DIABETES AND YOUR KIDNEYS
OR AS WE CALL IT “DIABETIC NEPHROPATHY”

The latest guidelines to keep you safe, healthy, fit, and out of danger from needing dialysis

A UCLA HEALTH EDUCATIONAL SEMINAR
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THE NUMBERS

- Chronic kidney disease (CKD) is a worldwide public health problem affecting more than 50 million people, and more than 1 million of them are receiving kidney replacement therapy.\(^1\)\(^2\) The National Kidney Foundation-Kidney Disease Outcomes Quality Initiative™ (NKF-KDOQI™) Clinical Practice Guidelines (CPGs) on CKD estimate that CKD affects 11% of the US population,\(^3\) and those affected are at increased risk of cardiovascular disease (CVD) and kidney failure. Kidney failure represents about 1% of the prevalent cases of CKD in the United States,\(^3\) and the prevalence of kidney failure treated by dialysis or transplantation is projected to increase from 453,000 in 2003 to 651,000 in 2010.\(^3\)^4

http://www2.kidney.org/professionals/kdoqi/guideline_diabetes/background.htm
Classification of Diabetes

I  Type 1 diabetes
   1A  Immune-mediated
   1B  Idiopathic

II  Type 2 diabetes

III Other specific types (Secondary diabetes)

IV Gestational Diabetes Mellitus

WHO Consultation 1999
HOW DIABETES HAPPENS

Type 1 Diabetes: Cells do not absorb glucose

Type 2 Diabetes: Cells do not absorb glucose

No insulin

Cells do not respond to insulin

http://www.bbc.co.uk/science/o/21704103
OBESITY AND INSULIN RESISTANCE

Adapted from http://themedicalbiochemistrypage.org/insulin.php
INSULIN RESISTANCE—FOR THE REST OF US

### Table 10. Stages of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (mL/min/1.73 m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or ↑ GFR</td>
<td>≥90</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild ↓ GFR</td>
<td>60–89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↓ GFR</td>
<td>30–59</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↓ GFR</td>
<td>15–29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney failure</td>
<td>&lt;15 (or dialysis)</td>
</tr>
</tbody>
</table>

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m² for ≥3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.
THE NEW WAY OF LOOKING AT KIDNEY DISEASE
KDIGO-NEWER (GLOBAL)
KIDNEY DISEASE IMPROVING GLOBAL OUTCOMES

https://www.slideshare.net/SumaneePrakobsuk/kdigo-ckd-2012
WHY DO KIDNEYS LEAK GLUCOSE INTO URINE IN DIABETES?

KIDNEY

An adaptive response to conserve glucose...

Glucose

...becomes maladaptive in Type 2 diabetes

SGLT2 plays a crucial role in renal glucose reabsorption

In Type 2 diabetes, the kidney's maximum glucose reabsorption threshold is exceeded, resulting in glycosuria

This highlights renal glucose reabsorption as a potential target for treatment of Type 2 diabetes

WHY DO KIDNEYS LEAK PROTEIN IN DIABETES

IT’S NOT REALLY ALL THAT SIMPLE
Diabetes
(hyperglycemia, hyperlipidemia)

AGE Effects
Oxidative Stress
RAAS Activation

Inflammation → Fibrosis

Diabetic Nephropathy
SIMPLY STATED: HOW DIABETES CAUSES KIDNEY DISEASE

WHAT DOES DIABETES IN MY KIDNEY LOOK LIKE?
HOW LONG DOES THIS DISEASE TAKE TO PROGRESS?
STAGES OF DM nephropathy

- **STAGE-1**
  HYPERFILTRATION

- **STAGE-2**
  SILENT STAGE

- **STAGE-3**
  INCIPIENT NEPHROPATHY

- **STAGE-4**
  OVERT NEPHROPATHY

- **STAGE-5**
  CHRONIC RENAL FAILURE → ESRD
HOW CAN MY DOCTOR MEASURE IT’S IMPACT?

- Measures to determine impact of diabetes on kidneys
- Urinalysis
- Urine protein / creatinine ratio
- Urine albumin/ creatinine ratio
- 24 hour urine protein
- Blood tests for blood urea nitrogen
- Blood tests for creatinine
- Blood test for cystatin C
DIABETES AND THE EYE-KIDNEY CONNECTION
ABNORMAL RETINA (DIABETIC RETINOPATHY)
The presence of nephropathy and retinopathy is 86% meaning if a doctor sees protein leakage in a Diabetic 70-90% of patients will have eye damage. Conversely if someone has kidney disease and diabetic eye disease is Confirmed 70-90% chance that kidney disease is also due to diabetes this is called concurrence.
KEEP YOUR A1C AT GOAL

http://www.ptsdiagnostics.com/a1c-and-complications.html
KEEP YOUR BLOOD PRESSURE AT GOAL
NKF GUIDELINES ON OTHER FACTORS THAT CAN HELP PREVENT PROGRESSION OF DM/DN OR OTHER VASCULAR COMPLICATIONS.

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Goal of Therapy</th>
<th>Recommending Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking</td>
<td>Complete cessation</td>
<td>ADA</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>&lt;130/85 mm Hg</td>
<td>JNC 7 (NHLBI), ADA</td>
</tr>
<tr>
<td>LDL-C</td>
<td>&lt;100 mg/dL, &lt;70 mg/dL is a therapeutic option</td>
<td>ATP III (NHLBI), ADA</td>
</tr>
<tr>
<td>Triglycerides, 200-499 mg/dL;</td>
<td>Non-HDL-C &lt;130 mg/dL</td>
<td>ATP III (NHLBI), ADA</td>
</tr>
<tr>
<td>HDL-C &lt; 40 mg/dL</td>
<td>Increase HDL-C (no set goal)</td>
<td></td>
</tr>
<tr>
<td>Prothrombotic state</td>
<td>Aspirin (75-162 mg/d)</td>
<td>ADA</td>
</tr>
<tr>
<td>Glucose</td>
<td>HbA1c &lt; 7%</td>
<td>ADA</td>
</tr>
<tr>
<td>Overweight and obesity (BMI ≥ 30 kg/m²)</td>
<td>Lose 10% of body weight in 1 year</td>
<td>OEI (NHLBI)</td>
</tr>
<tr>
<td>Physical inactivity</td>
<td>Exercise prescription</td>
<td>ADA</td>
</tr>
<tr>
<td>Adverse nutrition</td>
<td>Limit intake of saturated fat, cholesterol, sodium; control carbohydrate and caloric intake; protein, 0.8 g/kg/d if CKD present</td>
<td>ADA, AHA, and NHLBI ATP III, OEI, and JNC 7</td>
</tr>
</tbody>
</table>

HEART DISEASE IS A MAJOR KILLER IN DIABETES AND IN PROTEIN LEAKING DN ESPECIALLY

<table>
<thead>
<tr>
<th>Indication</th>
<th>Test</th>
<th>Comments</th>
<th>Professional Society Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Typical or atypical chest discomfort</td>
<td>Exercise ECG</td>
<td>Obtain cardiology consultation for pharmacological stress testing, imaging, or coronary angiography</td>
<td>ADA yes54, AHA yes56</td>
</tr>
<tr>
<td>Other symptoms that may suggest ischemia</td>
<td>Consider imaging modality for nondiagnostic ECG test result or with pharmacological stress test</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Unexplained dyspnea or fatigue</td>
<td>• Nuclear perfusion scan</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Jaw, neck, arm, or shoulder discomfort</td>
<td>• Echocardiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Abnormal ECG result</td>
<td>Consider pharmacological stress testing for those unable to exercise</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Dobutamine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Persantine</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Coronary angiography</td>
<td>No guidelines have specifically addressed the subset of patients with diabetes and CKD</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Clinically significant ischemia or noninvasive testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Diagnostic uncertainty on noninvasive testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consider screening for silent ischemia</td>
<td>Same approach as above</td>
<td>Controversial Data on improved clinical outcomes is lacking</td>
<td>ADA yes54, AHA no58</td>
</tr>
<tr>
<td>• Patient &gt; 35 years and sedentary with plans to begin a vigorous exercise program</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Carotid or lower-extremity atherosclerotic disease</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: ECG, electrocardiogram.
CKD

- Kidney Failure

- At Increased Risk
  - Diabetes
    - HTN, Age, Family History

CVD

- Heart Failure

- End-Stage

- Progression
  - Decreased GFR
  - Albuminuria

- Initiation
  - CVD Events
  - CAD, LVH
<table>
<thead>
<tr>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical compression of the kidneys by visceral obesity</td>
</tr>
<tr>
<td>RAS activation</td>
</tr>
<tr>
<td>Hyperinsulinemia</td>
</tr>
<tr>
<td>Sympathetic activation</td>
</tr>
<tr>
<td>Overnutrition</td>
</tr>
<tr>
<td>Glomerular hyperfiltration</td>
</tr>
<tr>
<td>Proteinuria-associated kidney damage</td>
</tr>
<tr>
<td>Blood pressure elevation</td>
</tr>
</tbody>
</table>
WHAT TO ASK ABOUT IN DOCTOR’S OFFICE

- Blood pressure goals 130/80 in protein-uric disease
- 140/90 otherwise per JNC-8
RENAL FUNCTION ASSESSMENT EVERY VISIT

Urine protein assessments (Urine protein/creatinine ratio), (urine albumin/creatinine ratio, 24 hour protein collections).

- Less specific but easily available urinalysis
- BUN and Creatinine
- Cystatin C and other new kidney health markers
RENIN ANGIOTENSIN ALDOSTERONE (RAAS) BLOCKADE

Renin-angiotensin system

- **Drop in blood pressure**
- **Drop in fluid volume**

Renin release from kidney

Renin acts on angiotensinogen to form **angiotensin I**.

ACE (angiotensin-converting enzyme) release from lungs

ACE acts on angiotensin I to form **angiotensin II**.

Angiotensin II acts on the adrenal gland to stimulate release of aldosterone.

Angiotensin II also acts directly on blood vessels, stimulating vasoconstriction (narrowing).

Aldosterone acts on the kidneys to stimulate reabsorption of salt (NaCl) and water (H₂O).

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Renal Sympathetic Activation in Hypertension

**Vascular Effects**
- Smooth muscle migration
- Vasoconstriction
- Wall Stiffness

**Cardiac Effects**
- Hypertrophy
- Arrhythmias
- Ischemia
- Heart Failure

**Renal Effects**
- Renin release
- RAAS
- Sodium retention
- Hyperuricemia
- Decreased renal blood flow
- BNP resistance

**Renal afferent nerves**

**Renal efferent nerves**
HOW TO CONTROL PROTEINURIA

- Control blood pressure at above goals (<130/80)
- Renin angiotensin aldosterone system
  - ACE: Lisinopril (end in pril)
  - ARB: Valsartan (end in sartan)
  - Direct angiotensin blockers (rarely used)
- Aldosterone blockers (mineralocorticoid antagonists)
- Calcium channel blockers (CCB non-dihydropyridine class)
  - They don’t end in “ine”: diltiazem and verapamil
OTHER ASPECTS OF KIDNEY DISEASE

- Lipid control (cholesterol – LDL, HDL, triglycerides)
- Increased risk as above
- Aspirin for prevention of heart attacks (MI)
Vitamin D metabolism

**Vitamin D₃**
- Cholecalciferol
- Made in the skin
- Found in oily fish, egg yolks, and fortified food

**Vitamin D₂**
- Ergocalciferol
- Found in fortified foods, salmon, mushrooms, and egg yolks

**Liver**
- Converts Vitamin D₃ and D₂ to 25-hydroxyvitamin D

25-hydroxyvitamin D
25(OH)D
Calcidiol

**Kidney**
- Converts 25-hydroxyvitamin D to 1,25 dihydroxyvitamin D

**Biologically active form**
- 1,25 dihydroxyvitamin D
- 1,25 (OH)₂D
- Calcitriol
Many patients with chronic kidney disease (CKD) are vitamin D deficient. D2 is sufficient in early disease. D3 (active vitamin D) or vitamin D analogues (VDRA) are needed in more severe disease. Keeping D2 replete may have beneficial effects on kidneys.
SECONDARY HYPERPARATHYROIDISM

- Vitamin D
- Calcium
- Phosphorous
- PTH (parathyroid hormone) maybe affected by this.
- Poor Phosphorous clearance can result in increased PTH levels in a futile attempt to get rid of excess phosphorous. This results in damage to blood vessels and possible calcification in body.
- This is opposed to primary and tertiary forms of hyperparathyroidism-which are beyond scope of our seminar.
URIC ACID

- Good chronic kidney disease care should also encompass measuring and controlling uric acid which is a risk factor for gout and accelerated kidney function decline.
- Allopurinol and febuxostat are agents that can control this within goal
- Not used in gout flares (other agents such as corticosteroids, colchicine, and if no kidney disease NSAIDS can be used)
Anaemia in CKD

Factors contributing to anaemia in CKD:

- High hepcidin level, inflammation, infection
- All may contribute to functional iron deficiency and impaired bone marrow responsiveness to erythropoietin
- Decreased erythropoietin production
- Absolute iron deficiency (malnutrition and poor absorption)
- Blood loss
- Short red blood cell life span
- Co-morbidities
- Deficiency of vitamin B₁₂ and folate
- Medication e.g. ACE inhibitors
- CKD mineral and bone disorder
- Bone marrow suppression by uraemia

Adapted from Agarwal AK. J A Med Dir Assoc 2006;7:S7–S12
CONTROLLING ANEMIA

- Poor control of anemia can result in worsening renal function due to higher likelihood of ischemia.
- Kidney disease results in anemia from erythropoietin deficiency and iron deficiency and/or iron unavailability due to inflammation (anemia of chronic disease)
- Erythropoeitin in its synthetic form(s) can be given to correct this problem
MAINTAINING A HEALTHY PROTEIN INTAKE

- Though protein can stress kidneys and force need to increase GFR
- A complex relationship exists between protein intake and progression in diabetics
- Low protein diets may be easier on kidney but protein calories are replaced by carbohydrates worsening diabetic and hypertensive control
- Moderate protein intake is acceptable in chronic kidney disease-though some people (Kalantarzadeh et.al.) advocate very low protein diets
- On dialysis this changes and a higher protein diet is advocated to avoid malnutrition
- In all cases low albumin or malnutrition increases risks for chronic kidney disease and dialysis patients tremendously
MAINTAINING ACID BASE BALANCE

• Serum bicarbonate is part of buffer system to keep body’s pH balance
• Kidneys usually regulate
• As kidneys become less effective in kidney disease organic acids (phosphate sulfate build up)
• This makes blood acidic – called a metabolic acidosis (since its due to kidneys and not lungs)
• Fixing this usually involves citrate or sodium bicarbonate- baking soda
• It has been shown control of acid base level with target of bicarbonate of 20 meq/L or more has been show to have effect of slowing down decline of kidney function in chronic kidney disease
A very dangerous relationship exists between kidney disease, cardiovascular health and phosphorous.

High phosphorous drives up PTH, FGF-23 and other really dangerous markers.

Clinical calcification is rare but can be deadly.

Even with high normal phosphorous and calcium increased risk of heart disease occurs.

Goal is to control phosphorous with binders on dialysis but increasingly also with chronic kidney disease.
### Table 2. Age- and Sex-Adjusted Cumulative Incidence Rates of CVD According to Quartiles of Serum Phosphorus and Serum Calcium Levels

<table>
<thead>
<tr>
<th>Quartile</th>
<th>Events No.</th>
<th>Patients at Risk No.</th>
<th>Age- and Sex-Adjusted 20-Year Incidence of CVD, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Serum Phosphorus Level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>137</td>
<td>815</td>
<td>16.4 (13.2-19.6)</td>
</tr>
<tr>
<td>2</td>
<td>140</td>
<td>868</td>
<td>17.9 (14.6-21.2)</td>
</tr>
<tr>
<td>3</td>
<td>129</td>
<td>915</td>
<td>17.5 (14.2-20.8)</td>
</tr>
<tr>
<td>4</td>
<td>118</td>
<td>770</td>
<td>21.1 (17.1-25.0)</td>
</tr>
<tr>
<td></td>
<td>Serum Calcium Level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>132</td>
<td>816</td>
<td>19.4 (15.7-23.0)</td>
</tr>
<tr>
<td>2</td>
<td>142</td>
<td>1023</td>
<td>16.4 (13.4-19.4)</td>
</tr>
<tr>
<td>3</td>
<td>102</td>
<td>698</td>
<td>17.2 (13.7-20.7)</td>
</tr>
<tr>
<td>4</td>
<td>148</td>
<td>831</td>
<td>19.9 (16.4-23.5)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; CVD, cardiovascular disease.
SI conversion factor: To convert serum calcium to millimoles per liter, multiply by 0.25.
*Quartile cutoff points for serum phosphorus level are shown in Table 1.
Serum calcium level quartiles (in milligrams per deciliter) were 1 (6.1-9.3), 2 (9.4-9.6), 3 (9.7-9.8), and 4 (9.9-11.2).
## Table 3. Levels of cFGF-23 and Associated Risk of Death within Serum Phosphate Quartiles in the Case-Control Sample.

<table>
<thead>
<tr>
<th>Phosphate Level</th>
<th>Median cFGF-23 Level (interquartile range)</th>
<th>P Value</th>
<th>Odds Ratio for Death (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patients Who Died (N = 200)</td>
<td>Patients Who Survived (N = 200)</td>
<td></td>
</tr>
<tr>
<td>All levels</td>
<td>2260 (1196–5296)</td>
<td>1406 (989–2741)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&lt;3.5 mg/dl</td>
<td>1790 (1175–3941)</td>
<td>1148 (927–2169)</td>
<td>0.008</td>
</tr>
<tr>
<td>3.5–4.4 mg/dl</td>
<td>2049 (1109–4865)</td>
<td>1131 (893–1629)</td>
<td>0.003</td>
</tr>
<tr>
<td>4.5–5.5 mg/dl</td>
<td>2207 (1186–5238)</td>
<td>1499 (1044–2262)</td>
<td>0.02</td>
</tr>
<tr>
<td>&gt;5.5 mg/dl</td>
<td>3541 (1871–10,491)</td>
<td>2686 (1527–6210)</td>
<td>0.29</td>
</tr>
</tbody>
</table>

* The odds ratios are for a one-unit increase in the natural log-transformed cFGF-23 level in all 400 patients and in each quartile of 100 patients.

AVOIDING DRUGS TOXIC TO THE KIDNEYS

- NSAIDs
- Toxic medications to kidneys (antibiotics, certain blood pressure medications and diuretics *if* used inappropriately)
- Certain herbal medications
- Heavy metal exposure
- Certain eye injections? (stay tuned)
- Any drug in wrong dose can be dangerous if dosing is not correct for level of kidney function
KLOTHO

- FGF 23 and klotho are new markers that we have found correlate with kidney disease.
- This is very new but suffice it to say that premature kidney damage is associated with premature aging.
- Klotho is known to play a role in aging in mice.
- Klotho for the classically inclined is known to be one of the three fates from Greek mythology who weaves the thread of life.
- This link between the kidney health and aging is not lost on anyone I am sure.
LIFE AND DEATH ARE IN THE KIDNEYS?
THANK YOU!

- Questions
- For more information please visit UCLA CORE KIDNEY WEBSITE
- https://www.uclahealth.org/core-kidney/
- These slides will be on there too under patient education... thanks!