Disclaimer for Bait and Switch

JNC 8 – due out 2011- now due out 2012
   JNC 7 2003
ATP IV - due out 2011 – now due out 2012
   ATP III 2002
Obesity Guidelines – due out 2011 – now due out 2012
   Obesity Guideline 1998
Truth in advertizing
SORRY
Missing: Invisible Bicycle

If not seen, please call (415) 814-9229
Obesity and Kidney Disease

ACOI 2011
A Disease is Not a Disease Unless It Affects the Kidneys

Joel Chinitz MD 1996
Obesity CKD - Case

55 yo gentleman presents for evaluation of proteinuria
PMH – obesity, HTN Family Hx – DMII
PE – BP 155/94 BMI 42
Labs : BUN/CRE 12/1.4, FBS 123, TG 145
  U P/C 4.2, U A/C 3.2, UA + 4 protein
Obesity CKD Case

Does obesity play a role in this gentleman’s CKD?

Does obesity alter progression in CKD?

What influence will obesity have on mortality in CKD?
Hypothesis: Obesity Causes Chronic Kidney Disease
Obesity/CKD Evidence

1. Obesity is associated with renal hemodynamic changes known to cause CKD
2. Adipose tissue possesses inflammatory and hormonal mediators of kidney injury
3. Population studies have shown an association of obesity with CKD (not all)
4. CKD patients who are obese progress to ESRD more rapidly

5. Obesity is associated with known risk factors for CKD – metabolic syndrome, DM, HTN, and sleep apnea

6. Treatment of obesity improves fixes all
Estimation of GFR in Obesity

Measurement of GFR difficult in obesity

3 methods:

- Iodothalamate - radioisotope gold standard
- Cockcroft-Gault (CG) – adjusted for adjusted body weight
- MDRD – adjusted for BSA (?BMI)

GFR vs. BMI is not a linear relationship
Estimation of GFR in Obesity

CG – (140 – age)(ABW)/ 72 X creatinine
ABW = 0.4(TBW-IBW)

MDRD (obesity) – MDRD/1.73 X BSA
? Adjust to BMI 22.5
Proteinuria

Measurement of proteinuria and microalbuminuria is critical in the diagnosis and prognosis of CKD.

The use of spot urine for protein, albumin, and creatinine has been a dependable and useful tool for the screening, diagnosis and treatment of CKD.
**Protein-creatinine ratio to estimate protein excretion**

The relation between total daily protein excretion and the total protein-to-creatinine ratio (mg/mg) determined on a random urine specimen. (Data from Ginsberg, JM, Chang, BS, Matarese, RA, Garella, S, N Engl J Med 1983; 309:1543.)
Obesity is associated with renal hemodynamic changes known to cause CKD

Pathophysiology

Obesity is associated with an increased GFR (hyperfiltration), increased renal plasma flow, and increased filtration fraction

vasodilation with efferent arteriole vasoconstriction leading to glomerular hypertension

prostaglandins, nitric oxide and All
Obesity Related Glomerulopathy

Renal biopsies in obese patients reveal glomerulomegaly and focal sclerosis.

Hyperfiltration and glomerular hypertension leads to damage as evidenced by decrease in GFR and proteinuria.

Same # of nephrons doing more work per nephron.

Hyperfiltration and diabetic nephropathy.
Population studies have shown an association of obesity with CKD (not all)

Is there a relationship?

Some (not all) studies have shown a relationship between obesity and CKD

Level of evidence – cohort or epidemiologic

Framingham Offspring – obesity not significant after adjustment for CV risks

“Supersize Me” RCT recruiting now
Adjusted relative risks among independent risk factors for end-stage renal disease
Adjusted Relative Risk for ESRD (Logarithmic Scale)

BMI Category

<18.5 kg/m²  18.5–24.9 kg/m²  25.0–29.9 kg/m²  30.0–34.9 kg/m²  35.0–39.9 kg/m²  ≥40 kg/m²
CKD patients who are obese progress to ESRD more rapidly

Limited evidence for the effect of obesity on established CKD

Associated with a decline in function in transplants, nephrectomy (donors), and IGA

Sheffield UK - retrospective cohort study 125 non diabetic patients. Baseline BMI and younger age were associated with more rapid progression
Obesity is associated with known risk factors for CKD – metabolic syndrome, DM, HTN, and sleep apnea

Obese patients are more likely to have known risk factors for CKD:

- Metabolic Syndrome
- Sleep Apnea
- DM – 7X
- HTN – 6X
- Dyslipidemia
Adapted from Chen et al. 2004
Complications of Obesity and CKD

Sleep Apnea

Sleep apnea is prevalent in CKD and obesity
Uncertain as to cause and effect
Treatment of OSA will improve HTN to a limited degree but improvement in CKD has not been documented
Treatment of obesity improves fixes all

Renal goals of surgical or medical treatment of obesity:

1. Normalize hyperfiltration
2. Decrease proteinuria
3. Slow progression of CKD
4. Improve DM and HTN control
Glomerular Filtration Rate (ml/min)

PRE

POST

P=0.01
CKD and Obesity Conclusions

Obesity is a modifiable risk factor for CKD

Obesity never comes alone

Obesity accelerates the decline in GFR (probably)

Estimation of GFR in obese patients is not perfect

Spot urine for protein, albumin and creatinine is a good screening test
Obesity and Survival with CKD

Obesity in general population leads to worse outcomes

What about CKD?
Obesity Mortality CKD

In male veterans Stage 3 and 4 CKD, obesity is associated with lower risk of death.
Is this an excess mortality of LBW patients with malnutrition?
Are there greater co-morbid conditions leading to LBW?
Is obesity protective in short term illnesses?
Thrifty gene and evolutionary survival benefit
Obesity and ESRD - Case

48 yo AA man with ESRD secondary to chronic GN is placed on hemodialysis 3X weekly.
He has a BMI of 38 and his course on dialysis is characterized by barely adequate dialysis and difficult to control PO4, HTN and lipids.
How will obesity influence this patient's mortality on dialysis?
How will obesity affect his chances for transplantation?
What if he lost weight? Would it influence outcomes in either scenario?
Obesity and Dialysis

Increased # dialysis patients who are less transplant eligible – increased dialysis patients who are obese

Difficulties in dialysis – access, co-morbidities and clearance

Survival in dialysis patients - Obesity Paradox
Obesity Paradox

There is a linear inverse relationship between mortality and BMI

Obesity paradox in other chronic diseases – CHF, COPD etc.

Risk factor paradox – cholesterol, BP and homocysteine
Obesity Paradox

Is obesity truly protective in high mortality (20-25%/year) population?

ESRD is a catabolic state. Obese patients are more hemodynamically stable.

Risk factor paradox

Are less relatively healthy obese patients transplanted?
GOOD WOMEN
They can bring balance to your life!
Obesity and Transplantation

Obesity Stage 2 (BMI > 35) - Contraindication to transplant in most centers due to high risk of complications

Delayed graft function and postop complications (wound infection)

Size mismatch

Gastric bypass and med absorption
Obesity and Transplant

Number of patients with obesity is increasing on the transplant list

“Weight List Paradox”

America Transplant Society CPG – BMI < 30
Registration for Kidney Waiting List, by BMI

- BMI 35-40
- BMI >= 40

% of new registrations

- 1980-1984
- 1985-1989
- 1990-1994
- 1995-1999
- 2000-2005
Time to Transplantation
Kidney Candidates

Percent Transplanted

Months

BMI:
- <25
- 25-30
- 30-35
- 35-40
- >40
A ‘Weight-Listing’ Paradox for Candidates of Renal Transplantation?
A ‘Weight-Listing’ Paradox for Candidates of Renal Transplantation?
Obesity and Transplant

Obesity post transplant
Metabolic syndrome
Immunosuppression
  Steroids
  Cyclosporine
  Tacrolimus
  Sirolimus
Obesity ESRD - Conclusions

Obesity is associated with improved survival in dialysis patients (HD > PD) – obesity paradox
Obese transplant patients do less well than non-obese patients
Obese transplant patients do better than obese dialysis patients
Weight loss does not improve outcomes
Metabolic syndrome post transplant
Obesity Treatment - Case

40 yo woman with obesity (BMI 44) is referred for proteinuria and HTN
Her GFR is normal and her U P/C 1.5 U A/C 0.8
BP is poorly controlled on 3 drugs (beta blocker, calcium blocker, and thiazide)
Obesity Treatment - Case

What treatments can be offered for her CKD?
Does treatment of obesity matter for CKD?
Which is better medical or surgical weight loss?
Are there any complications of weight loss therapy?
Treatment of Obesity Related Kidney Disease

REIN – ramipril secondary analysis

Weight loss programs surgical vs. medical
REIN Study: ACE Inhibition in Proteinuric Non-Diabetic Nephropathy

<table>
<thead>
<tr>
<th></th>
<th>Baseline SBP</th>
<th>Δ SBP</th>
<th>Baseline DBP</th>
<th>Δ DBP</th>
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<tbody>
<tr>
<td>Ramipril</td>
<td>149.8</td>
<td>-5.8 mmHg</td>
<td>92.4</td>
<td>-4.2 mmHg</td>
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<tr>
<td>Placebo</td>
<td>148.0</td>
<td>-3.4 mmHg</td>
<td>91.3</td>
<td>-3.4 mmHg</td>
</tr>
</tbody>
</table>

*Combined endpoint = doubling of baseline serum creatinine concentration or end stage renal failure

Differences in Urinary Protein Excretion
(Ramipril versus Placebo)

B.M.I. (Kg/m²)  <25  25 - 30  >30
**Cumulative Incidence of ESRD**

- **B.M.I \(<25 \text{ kg/m}^2**
  - HR(95% CI): 0.58 (0.31-1.09), p=0.09*
  - HR(95% CI): 0.80 (0.43-1.50), p=0.49*
  - HR(95% CI): 0.81 (0.45-1.47), p=0.49**

- **B.M.I \(25-30 \text{ kg/m}^2**
  - HR(95% CI): 0.55 (0.24-1.23), p=0.14*
  - HR(95% CI): 0.36 (0.20-0.65), p=0.001*
  - HR(95% CI): 0.38 (0.22-0.67), p=0.001**

- **B.M.I \(>30 \text{ kg/m}^2**
  - HR(95% CI): 0.14 (0.03-0.65), p=0.01*
  - HR(95% CI): 0.16 (0.05-0.52), p=0.002*
  - HR(95% CI): 0.18 (0.06-0.54), p=0.002**

**Patients at risk**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ramipril</th>
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<tbody>
<tr>
<td>Months</td>
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<tr>
<td>0-10</td>
<td>91</td>
<td>92</td>
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<td>10-20</td>
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<td>20-30</td>
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<td>40-50</td>
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<tr>
<td>50+</td>
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<tr>
<td>50+</td>
<td>15</td>
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</tbody>
</table>

*Crude.

*Calculated in a model including treatment (Ramipril versus placebo), BMI classes, BMI*treatment interaction term, gender, baseline systolic blood pressure, albumin, hemoglobin, urinary protein and GFR.

**Shrinkage corrected.
Change in microalbuminuria with weight loss by different types of intervention.

<table>
<thead>
<tr>
<th>Study ID</th>
<th>WMD (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>BS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chagnac A. (2003)</td>
<td>-49.66 (-97.02, -2.30)</td>
<td>0.47</td>
</tr>
<tr>
<td>Navarro-Diaz M (2006)</td>
<td>-10.84 (-16.70, -4.98)</td>
<td>15.52</td>
</tr>
<tr>
<td>Agrawal V. (2008)</td>
<td>-13.99 (-26.03, -1.95)</td>
<td>5.92</td>
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<tr>
<td>Life style modification</td>
<td></td>
<td></td>
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<tr>
<td>Cubeddu LX. (2007)</td>
<td>-8.90 (-12.62, -5.18)</td>
<td>22.17</td>
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<tr>
<td>Exercise</td>
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<td></td>
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<tr>
<td>Lazarevic G (2007)</td>
<td>-29.00 (-61.46, 3.46)</td>
<td>0.97</td>
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<tr>
<td>Medication</td>
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<tr>
<td>Low caloric diet</td>
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<tr>
<td>Vasquez B. (1984)</td>
<td>-17.50 (-22.69, -12.31)</td>
<td>17.41</td>
</tr>
<tr>
<td>Overall (I-squared = 50.0%, p = 0.051)</td>
<td>-13.87 (-17.12, -10.61)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

BS: Bariatric surgery
Comparing the effect of surgical and non-surgical methods of weight loss on change of creatinine clearance

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<tr>
<th>Study</th>
<th>WMD (95% CI)</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-surgical</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cubeddu LX. (2008)</td>
<td>-11.00 (-15.35, -6.65)</td>
<td>25.22</td>
</tr>
<tr>
<td>Saiki A. (2005)</td>
<td>5.00 (-4.20, 14.20)</td>
<td>22.58</td>
</tr>
<tr>
<td>Solerte SB. (1989)</td>
<td>12.00 (4.36, 19.64)</td>
<td>23.56</td>
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<tr>
<td>Morales E. (2003)</td>
<td>-1.10 (-22.08, 19.88)</td>
<td>14.43</td>
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<tr>
<td>Praga M. (1995)</td>
<td>-4.00 (-25.33, 17.33)</td>
<td>14.21</td>
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<tr>
<td>Subtotal (I-squared = 86.9%, p = 0.000)</td>
<td>0.46 (-11.46, 12.37)</td>
<td>100.00</td>
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<tr>
<td><strong>Surgical</strong></td>
<td></td>
<td></td>
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<tr>
<td>Navarro-Diaz M (2006)</td>
<td>-21.54 (-35.08, -8.00)</td>
<td>83.70</td>
</tr>
<tr>
<td>Chagnac A. (2003)</td>
<td>-35.00 (-65.68, -4.32)</td>
<td>16.30</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.431)</td>
<td>-23.73 (-36.12, -11.35)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

Note: In Chagnac study GFR is used as a proxy of creatinine clearance.
Conclusions – Weight Loss

Proteinuria is decreased by medical and surgical treatment of obesity

GFR – hyperfiltration is reversed by surgery
  GFR decline is probably stabilized by surgery

medical treatment has not been shown to do either
Kidney Complications of Anti Obesity Treatment

Medical/Surgical Treatment

Oxalate nephropathy

Amateur Weight Loss

Phosphate nephropathy

Chinese Herb Nephropathy

Electrolyte disorders – hypokalemic
Pathologic findings in oxalate nephropathy.

Nasr S H et al. CJASN 2008;3:1676-1683
Oxalate Nephropathy

Gastric bypass leads to enteric recirculation of oxalate (calcium/fat instead of calcium/oxalate binding)

Enteric recirculation of oxalate leads to massive hyperoxaluria with tubular toxicity and calcium oxalate precipitation leading to AKI

Orlistat can cause the same lesion

Nephrolithiasis
Serum Creatinine Concentration (12/05 - 4/06)

Orlistat 120 mg tid

First biopsy

Second biopsy
Chinese Herb Nephropathy

Chinese herbs nephropathy (CHN) is a rapidly progressive interstitial nephropathy reported after the introduction of Chinese herbs in a slimming regimen followed by young Belgian women.

Aristolochic acid
Renal interstitial fibrosis and urothelial carcinoma

**Chinese herb nephropathy (1992)**
Etiological factors: aristolochic acid highly suspected, ochratoxin A evoked

**Balkan endemic nephropathy (1956)**
Etiological factors: aristolochic acid highly suspected, ochratoxin A evoked

**Aristolochic acid nephropathy (1996–)**
Etiological factor: role of aristolochic acid proven

**Aristolochic acid - Balkan endemic nephropathy (2007–)**
Etiological factors: aristolochic acid highly suspected, ochratoxin A evoked

Similarities

Renal interstitial fibrosis, urothelial carcinoma, and aristolochic acid-related specific DNA adducts
Conclusions

Evidence suggests that obesity is a modifiable risk factor for CKD

Obesity comes with baggage

Obesity appears to be protective in high short term mortality diseases

Obese patients do better with transplant and weight loss pre-op should not mandatory

Weight loss and ACEI offer benefit