Pathogenesis

Diabetes

CKD  CVD

Arrows indicate relationships between diabetes, CKD, and CVD.
WORLD'S MOST POPULATED COUNTRIES

1. CHINA
2. INDIA
3. DIABETES
4. USA
5. BRAZIL
Renal Dysfunction Is Common in Patients with Type 2 Diabetes

- Approximately 40% of patients with T2DM show signs of CKD (stages 1–5)
- Approximately 20% of patients with T2DM show signs of renal failure (eGFR < 60 mL/min/1.73 m²)

Natural history of diabetic nephropathy

Adapted from Mogensen et al, Diabetologia 1979; 17: 71-76
Diabetic Glomerulosclerosis
Complications of CKD

Kidney functions

- Sodium balance
- Potassium excretion
- Acid excretion
- Calcium/phosphate balance
- Erythropoiesis

CKD
- Sodium retention and volume overload
- Hyperkalemia
- Metabolic acidosis
- ↑ phosphate
- ↑ PTH
- ↓ serum calcium
- ↓ calcitriol
- Anemia

Tx
- Sodium restriction
- Diuretics
- Dietary restriction
- Avoid NSAIDs
- Sodium bicarbonate
- Phosphate binders
- Calcimimetics
- Erythropoiesis-stimulating agents; iron replacement

↑ P04 → 2nd HPT
Composite ranking for relative risks by GFR and albuminuria (KDIGO 2009)

<table>
<thead>
<tr>
<th>GFR stages, description and range (ml/min per 1.73 m²)</th>
<th>G1</th>
<th>G2</th>
<th>G3a</th>
<th>G3b</th>
<th>G4</th>
<th>G5</th>
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<tbody>
<tr>
<td>High and optimal</td>
<td>&gt;105</td>
<td>75 - 89</td>
<td>45 - 59</td>
<td>30 - 44</td>
<td>15 - 29</td>
<td>&lt;15</td>
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<tr>
<td>90 - 104</td>
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<td>60 - 74</td>
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<td>Mild</td>
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<td>Mild-moderate</td>
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<tr>
<td>Severe</td>
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<tr>
<td>Kidney failure</td>
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<table>
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<tr>
<th>Albuminuria stages, description and range (mg/g)</th>
<th>A1</th>
<th>A2</th>
<th>A3</th>
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<tbody>
<tr>
<td>Optimal and high-normal</td>
<td>&lt;10</td>
<td>10 - 29</td>
<td>30 - 299</td>
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<td>High</td>
<td>300 - 1999</td>
<td>300 - 1999</td>
<td>≥2000</td>
</tr>
<tr>
<td>Very high and nephrotic</td>
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</table>
CVD and CKD Epidemiology

- Increased rates of LVH – 27% if CrCl > 50 ml/min vs 45% if CrCl < 25 ml/min
- Cardiovascular mortality rates of a 20 year old dialysis patient is the same as 80 year old individual in the general population
- Acute Decompensated Heart Failure National Registry (ADHERE) 57% had CKD stages 3 or 4, 7% were at stage 5 (68% receiving dialysis), and only 9% had normal kidney function
Prevalence of CKD by age & risk factor among NHANES participants, 1998-2012


Diabetes defined as either HbA1c >7%, self-reported, or currently taking glucose-lowering medications.

Hypertension defined as BP ≥130/≥80 for those with diabetes or CKD; otherwise BP ≥140/≥90, or taking medication for hypertension.
CKD

End-Stage
Kidney Failure
Heart Failure

Progression
Decreased GFR
CVD Events

Initiation
Albuminuria
CAD, LVH

At Increased Risk
DIABETES
HTN, Age, Family History
Chronic Heart Failure

- Epidemiology changing from acute management to managing the chronicity of cardiac dysfunction
- An incidence of 5 million persons
- Responsible for over 1 million yearly hospitalizations
- 280,000 deaths annually
Comorbid Conditions . . .
Associated with a worse prognosis

- Anemia (Hb < 10.0)
- Cirrhosis
- Peripheral Vascular Disease
- Hyponatremia (<135)
- Renal failure

Cardiovascular Outcomes with renal dysfunction

Cumulative incidence

- Cardiovascular death
- Unplanned ADHF admission

- Stratified by GFR

Reduced LVEF (LVEF\leq40\%)

LV systolic function (LVEF\geq40\%)

ADHERE Registry

• Registry of Acute Decompensated Heart Failure (ADHF)

  • 105,000 patient registry

Best predictors of outcome:
  BUN
  Creatinine
Cardio-Renal Syndrome

“Bidirectional pathological impairment of either the heart or the kidney due to acute or chronic primary dysfunction in the other organ (or impairment of both as a secondary phenomenon following systemic disease)”
Subtypes

- **Type I, acute CRS**
- Type II, chronic CRS
- Type III, acute renocardiac syndrome
- Type IV, chronic renocardiac syndrome
- Type V, secondary CRS – sepsis, amyloidosis
Cardio-Renal Syndrome

- CHF patients at increased risk for CRS:
  - Hypertension
  - Diabetes
  - Severe Vascular Disease
  - Elderly
Pathophysiology

- **Neurohormonal Factors:**
  - SNS, RAAS, AVP System

- **Hemodynamics:**
  - Loss of Cardiac Output
  - Transrenal perfusion pressure
  - Intrarenal hemodynamics
Neurohormonal Axis

- Sympathetic Stimulation
- Hypotension
- Decreased Sodium Delivery

Renin

Angiotensinogen

AI

ACE

AII

Adrenal Cortex

Pituitary

Aldosterone

Cardiac & Vascular Hypertrophy

Systemic Vasoconstriction

Thirst

Renal Sodium & Fluid Retention

Increased Blood Volume

Adenosine
CHF Hemodynamics

- Systolic or Diastolic CHF
- Exacerbations – Symptomatology seen objectively
  - Elevated PCWP
  - Elevations of INR, Alkaline Phosphatase
  - Elevations of Creatinine
2,557 patients underwent RHC
- Age 59 ± 15 years
- 57% were men
- Renal Function using estimated Glomerular Filtration Rate (eGFR)

Curvilinear Relationship Between CVP and eGFR According to Different Cardiac Index Values

Solid line = cardiac index < 2.5
Dashed line = cardiac index 2.5 to 3.2
Dotted line = cardiac index > 3.2

p = 0.0217
Kaplan-Meier Analysis of Event-Free Survival According to Tertiles of CVP

Cumulative survival

Follow up time (Years)

CVP = 0 - 3 mmHg
CVP = 4 - 6 mmHg
CVP = > 6 mmHg

P for trend < 0.0001

Renal Hemodynamics

- Transrenal perfusion pressure
  - \( TRPP = MAP - CVP \)
  - CVP influenced:
    - PAP – Oxygenation, Valve Dysfunction, CO
    - Volume Status
  - MAP – Perfusion Pressure
    - Cardiac Output
    - Systemic Vascular Resistance
Ultimately lack of adequate transrenal perfusion pressure:

→ Renal Hypoxia
→ Inflammation / Cytokine Release
→ Progressive loss of nephron function and structural

→ **Activation of the Neurohormonal cascade**
Cardio-Renal Syndrome

- Treatment Goals
  - Same goals as ADHF
    - Removal of Volume
    - Optimizing Hemodynamics

Complicated by chronic renal failure and acutely worsening renal function
Removal of Volume

- Loop Diuretics
- Brain Naturetic Peptide
- Arginine Vasopressin Antagonism
- Adenosine Antagonism
- Ultrafiltration
Loop Diuretics

- Goal → Deplete extracellular fluid volume
  - Balanced refilling interstitium to intravascular compartment

- Reality → Contraction of circulating volume → Activation of neurohormonal response
Impact of Diabetes on patients with CVD

Crude and adjusted odds ratio of CKD in those with CVD stratified by diabetes status (**p < 0.001 & *p < 0.05)
Multiple regression analysis of CVD and CKD in those individuals without diabetes.

<table>
<thead>
<tr>
<th>Variable</th>
<th>β</th>
<th>B</th>
<th>95% Confidence Interval</th>
<th>P</th>
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<tbody>
<tr>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>0.848</td>
<td>2.34</td>
<td>1.66</td>
<td>3.29</td>
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<tr>
<td>Hypertension</td>
<td>0.521</td>
<td>1.69</td>
<td>1.09</td>
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<tr>
<td>Cholesterol Status</td>
<td>0.109</td>
<td>0.90</td>
<td>0.62</td>
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<tr>
<td>Obesity (Reference = BMI&lt;30)</td>
<td>1.603</td>
<td>4.97</td>
<td>3.22</td>
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<tr>
<td>Smoking Status (Reference = Never Smoker)</td>
<td>0.784</td>
<td>2.38</td>
<td>1.36</td>
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<tr>
<td>Current Infection</td>
<td>0.075</td>
<td>1.08</td>
<td>0.48</td>
<td>2.43</td>
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<tr>
<td>C-reactive Protein</td>
<td>0.157</td>
<td>1.17</td>
<td>0.47</td>
<td>2.90</td>
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<tr>
<td>Education Level</td>
<td>0.168</td>
<td>1.18</td>
<td>0.79</td>
<td>1.77</td>
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**Sociodemographic Factors**

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<tr>
<td>Non-Hisp. White</td>
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<td>Reference</td>
<td>Reference</td>
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<tr>
<td>Non-Hisp. Black</td>
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<td>0.55</td>
<td>0.35</td>
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<td>0.089</td>
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<td>Hispanic</td>
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<td>0.77</td>
<td>0.48</td>
<td>1.23</td>
<td>0.089</td>
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<tr>
<td>Other</td>
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<td>0.27</td>
<td>1.53</td>
<td>0.089</td>
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<tr>
<td>Gender (Reference = Female)</td>
<td>0.542</td>
<td>1.72</td>
<td>1.19</td>
<td>2.49</td>
<td>&lt;0.005</td>
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<td>Age</td>
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Cardiovascular disease, diabetes and chronic kidney disease

Australian facts

Aboriginal and Torres Strait Islander people
Deaths per 100,000 population

Year

98 99 00 01 02 03 04 05 06 07 08 09 10 11 12

500 400 300 200 100

Aboriginal and Torres Strait Islander peoples
Non-Indigenous Australians
Aboriginal and Torres Strait Islander Australians are more likely than other Australians to have, be hospitalised for, and die from cardiovascular disease, diabetes, and chronic kidney disease—and at younger ages.

The difference was even greater for diabetes and chronic kidney disease. While just 5% of non-Indigenous adults had diabetes, 18% of Indigenous adults had the condition. For chronic kidney disease, 10% of non-Indigenous adults had the disease, but for Indigenous adults, this was 22%.
▪ Not only are these diseases more prevalent among Indigenous Australians, death rates are also higher. For cardiovascular disease, the Indigenous death rate was 1.5 times as high as for non-Indigenous Australians—280 and 183 deaths per 100,000 people, respectively.

▪ Diabetes contributed to 21% of all Indigenous deaths, compared with 10% of non-Indigenous deaths. For chronic kidney disease, these rates were 16% and 10%.
The gap in death rates between non-Indigenous and Indigenous Australians was widest among younger age groups—for example, the cardiovascular disease death rate for Indigenous people aged 35-44 was 8 times as high as for non-Indigenous people, falling to 4 times as high for the 55-64 year old age group.
Not only are Indigenous Australians more likely to have each of these conditions individually, they are also more likely to have all 3, and die from them!!

More than 10% of Indigenous deaths had all 3 conditions listed as causes of death. For non-Indigenous Australians, all 3 conditions were recorded in just 3% of deaths.
Management of the Triple Threat

- Anaemia
- Monitoring HbgA1C
- LVH, increase cardiac demand
- Evaluation, treatment with erythropoietin
- Clearance of drugs - Metformin, sulfonylureas, Glitazones, Insulin, etc.
- Antiarrhythmic drugs
- Lipid management - Fibrates, statins
Management of the Triple Threat

- Lipid management - Fibrates, statins
- HTN management/volume status
- Exacerbations of CHF, more difficult to treat blood pressure
- Proglitazone
- ACEI/ARB
Management of the Triple Threat

Ca/Phos/Vit D/2 nd hyperparathyroidism

- CAD, CHF, calcification, FGF23

Nutrition/diet

- Diabetic diet, Na restriction, potassium restriction, phos restriction, fluid restriction

Renal preservation

- Tobacco cessation, weight control

Preparation of RRT

RRT – PD vs HD, home vs in-center dialysis, nocturnal dialysis and transplant
Conclusions

• Diabetes is known to be associated with CKD and CVD independently.
• Diabetes is strongly associated with type II Cardio Renal Syndrome.
• Complex, self perpetuating haemodynamic and neuro-humoral factors participate in the development of CRS
• Presence of CKD marks poorer cardiac outcomes for patients with CVD
• ATSI Australians are more likely than other Australians to have, be hospitalized for and die from CVD, DM and CKD and at younger ages.
Thank you!