Inflammation
How it Affects the Dialysis Patient:
Potential Strategies
Sanofi Renal Clinical Consultant

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Objectives

- Define the inflammatory process in the dialysis patient population
- Review the malnutrition inflammation complex syndrome (MICS)
- Identify contributors to inflammation specific to the patients on dialysis
- Identify potential strategies to decrease inflammation in the dialysis patient
Inflammation

- Although inflammation is a physiologic response designed to protect us from infection, when unchecked and ongoing it may cause substantial harm.
- Elevated levels of pro-inflammatory mediators are observed in early stages of CKD and increase with progression of renal dysfunction.
- Inflammatory process in CKD and ESRD:
  - Nearly 50% of HD patients in an early study of 280 patients, were found to have an elevated C-reactive protein (CRP) level.


Complications and consequences

- A chronic inflammatory state is linked with complications of CKD.
  - Vascular degeneration
  - Loss of appetite
  - Myocardial fibrosis
- A chronically activated immune system may potentially impact:
  - Acceleration of atherosclerosis
  - Vascular calcification
  - Development of heart dysfunction


Markers of Inflammation and CKD
Pro-inflammatory mediators - Cytokines

- Cytokines are soluble proteins with low molecular weight that are produced in response to an antigen and other signals and function as chemical messengers regulating various aspects of the innate and humoral immune systems.\(^1\)
- It is not known whether inflammation reflects vascular injury or is instead a cause of vascular injury. However, recent data suggest that inflammatory biomarkers, such as interleukin-6 (IL-6) and the acute phase reactant C-reactive protein (CRP), are not only markers but also mediators of athero-thrombotic disease in man.\(^2\)


Acute phase reactants for which blood concentrations are measured as markers of inflammation in patients with renal insufficiency

<table>
<thead>
<tr>
<th>Positive Acute-Phase Reactants</th>
<th>Negative Acute-Phase Reactants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pro-inflammatory cytokines</td>
<td>Nutritional markers</td>
</tr>
<tr>
<td>• IL-6</td>
<td>• Albumin</td>
</tr>
<tr>
<td>• TNF-α ( cachectin)</td>
<td>• Transferrin or TIBC</td>
</tr>
<tr>
<td>• Other interleukins (IL-1β etc.)</td>
<td>• Prealbumin (transferrin)</td>
</tr>
<tr>
<td>Other positive acute-phase reactants</td>
<td>• Cholesterol</td>
</tr>
<tr>
<td>• CRP</td>
<td>Other negative acute-phase reactants</td>
</tr>
<tr>
<td>• Serum amyloid A</td>
<td>• Histidine-rich glycoprotein</td>
</tr>
<tr>
<td>• Ferritin</td>
<td></td>
</tr>
<tr>
<td>• Fibrinogen, α₁-antitrypsin T, haptoglobin</td>
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</tr>
</tbody>
</table>


Malnutrition Inflammation Complex Syndrome (MICS)
Contributors to poor outcome

- Protein-energy malnutrition (PEM)
- Inflammation
- Strong association between PEM and inflammation
  - Malnutrition-inflammation complex syndrome (MICS)
  - Malnutrition, inflammation, and atherosclerosis (MIA) syndrome


Malnutrition inflammation complex syndrome (MICS): Causes and Consequences

- Low nutrient intake
- Dialysis related factors
- Oxidative & carbonyl stress
- Uremia, uremic toxins
- Volume overload
- Malnutrition-Inflammation Complex Syndrome (MICS)
- Clearance of inflammatory cytokines
- Refractory anemia
- Atherosclerotic CV disease
- Diuretics related factors

Potential Therapeutic Strategies

Suggested steps to target persistent inflammation

1. Evaluate and treat co-morbidities that may cause inflammation
   - Infectious complications
   - Silent ischemic heart disease
   - Intercurrent clinical events
   - Failed kidney transplant
   - Volume overload
   - Inflammatory diseases e.g. diabetes, HTN
   - CKD-MBD

2. Evaluate and treat potential dialysis-related causes of inflammation
   - Infectious complications of HD access
   - Thrombosed fistula or graft
   - Incompatible dialysis
   - Incompatible membranes
   - Bioincompatible dialysis fluids
   - Uropoietic dialysate
   - Peritonitis

3. Consider anti-inflammatory treatment strategies
   - Nutritional intervention
   - Physical training
   - Pharmacological intervention

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CKD-MBD: PTH, Calcium, Phosphorus and Inflammation

A Relationship?

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Association of low serum iPTH with MICS and survival

- Low serum PTH may be associated with:
  - Adynamic bone disease
  - Hypercalcemia
  - High calcium load
  - Administration of vitamin D or calcimimetics
  - Proposed: a low PTH may exist in the setting of MICS

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**Association of low serum iPTH with MICS and survival**

- 748 Maintenance HD patients from the *Nutritional and Inflammatory Evaluation in dialysis (NIED) Study*. The patients were followed up to 63 months.

  Factors associated with iPTH values < 150 pg/mL
  - More likely Hispanic
  - Less likely African American
  - 70% diabetic
  - Higher co-morbidity score
  - Lower serum albumin
  - Smaller biceps skinfold and mid-arm muscle circumference
  - MIS was higher in patients with PTH <150 pg/mL, indicating worse nutritional status
  - Received lower doses of EPO and vitamin D
  - Associated with elevated inflammatory markers

**PTH and MICS**

After adjustment for age, gender, race/ethnicity, diabetes, vintage and multivariate adjustment for selected markers of malnutrition and inflammation, a serum PTH in the range of 100-150 pg/mL was associated with the greatest survival compared to other PTH levels. A low PTH may be a facet of the MICS in HD patients. Appropriate interventions aimed at improving the nutritional and inflammatory status of CKD patients may help implement better management strategies for low PTH and presumed adynamic bone disease.

**Other CKD-MBD interventions: Calcium Balance**

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Rationale</th>
</tr>
</thead>
</table>
| Calcium balance | The increase of CRP in stable dialysis patients may be due to the stimulation of monocytes/macrophages by dialysis contaminants and may promote atherosclerotic changes. Associated with this inflammatory state, other cofactors are present:
- High oral intake of calcium salts
- Excessive vitamin D therapy,
- Positive calcium balance potentially caused by excessive dialysate calcium,
- Metabolic alkalosis may also promote calcium precipitation. |

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CKD-MBD interventions: Phosphorus

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<tr>
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</table>
| Control Phosphorus | - A study of 133 CKD stage 3 and 4 patients concluded a higher eGFR was protective in terms of avoiding inflammation.  
- Serum phosphorus was an independent risk factor for the presence of an inflammatory state as defined by CRP ≥ 3 mg/L.  
- Conclusion: Elevated serum phosphorus might play a role in the development of inflammation in CKD.2 |


Potential dialysis-related causes of inflammation

- Infectious complications of hemodialysis access
- Thrombosed fistula or graft
- Inadequate dialysis
- Bio-incompatible membranes
- Dialysate
- Peritonitis

Potential dialysis-related causes of inflammation

<table>
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<th>Potential Rationale</th>
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<tbody>
<tr>
<td>Biocompatible Membranes</td>
<td>Several dialysis membranes induce activation of elements of the immune system, which mediate inflammatory reactions, and / or take part in the production of acute-phase proteins1.</td>
</tr>
<tr>
<td>Hemodiafiltration</td>
<td>Enhanced removal and lower levels of small, medium and protein bound solutes. Some of these solutes are markers or causative agents of inflammation, SHPT, dyslipidemia, and cardiovascular disease.2</td>
</tr>
<tr>
<td>Daily Dialysis</td>
<td>Improved fluid and phosphorus management and a reduction in left ventricular mass index and inflammatory factors as compared with conventional hemodialysis.2</td>
</tr>
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Potential dialysis-related causes of inflammation under investigation: Dialysate

- Conventional dialysate: dialysate can have no more than 200 colony-forming units (CFU) of bacteria and 2 endotoxin units (EU) per mL
- Ultrapure dialysate: <0.1 CFU/mL and <.03 EU/mL

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Potential benefits of ultrapure dialysate</th>
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<tbody>
<tr>
<td>Ultrapure dialysate</td>
<td>- Prevents the rise of lipoprotein(a) potentially decreasing risk of CV disease³</td>
</tr>
<tr>
<td></td>
<td>- CRP and IL-6 significant and sustained decrease in mean values⁴</td>
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<td></td>
<td>- Weight gain, ↑MAMC,*↑albumin⁴</td>
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</tbody>
</table>

*Mid-arm muscle circumference


Inflammation and peritoneal dialysis

- Extrinsic Factors
  - Uremia
  - PDFs (peritoneal dialysis fluids)
  - Infections, especially peritonitis

- Intrinsic Factors
  - Mesothelium
  - Submesothelial compact zone
  - Submesothelial blood vessels
  - EMT (Epithelial-to-Mesenchymal Transition)
  - Receptors for GDPs (glucose degradation products) AGE (advanced glycation end-products)
  - Macrophages


Inflammation and PD

Present Therapeutic Interventions

- PD-related factors
  - Use more biocompatible PDF
  - Avoid fluid overload
  - Preservation of residual renal function
  - Peritoneal rest

- Acute Peritonitis
  - Appropriate and adequate length of antimicrobial treatment
  - Temporary switch to HD following recurrent peritonitis
  - Angiotensin II blockade
  - Adequate nutritional status in protein and energy supplement
  - Tight control of lipid profile

## Anti-inflammatory treatment strategies

- **Nutritional intervention**
- **Physical training**
- **Pharmacological intervention**

### Nutritional interventions: Soy

<table>
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<tbody>
<tr>
<td>Soy</td>
<td>- 25 HD patients with inflammation as defined by CRP &gt; 10 mg/L.</td>
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<td>- 8 wk double blinded intervention with isoflavone containing soy based nutritional supplement or isoflavone free milk based supplement.</td>
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<td></td>
<td>- Study supports an anti-inflammatory pro-nutritional effect of dietary soy in ESRD patients with underlying systemic inflammation and poor nutrition.¹</td>
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### Nutritional interventions: Omega 3

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<tr>
<td>Omega-3 fatty acids</td>
<td>- 145 HD patients: studied the association of both the ratio of omega-6 to omega-3 fatty acids and the intake of omega-3 fatty acids alone with CRP and mortality.</td>
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<tr>
<td></td>
<td>- Each 1 unit higher dietary omega-6 to omega-3 ratio was associated with a 0.55 mg/L increase in serum CRP level (p&lt;0.03).</td>
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<td></td>
<td>- Higher dietary omega-3 intake alone was associated with a non-significant trend toward a decrease in serum CRP levels</td>
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<tr>
<td></td>
<td>- A trend toward increased risk of death was observed in maintenance HD patients with higher dietary omega-6 to omega-3 intake ratios.</td>
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Nutrition interventions: AGEs

- Advanced glycation end products (AGEs), also known as glycotoxins
  - Stimulate synthesis and release of pro-inflammatory cytokines
  - AGEs are spontaneously produced in human tissue as a part of normal metabolism
  - Elevated levels are associated with cardiovascular disease
  - High levels of AGEs are generated in standard diets, where protein and lipids, mixed with reactive sugars are routinely processed under high temperatures, such as broiling, roasting, or grilling

Nutrition intervention: AGEs

- High temperature and low moisture drive AGE formation in food.
- A brief heating time, low temperature, high moisture and / or pre-exposure to an acidified environment limit new AGE formation in food.
- Significantly reduced dietary AGEs can be achieved by:
  - Increased consumption of:
    - Fish, legumes, low-fat milk products, vegetables, fruits, whole grains
  - Decreased consumption of:
    - Solid fats, fatty meats, full-fat dairy products, and highly processed foods

Resistance Training in CKD Patients

- 26 adults 65 + 10 yrs with CKD not on dialysis
- Randomly assigned to resistance training or a control group for 12 weeks.
- Protein intake provided for both groups: 0.6 gm/kg body wt./day.
- Resistance training reduced inflammation and improved nutritional status in individuals with moderate CKD

<table>
<thead>
<tr>
<th>Markers that demonstrated significant results</th>
<th>Resistance Training</th>
<th>Control Subjects</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum CRP</td>
<td>-1.7 mg/L</td>
<td>1.5 mg/L</td>
<td>P=0.05</td>
</tr>
<tr>
<td>IL-6</td>
<td>-4.2 pg/mL</td>
<td>2.3 pg/mL</td>
<td>P=0.01</td>
</tr>
<tr>
<td>type I muscle fiber</td>
<td>+24%±31%</td>
<td>-14%±34%</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>type II muscle fiber</td>
<td>+22%±41%</td>
<td>-13%±18%</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Muscle strength</td>
<td>+28%±14%</td>
<td>-13%±22%</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>
Anti-inflammatory response related to physical training in healthy adults

  - 13,748 participants > 20 years old.
  - Purpose: examine the association between physical activity and C-reactive protein concentration in a national sample of the U.S. population.
  - Conclusion: physical activity may reduce inflammation, which is a critical process in the pathogenesis of cardiovascular disease.\(^1\)
- Similar results noted in other healthy groups, specifically CRP was reduced as a result of aerobic / resistance training.\(^2\)


Pharmacological interventions

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Statins and reduction of inflammation

Many studies have looked at statins and reduction of inflammation. Summaries of two significant studies:

- A meta-analysis of 9 RCTs with 3,098 patients:
  - 6 studies compared statins to placebo
  - 3 studies compared to no treatment
  - Use of statins was associated with a significant decrease in serum hs-CRP level compared with that of controls. (p<0.0001)\(^3\)
- 4D study 1,255 type 2 diabetic HD patients. Atorvastatin had no significant effect on the composite primary end point of cardiovascular death (CV), nonfatal myocardial infarction, and stroke.\(^2\)
- A post-hoc analysis demonstrated that CRP was highly predictive of outcome, but atorvastatin treatment was not associated with a reduction in the relative risk of CV events or mortality in patients with or without inflammation.\(^3\)

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-receptor blockers (ARBs)

ACEIs and ARBs, commonly prescribed for dialysis patients, may have a positive effect on inflammation. Study examples:

- A cross-over study of 15 HD patients compared the effect of ACEI inhibitors and ARBs over one week on markers of oxidative stress, inflammation, and fibrinolysis during hemodialysis.
  - In this small study, during hemodialysis, valsartan (ARB) induced a greater anti-inflammatory effect as compared with ramipril (ACE).
  - Ramipril seemed to prevent dialysis-induced endothelial dysfunction as measured by levels of vWF.

- An observational study of 22,800 dialysis patients, over six years in length, found an ARB, in combination with another antihypertensive medication (but not an ACEI), may have a beneficial effect on cardiovascular mortality.

Hemodialysis patients: phosphate binders and markers of inflammation

<table>
<thead>
<tr>
<th>Author</th>
<th># Patients</th>
<th>Length</th>
<th>Effect on markers of inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yamada</td>
<td>36</td>
<td>24 wks</td>
<td>Reduction in hs-CRP levels in the sevelamer group</td>
</tr>
<tr>
<td>Peres</td>
<td>31</td>
<td>1 year</td>
<td>Reduction in TNFα and CRP in the sevelamer group</td>
</tr>
<tr>
<td>Ferramosca</td>
<td>108</td>
<td>1 year</td>
<td>• CACS increased in calcium group (p&lt;0.05) but not in sevelamer group (p=NS) • The changes in total and low-density lipoprotein cholesterol, apolipoprotein B, and hs-CRP were significantly different between treatment groups (all P &lt; .01). These markers significantly decreased from baseline in the sevelamer group.</td>
</tr>
<tr>
<td>Brandenburg</td>
<td>41</td>
<td>8 wks</td>
<td>Fetuin A (calcification inhibitor) increased by 21% in sevelamer group</td>
</tr>
</tbody>
</table>


Hyperphosphatemia and subclinical endotoxemia are important sources of inflammation in HD.

<table>
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<tr>
<th>Author</th>
<th># Patients</th>
<th>Length</th>
<th>Effect on markers of inflammation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Navarro-Gonzalez</td>
<td>59 patients</td>
<td>3 months</td>
<td>• Ca acetate group: • IL-6 increased • CD14 levels and endotoxin levels did not change • Sevelamer group: • hs-CRP and IL-6 significantly decreased (p=0.01 CRP) (p=0.01 IL-6) • CD14 decreased by 15.2% and endotoxin levels by 22.6% (p&lt;0.01)</td>
</tr>
</tbody>
</table>

Heparin and Vitamin D
Examples of research related to inflammation reduction

**Heparin**
- 33 HD patients; 3 groups
  1. Heparin
  2. Low molecular weight heparin (LMWH)
  3. Control
- Each patient was treated to one of the above for one dialysis session.
- Oxidative stress and inflammation markers significantly increased in groups 1 and 3 (p < .05) as compared to baseline, while there was no change from baseline in the LMWH group.1

**Vitamin D**
- 1 year prospective study with 158 HD patients examined the effects of cholecalciferol supplementation on mineral metabolism, inflammation and cardiac parameters
- Cholecalciferol increased mineral metabolism control with less use of active vitamin D, decreased inflammatory parameters with reduction of erythropoiesis stimulating agent consumption, and improved cardiac dysfunction (reflected by lower BNP levels and decreased LVMI). These effects may be related to the direct action of 25(OH)D on target cells and/or to persistent renal or extrarenal 1α-hydroxylation.2


**Other pharmacological interventions**

<table>
<thead>
<tr>
<th>Medication</th>
<th>Research Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gamma-tocopherol</td>
<td>In a study completed by 57 HD patients, gamma-tocopherol and Docosahexaenoic acid (DHA) were well tolerated and reduced selected serum biomarkers of inflammation in HD patients.1</td>
</tr>
<tr>
<td>IL-1 antagonism (IL-1β, a pro-inflammatory cytokine, which is elevated in dialysis patients)</td>
<td>A pilot randomized placebo-controlled trial to evaluate the efficacy of the administration of recombinant human IL-1 receptor antagonist (IL-1ra) on biomarkers of inflammation and nutrition. The study found biomarkers of inflammation are lowered with IL-1ra administration.2</td>
</tr>
<tr>
<td>N-acetylcysteine (NAC)</td>
<td>Short-term oral NAC treatment resulted in reduction of circulating IL-6, suggesting that such treatment could be a useful strategy in blunting the inflammatory response in PD patients.3</td>
</tr>
</tbody>
</table>


**Discussion**

What anti-inflammatory treatment strategies can you suggest for your patients?
- Nutritional intervention
- Physical training
- Pharmacological intervention
Conclusion

- Chronic kidney disease is known to cause elevation in several pro-inflammatory mediators.
- Many factors contribute to the elevation of these mediators.
- Dialysis practices, nutrition, physical exercise, and medications may have a positive effect on reducing these inflammatory mediators.