ESRD Care – Gender Differences

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April 20, 2016
Disclosure Statement

I have nothing to disclose
Women and Kidney Disease

- Basic physiologic gender differences
- Impact of health care provider bias
- Epidemiology of gender and kidney disease
- Gender disparities in ESKD: vascular access
- Special Issues: Pregnancy
- Care of the woman with kidney disease
- Unanswered questions and comments
Women and Kidney Disease

• The prevalence of kidney disease is higher in women than men yet......
• Most studies of ESKD lump men and women together and assume any underlying pathophysiology is the same

CDC CKD Fact Sheet 2012
Women and ESKD

• Prevalent ESKD patients:
  • 44.3% of patients on hemodialysis are women
  • 47% of patients on PD are women.
  • Women on dialysis do not experience the survival benefit seen in those not on dialysis.
    • lower cardiovascular survival benefit
    • higher noncardiovascular mortality rate
    • markedly higher mortality rates seen in women less than 45 years of age on dialysis.

ACKD, 2013, 20(5):411
Women lose their “advantage” when they get ESKD
Women and Kidney Disease

• Basic physiologic differences between men and women (pre-menopausal)
  • Women have smaller body mass (height and weight) and in thus have smaller kidneys
  • Women have a higher percentage of body water (70% vs 60%) – due in part to a higher fat/muscle ratio
  • Men have higher hemoglobin, vitamin K levels and platelet counts
  • Women heal faster from external wounds and have higher levels of WBC’s both neutrophils and lymphocytes
Women and Kidney Disease

• Psychosocial differences
  • The “caregiver role”
    • Women take on more household duties
    • Women report more stress
    • This applies to child care as well as elder care
  • Gender Bias
    • Doubling of stress may occur if female and of minority race or ethnicity
    • As recently as Nov 2011 it was legal to charge women more for health insurance or deny it altogether in 37 states

Women and Kidney Disease

• Insurance Bias
  • Prior to the ACA in 2014, more than half of individual plans charged higher premiums for a 40-year-old female non-smoker than for a 40-year-old male smoker.
  • The practice of charging women more than cost women roughly $1 billion per year in 2012.
  • 90 percent of individual health plans didn’t provide any routine maternity benefits.
  • In all but five states, being pregnant was a pre-existing condition that prevented a woman from purchasing individual health insurance at all once they were pregnant.
Women and Kidney Disease

• Insurance Bias
  • Women in the 20 states that have not expanded Medicaid are not eligible for subsidies to purchase exchange plans unless their incomes are at least 100 percent of poverty level.
  • Stringent guidelines for Medicaid eligibility in those states mean that many women with incomes below the exchange subsidy threshold are not eligible for Medicaid
  • The ACA’s health insurance reforms remain unavailable to these women
  • The impact on pre-ESKD care in women is unknown
Women and Kidney Disease

• Healthcare Provider Gender Bias
  • “Women get sick, but men die”
  • Symptoms are more likely to be ascribed to “anxiety”
  • Men are more likely to be referred for work up of chest pain\(^1\)
  • More commonly ascribed to other causes (incorrectly)
  • Poorer outcome when referred for revascularization\(^2\)

\(^1\)BMC Fam Pract. 2011 Jun 6;12:45, \(^2\)NEJM, 1991 325:221-225
Women and Kidney Disease

• Healthcare Provider Gender Bias
  • Women are less likely to be diagnosed with COPD\(^2\)
  • Women are given more medication than men, especially psychotropic drugs\(^3\)
  • Women with colon cancer visit the physician more times than men before diagnosis\(^3\)

• Prevalence of sexual misconduct by adult healthcare providers is as high as 10%
  • 91% of the abusers are men\(^4\)

Women and Kidney Disease

• Locus of control and Body Image¹
  • Women may have more external locus of control
  • Body image dissatisfaction is more common in women (may be changing)
    • May impact choice of dialysis access or modality
• Effect on medication adherence unpredictable
  • High external locus of control - more adherent
  • High body image dissatisfaction - less adherent if medication is perceived to be contributing e.g. prednisone causing weight gain, cyclosporine causing hair growth

Women and Kidney Disease

• Psychosocial Stressors in women with CKD
  • Financial (not gender related)
    • Loss of employment due to illness, time for dialysis, etc
    • Medication expense
    • Co-morbid conditions
  • Family obligations
    • Need for “back-up” caregiver for children or elderly parents when at doctor or dialysis session
Women and Kidney Disease

- Gender bias in nephrology
  - Women are referred later for renal replacement therapy (multivariate odds ratio 1.7, CI 1.65-1.76)\(^1\)
    - Kidney function is worse at a given creatinine value
  - Women receive fewer AV fistulas than men, irrespective of race\(^2\)
    - Perception that vessels will be smaller
    - Bias that women do poorly with AVF
      - Data from 1999-2000
    - Unknown bias?

Women and Kidney Disease

Table 4
Logistic model: predictors of AVF use among incident ESRD patients in networks 5, 6, 8, 11, and 13b

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Adjusted OR of AVF use</th>
<th>95% CI</th>
<th>p value</th>
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<tbody>
<tr>
<td>Race</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Black</td>
<td>1.00</td>
<td>0.92–1.09</td>
<td>0.9455</td>
</tr>
<tr>
<td>White a</td>
<td>1</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.64</td>
<td>0.59–0.69</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male a</td>
<td>1</td>
<td>–</td>
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<tr>
<td>Age</td>
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<tr>
<td>18–29</td>
<td>0.61</td>
<td>0.47–0.80</td>
<td>0.0004</td>
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<tr>
<td>30–39</td>
<td>0.80</td>
<td>0.67–0.96</td>
<td>0.0155</td>
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<td>40–49</td>
<td>0.89</td>
<td>0.78–1.01</td>
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<tr>
<td>50–59</td>
<td>1.01</td>
<td>0.90–1.13</td>
<td>0.8693</td>
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</tbody>
</table>

AVF Fistula as Initial Access – USRDS 2012 Data

• 202,999 pts who began dialysis between 2006-2009 and received prior nephrology care
• Data from the CMS Medical Evidence Form 2728
• Logistic regression performed controlling for the following covariates:
  • age, race, gender, body mass index, height, history of alcohol abuse, history of drug abuse and comorbidities including diabetes, history of coronary artery disease, congestive heart failure, peripheral arterial disease, cerebrovascular disease and chronic obstructive pulmonary disease, pre-dialysis access to nutritional counseling, ability to ambulate and lack of insurance coverage
  • An interaction between gender, age and race was noted and so analysis were performed separately for racial and age groups

Markell et al. NKF Spring Meeting 2016
Odds for AVF Fistula as Initial Access – USRDS 2012 Data

<table>
<thead>
<tr>
<th>Female vs Male</th>
<th>OR for AVF</th>
<th>95 % CI</th>
<th>p-value</th>
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<tbody>
<tr>
<td>Non-Black, age 19-45</td>
<td>0.65</td>
<td>0.61</td>
<td>0.70</td>
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<tr>
<td>Black, age 19-45</td>
<td>0.60</td>
<td>0.56</td>
<td>0.65</td>
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<tr>
<td>Non-Black, age 46-55</td>
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<td>0.66</td>
<td>0.75</td>
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<td>Black, age 46-55</td>
<td>0.65</td>
<td>0.61</td>
<td>0.70</td>
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<td>Non-Black, age 56-65</td>
<td>0.70</td>
<td>0.67</td>
<td>0.74</td>
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<td>Black, age 56-65</td>
<td>0.65</td>
<td>0.61</td>
<td>0.69</td>
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<td>Non-Black, age 66-75</td>
<td>0.75</td>
<td>0.72</td>
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<tr>
<td>Black, age 66-75</td>
<td>0.69</td>
<td>0.65</td>
<td>0.74</td>
</tr>
<tr>
<td>Non-Black, age 76+;</td>
<td>0.67</td>
<td>0.64</td>
<td>0.71</td>
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<tr>
<td>Black, age 76+;</td>
<td>0.62</td>
<td>0.58</td>
<td>0.66</td>
</tr>
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</table>

Markell et al. NKF Spring Meeting 2016
Why aren’t women starting dialysis with an AV Fistula in the age of “fistula first”?

- Late referral? Missed diagnosis?
  - Our analysis suggest that time under nephrologists care does not affect odds of fistula placement
- Surgeon bias?
  - Perception that vessels may be too small?
- Patient bias?
  - Concern that fistulae are “ugly”?  
  - Not wanting to get “stuck”?  
  - Poor education regarding the necessity to have a fistula placed early?

**THIS ISSUE CLEARLY WARRANTS MORE INVESTIGATION**
Women and Kidney Disease

- Women are referred later for transplant or not at all
- In a study of over 10,000 patients, crude rates of wait-listing per 100 person-years of ESRD were lower for female patients than male patients in both the pediatric (28.89 versus 34.18) and adult (3.94 versus 6.54) populations.

Women and Kidney Disease - Transplant

- After adjusting for confounders by multivariate analysis:
- In children with ESRD,
  - Girls were 14% less likely to be listed than boys (relative hazard [RH] 0.86; 95% confidence interval [CI], 0.78 to 0.93)
- In adults
  - Women were 18% less likely to be listed than men (RH 0.82; 95% CI, 0.72 to 0.93).

Women and Kidney Disease

- Adherence to transplant medications
  - Social support by men acts as a deterrent to adherence in female transplant recipients, while women enhance adherence in male patients.¹
- Living Kidney donation²
  - Overall women donate more kidneys
  - 36% of wives versus 6.5% of husbands who are acceptable donors go on to donate a kidney; (P = 0.003)
  - Reasons are unclear - economics? Physician bias?

Women and Kidney Disease

- Although the prevalence of CKD is higher in women
- Men may progress to ESRD more rapidly – meta analysis using 68 studies
  - IgA nephropathy
  - Membranous nephropathy
  - Possibly APKD
- Diabetic patients were excluded

NEUGARTEN J et al. JASN 2000;11:319-329
Women and Kidney - Disease

• The “female advantage”
• Cox proportional-hazards regression analyses of the effects of age, gender, and GFR at baseline on the competing risks renal failure and death (n=3047)
• Female gender – kidney failure 0.35, 95% confidence interval 0.21–0.59, p<0.0001; death - 0.55, confidence interval 0.48–0.62, p<0.0001

Women and Kidney Disease

- “Female Advantage” does not extend to diabetes
  - Cardiovascular risk increases to higher than men
    - After combining studies that adjusted for other cardiac risk factors, the relative risk of coronary death from diabetes is 2.58 (95% CI 2.05–3.26) for women and 1.85 (1.47–2.33) for men ($P = 0.045$).

*Diabetes Care* 23:962–968, 2000
Women and Kidney Disease

• Progression to ESRD
  • Provisional data (Abstract only) suggests that women with diabetes progress to ESRD at rates comparable to men
  • Diabetes is associated with reduced estradiol levels, which may impact intra-renal fibrosis and mesangial cell expansion

American Physiological Society (2007, August 9). The 'Female Advantage' In Kidney Disease Does Not Extend To Diabetic Women.
Women and Kidney Disease

• “Female” Hormones
  • Estrogen
    • Steroid hormone
    • Estrogen is present in at least three forms in women
      • Estrone (E1), estradiol (E2), Estriol (E3)
    • It is produced from testosterone by aromatase
    • It acts at the nucleus on the estrogen response element via the estrogen receptor
Women and Kidney Disease

• “Female” Hormones
  • Some extra-renal effects of estrogen
    • Causes secondary sex characteristic development
    • Increases bone formation
    • Increases clotting and wound healing
      • Increased clotting factors, decreased AT3
    • Increases HDL
    • May affect mood and cognition
Women and Kidney Disease

• Effects of estrogen (E2) on the kidney
  • 3 estrogen receptors have been identified in the kidney - ERα, ERβ, and GPR30 (G protein receptor coupled)
  • E2 decreases collagen synthesis by mesangial cells, including mediated by TGFβ and AII
  • E2 can act as an anti-oxidant
  • May be responsible for the “female advantage” in progression of CKD
Women and Kidney Disease

• Progesterone
  • Steroid hormone synthesized from pregnenolone
  • Acts on a nuclear receptor
  • May have neuroprotective effects
  • Made by men as well as women
  • May have antiinflammatory and immune modulatory effects
• Hypothalamic dysfunction occurs early in CKD and affects hormone levels
Women and Kidney Disease

- Abnormal hypothalamic-pituitary function
  - Alteration of GnRH
    - Loss of pulsatile secretion
    - Aberrant LH secretion
  - Most studies were performed between 1968-80!
- Hyperprolactinemia
  - Decreased renal clearance
  - Increased pituitary secretion

Women and Kidney Disease

- >90% of dialysis patients have menstrual disorders
- Menses resume following successful kidney transplant (creat <1.4 mg/dl) in >70% of pre-menopausal women
- Latency 5-7 months
- Progesterone levels lower
- 10.4% infertility diagnosis
- 48.5% unintended pregnancies!

Women and Kidney Disease

- Estradiol pharmacokinetics are altered in CKD
  - Free and total plasma concentrations are higher
  - No change in estrone
  - Neither removed by dialysis
- Implications for oral estrogen dosing
  - 50% reduction for HRT?
  - Dosing of birth control pills?
- No information on pharmacokinetics of progestins

Women and Kidney Disease

- Pharmacokinetics (general)
  - 2010 Nature editorial lamented the lack of women subjects in pharmaceutical trials
- Molecular Factors
  - Differences in CYP450 isoforms
  - Differences in P-glycoprotein transporter
- Physiologic Factors
  - The volume of distribution of drugs
  - Higher body water and fat
  - Smaller organ size

Women and Kidney Disease – Disease Risk – Atherosclerosis

- Normal kidney function - prevalence is lower at all age groups
Women and Kidney Disease

• Data from Women’s Health Study suggest that GFR <60 ml/min is associated with increased risk of cardiovascular disease death
  • No increase in CVD per se
  • No comparison to men with CKD
  • Complex association
    • Confounded by coincident risk factors for kidney disease and CV mortality

¹BMJ 2009, 338:b2392
Women and Kidney Disease

- Hemodialysis
  - Fatter women have higher risk of cardiovascular disease than men
  - Especially if they have a higher percentage of body fat

*J Ren Nutr.* 2011 Dec 6
Women and Kidney Disease - normal kidney function

- Incidence of stroke is lower in women until around age 85
Women and Kidney Disease

- Effects of decreased creatinine clearance on stroke risk\(^1\)
  - Data only available for men
  - Increased risk with decreasing GFR
  - Confounded by use of anti-hypertensive agents, hypertension control, diabetes and other risk factors
- Increased risk of atrial fibrillation in CKD\(^2\)
  - Not influenced by gender

\(^1\)Circulation. 2011;123:2946-2953
Women and Kidney Disease – Disease Risk

• Cancer Risk
  • Breast Cancer
    • Increased incidence following kidney transplantation
    • Conflicting data – no definitive increase noted
  • Papillomavirus
    • Papillomavirus may reactivate in kidney transplant recipients
    • 14-fold increased risk of cervical cancer, up to 50-fold of vulvar cancer and up to 100-fold of anal cancers in women

• Skin cancers
  • Studies not broken down by gender
  • Overall increased risk for non-melanoma skin cancers

*JAMA.* 2011 Nov 2;306(17):1891-90, Transplantation 91(1):8-10
Women and Kidney Disease – Disease Risk

- Bone Disease
  - Actual fracture risk unknown but is increased overall in CKD
  - DEXA may not predict fracture risk in CKD, especially at Stage >4-5
  - No data on kidney transplant recipients

Women and Kidney Disease

- Bone disease in CKD is multifactorial

<table>
<thead>
<tr>
<th>Osteoporosis</th>
<th>Metabolic bone disease in CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic heparin</td>
<td>Osteitis fibrosa cystica</td>
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<tr>
<td>Steroids</td>
<td>Osteomalacia</td>
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<tr>
<td>Hypogonadism</td>
<td>Adynamic bone disease</td>
</tr>
<tr>
<td>Hyperprolactinemia</td>
<td>Amyloid bone disease</td>
</tr>
<tr>
<td>Poor nutrition</td>
<td></td>
</tr>
<tr>
<td>Vitamin D deficiency</td>
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</tr>
<tr>
<td>Hyperparathyroidism</td>
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</tr>
<tr>
<td>Metabolic acidosis</td>
<td></td>
</tr>
<tr>
<td>Limited physical activity</td>
<td></td>
</tr>
<tr>
<td>CKD, chronic kidney disease</td>
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</tr>
</tbody>
</table>
Women and Kidney Disease – Disease Risk

- Anxiety and Depression
  - Prevalence higher in the general female population
  - Prevalence of major depressive disorder was 21% in patients with CKD stages 2-5– but the largest study included only TWO women (and 270 men!)¹

- Associated with increased risk for hospitalization in dialysis patients (again not stratified by gender) – only 2 women out of cohort of 88

Women and Kidney Disease

Risk of Hospitalization and Death in Patients with CKD
Women and Kidney Disease

• Specific dialysis related issues
  • Peritoneal Dialysis
    • Anatomic effects
      • Squamous metaplasia of ovaries\(^1\)
      • Obstruction of peritoneal catheter by Fallopian Fimbria\(^2\)
      • Hemoperitoneum due to retrograde menstruation or peritoneal endometriosis\(^3\)
  • Body Image Issues
    • Alteration of waist circumference
    • Presence of catheter

Women and Kidney Disease

- Pregnancy and CKD
  - Acceleration of disease progressions?
  - Increased risk of pre-eclampsia?
  - 68-98% live birth rate
    • Depends on degree of kidney function and underlying disease
- Pregnancy and Dialysis
  - High rate of premature labor
  - Difficulty in diagnosing pre-eclampsia
  - Intensive dialysis with aggressive blood pressure control necessary

Women and Kidney Disease

- Pregnancy and Dialysis - complications

- Preterm premature rupture of membranes ($n=7; 6.6\%$)
- Preterm labour ($n=35; 33\%$)
- Fetal distress ($n=31; 29.2\%$)
- Intrauterine growth restriction ($n=11; 10.4\%$)
- Hypertensive disease ($n=9; 8.5\%$)
- Others ($n=9; 8.5\%$)
- Antepartum haemorrhage ($n=4, 3.8\%$)

Woman and Kidney Disease

- Pregnancy and Dialysis - Outcomes

225 conceptions

188 (83.6%) completed ≥20 weeks

178 (79.1%) live births

18 (8%) term deliveries

24 (10.7%) therapeutic abortions

13 (5.8%) miscarriages

10 (4.5%) stillbirths

160 (71.1%) preterm births

Women and Kidney Disease

- Kidney Transplantation and Pregnancy
  - Actual incidence rate is unknown
  - Recommendation to start contraception prior to transplantation
    - Low dose estrogen and progesterone or progestin only hormone therapy is recommended unless contraindicated
Women and Kidney Disease

- **Kidney Transplantation and Pregnancy**
  - American Society of Transplantation Consensus Opinion recommends pregnancy under the following conditions
    - serum creatinine <1.5 mg/dl, with <500 mg/24 h protein excretion
    - no concurrent fetotoxic infections
      - E.g. CMV
    - no use of teratogenic or fetotoxic medications
      - Remember black box warning for mycophenolate
      - ACE inhibitors and ARB’s also contraindicated
    - immunosuppressive dosing is stable at maintenance levels
    - It is no longer suggested that the patient wait 2 years
Women and Kidney Disease

• Recommendations for Preventive Care
  • Neither the NKF KDOQI guidelines nor the ISN KDIGO guidelines address gender issues
  • Recommendations are global
  • Most guidelines for CKD Stages 1-3 are based on guidelines for the general population
Women and Kidney Disease

• Weight management
  • No data by gender
  • NHANES data suggest that obese patients with CKD are inactive and could benefit from lifestyle interventions¹
    • 50% of patients with CKD were trying to lose weight
    • Caloric intake was lower than obese non-CKD patients
    • 8% of CKD patients use weight loss products that may be high in protein or potassium

• Bariatric Surgery²
  • May decrease proteinuria
  • Improves glucose tolerance, but....

Women and Kidney Disease

- Bariatric Surgery may lead to ESRD (J-I bypass)
  - Poor excretion of oxalate due to fat malabsorption
  - Decreased urine volume and urinary citrate
  - Oxalate stone formation or nephropathy
And for dialysis patients:

Am J Clin Nutr 2005, 81: 543
Sarcopenia Increases Death Risk in HD

Number at risk

<table>
<thead>
<tr>
<th>Condition</th>
<th>0</th>
<th>5</th>
<th>10</th>
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<tbody>
<tr>
<td>Appropriate muscle mass and strength</td>
<td>134</td>
<td>112</td>
<td>79</td>
<td>68</td>
<td>53</td>
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<td></td>
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</tr>
<tr>
<td>Low muscle mass</td>
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<td>32</td>
<td>27</td>
<td>20</td>
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<tr>
<td>Low muscle strength</td>
<td>78</td>
<td>67</td>
<td>45</td>
<td>33</td>
<td>22</td>
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<tr>
<td>Sarcopenia</td>
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</table>

CJASN 2014, 9(10):1720
Women and Kidney Disease – General Recommendations:

- Cardiovascular Risk Interventions
  - NO specific guidelines for women
  - General recommendations for achievement of target cholesterol and triglyceride values (KDOQI)
    - Not recommended to start statins in ESKD
  - No data to suggest that these interventions affect cardiovascular outcomes in CKD/ESKD patients
Women and Kidney Disease – General Recommendations

• Bone Health
  • NO specific guidelines for women – maintenance of calcium phosphate product <55, intact PTH at target for CKD Stage, use of Vitamin D products
  • Bone biopsy recommended prior to initiation of bisphosphonate therapy for CKD Stage 4 or greater (KDIGO)
  • For kidney transplant recipients there are no separate guidelines due to lack of evidence (KDIGO)
  • Clearly this is an area where more research is needed
Women and Kidney Disease

• A few unanswered Questions (the list seems endless)
  • Should men and women be studied separately in CKD trials?
  • Should estrogen deficient women with CKD receive hormone replacement?
    • Dialysis patients?
    • Kidney Transplant recipients?
  • How do we educate health care providers in order to avoid bias?
  • How do we improve psychosocial stressors?
    • Daycare or Elder care at Dialysis Centers and Transplant clinics?
    • Education of partners regarding CKD/ESKD?
    • Support groups?
Women and Kidney Disease - Summary and Conclusions

- Women differ from men in many physiologic aspects, some of which probably persist in ESKD
- Gender disparities are frequent in the care of women in general and in the woman with ESKD
- When a woman starts dialysis she often “loses her gender”
- Few studies have specifically addressed the needs of women with CKD/ESKD
- Many assumptions about care have been made based on results from men
Women and Kidney Disease - Conclusion

• Cats are not small dogs, and women are not small men
• It is hoped that research monies will be allocated for the investigation of the questions that have been raised today