Research UK 2005
- UK Renal Registry 2006
- USRDS 2006
- ADEMEX
- HEMO
- Cano et al. JASN 2007
- Intensified nutrition
- Homocysteine lowering
- Jamieson et al. JAMA 2007
- Wanner et al. NEJM 2005
- Fellström et al. NEJM 2009
- AURORA
- FOSIDIA
- L
- P=0.09
- Zannad et al. KI 2006
- CHOIR
- Singh et al. NEJM 2006
- Drueke et al. NEJM 2006
- CREATE
Overflow of Manuscripts on Systemic Inflammation in CKD

Oh.. please do not put the manuscript there - that is where I am going to put my head.
At What Point in the Natural History of Chronic Kidney Disease do Inflammation Become Evident?

Causes of Altered Cytokine Balance in CKD


IL-6 -174 genotype and response to vaccination
Elevated CRP Levels Are a Common Finding in Patients on Dialysis

Analysis of CRP levels in 1,761 patients on HD

HD, haemodialysis; CRP, C-reactive protein

Bradbury B et al. 39th Annual Meeting of the American Society of Nephrology; November 14–19, 2006; San Diego, CA
CRP - A Moving Target

Hazard ratios for death following adjustment for age, sex, vintage, co-morbidity (Davis score) and type of access

- 3 month observational study with weekly hsCRPs
- n=228 prevalent HD pts

Snaedal et al. In Press AJKD 2009
Less Inflammation in Asian Dialysis Patients

Europe (Stenvinkel et al)  
Korea (Noh et al)  
CRP cut-off 8 mg/l

Prevalence (%)  
0 10 20 30 40 50 60 70 80 90 100

Europe (Stenvinkel et al)  
Japan (Iseki et al)  
CRP cut-off 10 mg/l

Prevalence (%)  
0 10 20 30 40 50 60 70 80 90 100

Europe (Stenvinkel et al)  
Hongkong (Wang et al)  
CRP cut-off 10 mg/l

Prevalence (%)  
0 10 20 30 40 50 60 70 80 90 100
Inflammation Biomarkers Are Risk Predictors in CKD Patients

The association of sudden cardiac death with inflammation and other traditional risk factors

Rulan S. Parekh\textsuperscript{1,2,4}, Laura C. Plantinga\textsuperscript{3,4}, W.H. Linda Kao\textsuperscript{3,4}, Lucy A. Meoni\textsuperscript{1,4,5}, Bernard G. Jaar\textsuperscript{1,3,4}, Nancy E. Fink\textsuperscript{1,3,4}, Neil R. Powe\textsuperscript{1,3,4,6}, Josef Coresh\textsuperscript{1,3,4,5} and Michael J. Klag\textsuperscript{1,3,4,6}

Suliman et al. QJM 2008

Bologa et al. AJKD 1998

Zimmermann et al. KI 1999

Heine et al. KI 2008

Suliman et al. QJM 2008

KI Sept 2008

Survival, %

Survival time (months)

0 200 400 500 600 700 800

Survival, %

Routine CRP

18

0.6

0.4

0.2

0.0

Time (months)

0 10 20 30 40

500-day prospective study in hospitalization or surgery

IL-6

Low IL-6

High IL-6

p<0.001

CD14\textsuperscript{+}CD16\textsuperscript{-} monocytes
Inflammation – A Catalyst for Other Cardiovascular Risk Factors? (I)


Metry et al. EJCI 2008

Carrero et al. JASN 2009

Carrero et al. CJASN 2008
The inflammation-catalyst hypothesis:
Persistent inflammation may exacerbate the effect of other concurrent risk factors. The presence of persistent inflammation magnifies the risk of poor outcome via mechanisms related to self-enhancement of the inflammatory cascade and exacerbation of wasting and vascular calcification processes.
Inflammation – A Catalyst for Other Cardiovascular Risk Factors? (II)

52 non-diabetic CAPD patients

The distinct subset of CD14++ CD16+ monocytes is characterized by their unique pattern of chemokine receptors.

Chemokines and Their Receptor CCR5 Play a Role in the Pathogenesis of Atherosclerosis

Blockade of the CCR5 may provide a novel therapeutic approach in inflamed dialysis patients.

It is suggested that all the Δ alleles originated from a single mutation event that occurred 1000 yrs BC and that subsequent epidemics of plague (or smallpox) put a selective pressure on the CCR5 gene.

Patients with a dysfunctional CCR5 due to the gene polymorphism CCR5 deletion 32 (CCR5Δ32) have improved prognosis in atherosclerotic disease (Szalai et al. Atherosclerosis 2001)

Muntinghe et al. In Press JASN 2009

Incident dialysis patients
- NECOSAD (n=413)
- MIA (n=302)
Multiple Causes of Wasting Beside Malnutrition

Fouque et al. KI 2008
Inflammation and Wasting have Additive Effects on Cardiovascular Death

Data adjusted for age, gender and diabetes mellitus

Surviving (%)

Observation time (months)

N=310
Likelihood ratio 34.5
P<0.0001

Avesani et al. Kidney Int 2007
Excess mortality due to interaction between protein-energy wasting, inflammation and cardiovascular disease in chronic dialysis patients

Mortality rates (100 person years)

815 incident dialysis pts followed 7 yrs

Expected death rates

Suggest the existence of a syndrome where the whole is more than its parts

NDT 2008
CRP: Is it a risk **factor** or just a **marker**?
C-reactive protein and its role in metabolic syndrome: mendelian randomisation study


Common haplotypes for the CRP region

<table>
<thead>
<tr>
<th></th>
<th>Estimated frequency (SE)</th>
<th>Plasma CRP (mg/L) (geometric mean, 95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CGC</td>
<td>0.37 (0.006)</td>
<td>1.81 (1.66-1.96)</td>
</tr>
<tr>
<td>CGT</td>
<td>0.26 (0.005)</td>
<td>1.70 (1.58-1.83)</td>
</tr>
<tr>
<td>CAC</td>
<td>0.30 (0.006)</td>
<td>2.03 (1.90-2.18)</td>
</tr>
<tr>
<td>GGT</td>
<td>0.07 (0.003)</td>
<td>1.39 (1.23-1.56)</td>
</tr>
</tbody>
</table>

- To generate unconfounded and unbiased estimates of any causal association between CRP and the metabolic syndrome.
- CRP haplotypes **not** associated with potential confounding variables.
**Conclusion:** CRP is a risk marker not a risk factor. Inflammation may rather play a causal role in vascular disease via upstream effectors.
Emerging Biomarkers for Evaluating Cardiovascular Risk in the Chronic Kidney Disease Patient: How Do New Pieces Fit into the Uremic Puzzle?
IL-6 Predicts Poor Outcome in ESRD

Bologna et al. AJKD 1998

Interleukin-6 is an independent predictor of mortality in patients starting dialysis treatment

Roberto Pequito-Filho, Peter Bárány, Bengt Lindholm, Olof Heimbürger and Peter Stenvinkel

Interleukin-6 is a stronger predictor of total and cardiovascular mortality than C-reactive protein in haemodialysis patients

Vincenzo Panciël1, Umberto Maggiore2, Daniele Taccola1, Massimilano Miglieri1, Giovanni Manca Rizzo1, Cristina Campani1, Alessio Bertini1, Stefano Sposini1, Rafael Pereira-Garcia1, Paolo Rindi1, Roberto Fiala1 and Cito Tetta1

Plasma Interleukin-6 Predicts Cardiovascular Mortality in Hemodialysis Patients

Madhumathi Rao, MD, Daqing Guo, MD, Mary C. Perianayagam, PhD, Hoone Tighiouart, MS, Bertrand L. Jaber, MD, Brian J.G. Pereira, MD, Vaidyanathapuram S. Balakrishnan, MD, and the HEMO Study Group

900-day prospective study in 90 HD patients with no acute infection, hospitalization or surgery
Pro-atherogenic Effects of IL-6

IL-6 exacerbates early atherosclerosis in mice (Huber et al. Arterioscler Thromb Vasc Biol 1999)

High IL-6 reflects endothelial dysfunction (Nawawi et al. Atherosclerosis 2003)

IL-6 decrease adiponectin mRNA (Bruun et al. Am J Physiol Endocrinol Metab 2003)

IL-6 expression is involved at the fibrous plaque stage (Elhage et al. Atherosclerosis 2001).

Chlamydia pneumoniae IgA and elevated level of IL-6 may synergize to accelerate coronary artery disease (Jha et al. J Cardiol 2008)

Polymorphism in the IL-6 promoter region is associated with markers of subclinical atherosclerosis (Hulkonnen et al. Atherosclerosis 2008)
Catabolic Effects of IL-6

- Stimulates breakdown of muscle protein (Cederholm et al. AJCN 1999)
- IL-6 inhibits the secretion of IGF-1 (Barbieri et al. Am J Physiol Endocrinol 2003)
- IL-6 receptor antibody inhibit muscle atrophy in IL-6 transgenic mice (Tsujinaka T et al. JCI 1996)
- IL-6 inhibits the secretion of IGF-1 (Barbieri et al. Am J Physiol Endocrinol 2003)
- IL-6 infusion reduces food intake and gastric emptying (McCarthy Res Nurs Health 2000)
- Activation of the acute phase response by IL-6 requires high rates of hepatic protein synthesis

Activation of the acute phase response by IL-6 requires high rates of hepatic protein synthesis
Variants in the IL-6 Gene is Associated with Vascular Disease and Metabolic Syndrome

Brief Genetics Report
Interleukin-6 Gene Polymorphism and Insulin Resistance

Variation in the Interleukin-6 Receptor Gene Associates With Type 2 Diabetes mellitus, IL-6 Haplotypes, Inflammation, and Risk for Cardiovascular Disease in a Multiethnic Dialysis Cohort

Yongmei Liu,* Yvette Berthier-Schaad,++ Margaret D. Fallin,† Nancy E. Fink,‡ Russell P. Tracy,§ Michael J. Klag,† Michael W. Smith,‡,¶ and Josef Coresh†

*Wake Forest University School of Medicine, Winston-Salem, North Carolina; †Johns Hopkins Medical Institutions, Baltimore, Maryland; ‡Laboratory of Genomic Diversity and §Basic Research Program, SAIC-Frederick, National Cancer Institute, Frederick, Maryland; and ¶University of Vermont, Burlington, Vermont
Multiple Inflammatory Pathways Contribute to the Development of CVD

Functional Variants in the Lymphotoxin-α Gene Predict Cardiovascular Disease in Dialysis Patients

Yongmei Liu, Yvette Berthier-Schaad, Laura Plantinga, Nancy E. Fink, Russell P. Tracy, Wen Hong Kao, Michael J. Klag, Michael W. Smith and Jan Kovesh

Wake Forest University School of Medicine, Winston-Salem, North Carolina; Johns Hopkins School of Medicine, Baltimore, Maryland; Laboratory of Genomic Diversity and Basic Research Program, National Institute, Frederick, Maryland; and University of Vermont, Burlington, Vermont.

TNF-β that is encoded by lymphotoxin-α gene (LTA) regulates adhesion molecules and inflammation. A genome-wide case-control study showed that LTA gene variants predisposed to cardiovascular disease. In a prospective study of 775 dialysis patients, LTA and IL-6 gene variants were tested as independent predictors of risk. Four polymorphisms in the LTA gene and one in the IL-6 gene were genotyped in patients and controls from medical records. During a mean follow-up of 2.6 yr, 294 first-incident CVD events occurred. The LTA variant predicted higher adjusted CVD risk (hazard ratio HR 1.33 for each additional copy of the Asn allele, 95% confidence interval 1.14 to 1.55; P = 0.0003). Two other nonsynonymous polymorphisms in IL-6 (174G and 572C) were associated with lower inflammatory activity and CVD risk. LTA haplotypes (based on the single nucleotide polymorphisms) were associated with inflammatory markers and predicted CVD risk (P = 0.0003) after adjustment. LTA genotype associations were independent of the IL-6 −174G/C genotype association that was reported. LTA and IL-6 gene variants independently predicted risk for CVD among dialysis patients, suggesting that activity in multiple inflammatory pathways contribute to the development of CVD.


“Lymphotoxin-α and IL-6 gene variants independently predicted risk for CVD among dialysis patients”.

Could the development of gene chips help us to identify risk patients?
Classical Pro-inflammatory Cytokines are not the Sole Mediators of Muscle Loss

Many studies show that neutralization of one or more of the classical cytokines does not lead to amelioration of muscle atrophy.

Newly described member of the TNF superfamily which induce
- cellular growth and proliferation
- angiogenesis
- osteoclastogenesis
- stimulation of apoptosis

TWEAK induces skeletal muscle atrophy through inhibition of the ubiquitin-proteasome and NF-κB systems

TNF-related weak inducer of apoptosis (TWEAK) is a potent skeletal muscle-wasting cytokine

Charu Dogra, Harish Changotra, Nia Wedhas, Xuezhong Qin, Jon E. Wergedal, and Ashok Kumar

Musculoskeletal Disease Center, Laboratory for Skeletal Muscle Physiology and Neurobiology, Jerry L. Pettis Memorial Veterans Administration Medical Center, Loma Linda, California, USA; and Loma Linda University School of Medicine, Loma Linda, California, USA
Levels of TWEAK Modulate the Effects of Inflammation on Outcome in Prevalent Dialysis Patients

- sTWEAK plasma levels may be associated with cardiovascular and all-cause mortality in HD patients with systemic inflammation through pathways that may relate to increased muscle wasting.
- TWEAK may be a major mediator of skeletal muscle loss in inflamed disease states.

Carrero et al. CJASN 2008
Pentraxin 3 - a New Kid on the Block

Interleukin-6

Toll-like receptor
TNF-α
IL-1β

Mononuclear cells
Fibroblasts
Endothelial cells
Adipocytes (?)

Short pentraxins
- CRP
- SAP

Long pentraxins
- PTX3

Opsonization
Inflammation tuning
Complement activation
Resistance to pathogens
Plasma Pentraxin 3 in Patients with Chronic Kidney Disease: Associations with Renal Function, Protein-Energy Wasting, Cardiovascular Disease, and Mortality

Mengli Tong, Juan Jesús Carrero, Rashid Qureshi, Björn Anderstam, Olof Heimbürger, Peter Bárány, Jonas Axelsson, Anders Alvestrand, Peter Stenvinkel, Bengt Lindholm and Mohamed E. Sullman

Divisions of Baxter Novum and Renal Medicine, Department of Clinical Science, Intervention and Technology, Karolinska Institutet, Karolinska University Hospital Huddinge, Stockholm, Sweden; and Division of Renal Medicine, Hangzhou Hospital of Traditional Chinese Medicine, Hangzhou, China

CJASN 2007
Correlations Between PTX3, Urinary Albumin Excretion and Endothelial Function

PTX3, ng/ml

U-Albumin, mg/24 hours

Rho=0.22; p=0.002

CKD 5 patients

Suliman et al. Submitted 2007

CJASN 2008
12 Weeks of ACEI Treatment (Ramipril) Normalizes Endothelial Dysfunction and PTX3

- 49 selected typ-2 diabetic patients with GFR ≥90 ml/min and urinary protein excretion 500-3000 mg/day.
- Open label study The study was registered in clinicaltrials.gov as NCT00674596

Yilmaz et al. CJASN 2009
Which Way To Go Regarding Treatment?

An Outline of the Uremic Syndrome

- Retention of Na and water
- Retention of potassium
- Retention of phosphate
- Retention of toxic metabolites
- Disturbed hormonal secretion
- Disturbed kidney metabolic function

- Edema
- Arterial hypertension
- Ocular disturbances
- Peripheral neuropathy
- Malnutrition
- Pruritus
- Immune depression
- Gastrointestinal disturbances
- Protein calcification
- Hyperintoxication
- Arrhythmias
- Renin excess
- Hypertriglyceridemia
- Glucose intolerance
- Erythropoietin deficiency
- Broken red cell production
- Anemia
- Calcium malabsorption
- Hypocalcemia
- Secondary hyperparathyroidism
- Osteosclerosis
- Skeletal deformities
- Pericarditis
- Peripheral ischemia
- Cardiac tamponade
- Spontaneous bone fractures

- Bone dissolution
- Calcium deficiency conversion of vitamin D into active products
- Resistance to PTH
- Resistance to vitamin D
- Osteitis fibrosa
- Bone pain
- Decreased insulin metabolism
- Osteomalacia
- Rickets

- Pulmonary edema
- Pseudo-gout
- Cardiac arrest
- Cardiac failure
- Gastrointestinal bleeding
- Infectious diseases
- Convulsions
- Gastrointestinal bleedings

There will never be a silver bullet
Integrated Treatment Approach of Inflammatory-Associated Wasting

Stenvinkel et al. *Semin Dial* Nov 2004

- **Adequate energy and protein intake**
- **Correction of acidosis, anemia, vitamin supplementation**
- **Dietary and pharmacological anti-inflammatory and anti-oxidative treatment**
- **Targeted anti-cytokine therapy**

**Adequate dialysis treatment**
How Do We Handle Dialysis Patients with Signs of Inflammation?

Evaluate and treat co-morbidities that may cause inflammation:
- Infectious complications
- Silent ischemic heart disease
- Intercurrent clinical events
- Peridontal disease
- Failed kidney transplant
- Volume overload
- Inflammatory diseases

Consider anti-inflammatory treatment strategies:
- Nutritional intervention
- Physical training
- Pharmacological intervention


Percentage of patients with a normal CRP level at baseline and at 12-mo follow-up

- Short daily HD
  - P < 0.01
- Conventional HD
  - P = 0.56

Volume overload
Inflammatory diseases
Bioincompatible dialysis fluids
- Peritonitis
- Hemodialfiltration
Novel Approaches to the Treatment of Inflammation-Related Wasting in Dialysis

**Table 1**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cancer</th>
<th>Aids</th>
<th>Chf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progesterone derivatives</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Cannabinoids</td>
<td>++</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Cyproheptadine</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Insulin</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Ghrerin</td>
<td>+</td>
<td>+</td>
<td>?</td>
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<tr>
<td>Pentoxifylline</td>
<td>−</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Thalidomide</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Anti-cytokine antibodies and soluble receptors</td>
<td>−/?</td>
<td>+</td>
<td>−</td>
</tr>
<tr>
<td>Anti-inflammatory cytokines</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Growth hormone</td>
<td>−</td>
<td>+/++</td>
<td>++</td>
</tr>
<tr>
<td>Insulin-like growth factor-1</td>
<td>−</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Melatonin</td>
<td>+</td>
<td>?</td>
<td>?</td>
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<tr>
<td>Somatostatin</td>
<td>+</td>
<td>?</td>
<td>?</td>
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<tr>
<td>Anabolic steroids</td>
<td>+</td>
<td>?</td>
<td>?</td>
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<tr>
<td>β₂-Adrenergic agonists</td>
<td>?</td>
<td>?</td>
<td>−</td>
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<tr>
<td>n-3-Fatty acids</td>
<td>+</td>
<td>?</td>
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<tr>
<td>Hydrazine sulfate</td>
<td>+</td>
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<td>?</td>
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<tr>
<td>Prostaglandin inhibitors</td>
<td>+</td>
<td>?</td>
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<tr>
<td>ACE inhibitors</td>
<td>+</td>
<td>?</td>
<td>+</td>
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<tr>
<td>EPO</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>?</td>
<td>?</td>
<td>++</td>
</tr>
<tr>
<td>ATP</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Creatine</td>
<td>+</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Proteasome inhibitors</td>
<td>?</td>
<td>?</td>
<td>+</td>
</tr>
</tbody>
</table>
| For more details, see text. Data referred to clinical trials only. +, slight beneficial effect; ++, relatively good results; ++++, satisfactory treatment; −, unsuccessful trial; ?, not available. Table adapted from reference [56].

Argilés et al. Drug Discovery Jan 2008
A man should never speak longer in public than he can make love in private.
What Did He Say?

- Inflammation biomarkers consistently predicts poor outcome in dialysis patients.
- Recent evidence suggest that inflammation serve as a catalyst for other risk factors and magnify the risk of poor outcome via exacerbation of both wasting and vascular processes.
- Evidence suggest that whereas the short pentraxin CRP is not causal in the pathology of vascular disease IL-6 is.
- In CKD the long pentraxin PTX3 is linked to endothelial dysfunction and urinary albumin excretion.
- CKD is characterized by a loss of phenotypic plasticity - the uremic phenotype may be much more susceptible to underlying genetic variants.
Welcome to the ISBP 2009 Stockholm
Date: 17-19 Sept 2009
“Art is I - Science is We”

Claude Bernard