Be it resolved that kidney transplantation is NOT a unique consideration for pre-transplant para-thyroidectomy

John S. Gill, MD,MS,
Associate Professor of Medicine,
President Canadian Organ Replacement Register
Michael Smith Scholar

Be it resolved that kidney transplantation is NOT a unique consideration for pre-transplant para-thyroidectomy

John S. Gill, MD,MS,
Associate Professor of Medicine,
President Canadian Organ Replacement Register
Michael Smith Scholar

Vegetarian

Vegetarians are more likely to seek hard evidence before cutting open someone's neck

These are the facts (and they are indisputable)

- **Indications for para-thyroidectomy in dialysis patients are poorly defined**
- **Pre-transplant identification of patients who will develop tertiary hyperparathyroidism after transplantation is difficult**
- **Potential consequences of tertiary hyperparathyroidism are rarely serious or too poorly understood to recommend pre-transplant parathyroidectomy**
  - **Hypercalcemia is common, usually transient, rarely serious and is not associated with long-term outcome**
  - **Bone disease is poorly understood**
  - **Vascular calcification is poorly understood**
- **Medical options exist for treatment of tertiary hyperparathyroidism after transplantation**
- **If required parathyroidectomy after transplantation can be safely performed**

Indications for para-thyroidectomy in dialysis patients are poorly defined

"There are no studies evaluating PTHectomy of either moderate or high quality that show a beneficial or harmful effect of this treatment on mortality, CVD, hospitalization, fractures, quality of life, on bone or cardiovascular outcomes, or on biochemical outcomes"

KDIGO Guidelines 2009

KDOQI – In dialysis patients Parathyroidectomy may be considered when

- HPT is severe and "refractory" to medical management usually after a trial of calcitriol, a vitamin D analog, or cinacalcet
- When medical management results in an unacceptable rise in Ca or P
- When medical management is not tolerated

“Refractory HPT” is hard to define

- PTH >85 pmol/l – 22% respond to cinacalcet
- PTH 53-85 pmol/l – 60% respond to cinacalcet
- PTH >32-53 pmol/l – 81% respond to cinacalcet

- Respond = ability to achieve PTH < 32 pmol/l

“Refractory HPT” is hard to define

- PTH >85 pmol/l – 22% respond to cinacalcet
- PTH 53-85 pmol/l – 60% respond to cinacalcet
- PTH >32-53 pmol/l – 81% respond to cinacalcet

(Respond = ability to achieve PTH < 32 pmol/l)

- NON – Responders might warrant PTHectomy BUT this is NOT a TRANSPLANT SPECIFIC ISSUE!!!

These are the facts (and they are indisputable)

- Indications for para-thyroidectomy in dialysis patients are poorly defined
- **Pre-transplant identification of patients who will develop tertiary hyperparathyroidism after transplantation is difficult**
- Hypercalcemia is common, usually transient, rarely serious and is not associated with long-term outcome
- Medical options exist for treatment of tertiary hyperparathyroidism after transplantation
- If required parathyroidectomy after transplantation can be safely performed

Definition

- Tertiary Hyperparathyroidism
  - Persistent hyperparathyroidism despite provision of normal kidney function after transplantation

Natural History of Hyperparathyroidism After Kidney Transplantation

- PTH levels shows a biphasic decline after TX
  - A rapid drop (by 50%) over 3-6 months attributed to a reduction in PTH mass
  - Then a gradual protracted decline (years)

- PTH cells have a long life span (20yrs) – very slow involution of hyperplastic cells after TX (PTH levels continue to slowly decrease over time)

- About 25% will have elevated PTH levels one year after transplantation despite successful transplantation

Tertiary Hyperparathyroidsim

- Pre-tx Risk Factors
- Prolonged dialysis
- High PTH,Ca,P, alkaline P,
- Large glands on U/S

- Post-tx Risk Factors
- Level of graft function
- Steroids
- Low vitD3 and calcitriol levels
- Decreased expression of vit D and calcium sensing receptors in PTH glands

Point: Tertiary Hyperparathyroidism is dependent on PRE and POST TX Factors and thus is difficult to predict PRIOR to transplantation in Individual Patients

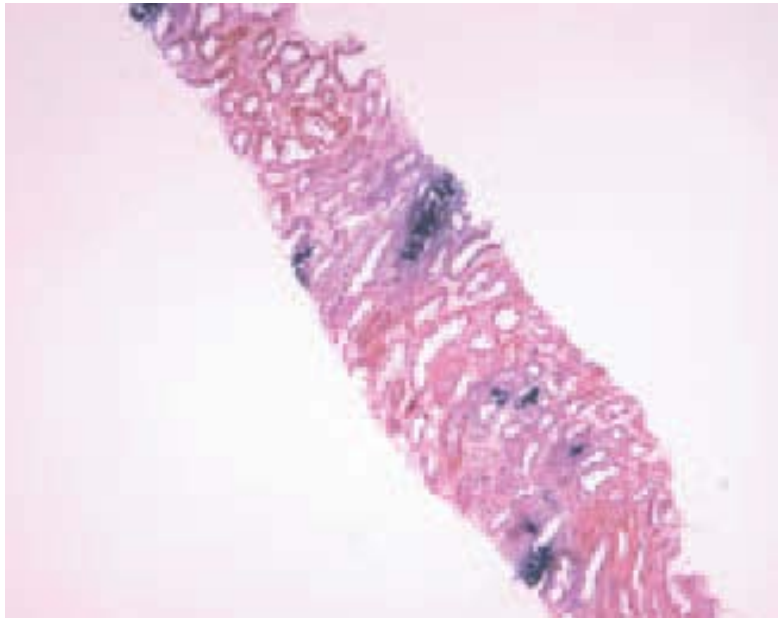
These are the facts (and they are indisputable)

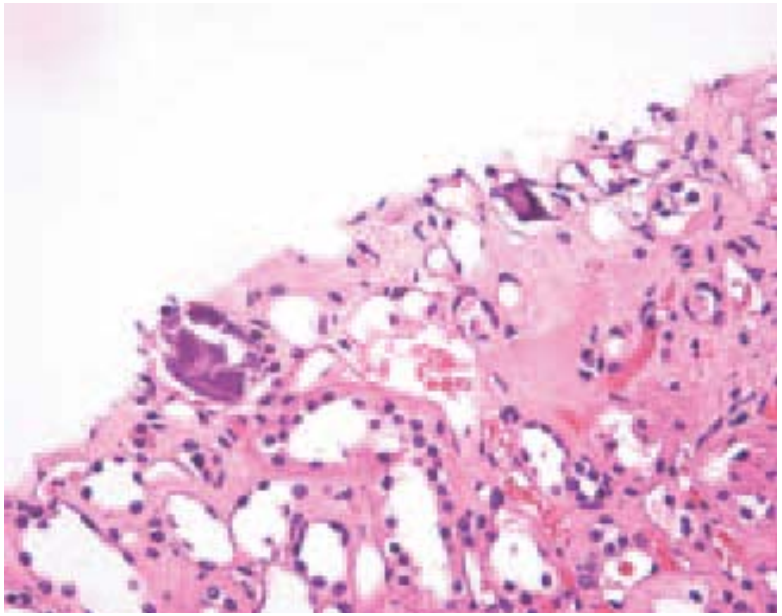
- Indications for para-thyroidectomy in dialysis patients are poorly defined
- Pre-transplant identification of patients who will develop tertiary hyperparathyroidism after transplantation is difficult
- **Potential consequences of tertiary hyperparathyroidism are rarely serious or too poorly understood to recommend pre-transplant parathyroidectomy**
  - **Hypercalcemia is common, usually transient, rarely serious and is not associated with long-term outcome**
  - **Bone disease is poorly understood**
  - **Vascular calcification is poorly understood**
- Medical options exist for treatment of tertiary hyperparathyroidism after transplantation
- If required parathyroidectomy after transplantation can be safely performed

Hypercalcemia Post Tx - Mechanism

- High PTH stimulates renal production of caclitriol, increased gut absorption of calcium as well as mobilization of Ca from bone
- Correction of uremia decreases skeletal resistance to PTH , increased osteoclast activity and resorption
- Resorption of soft-tissue calcification

Calcium Deposition In Renal Allograft





Hypercalcemia after Renal Transplantation

John S Gill[1] MD, MS
Caren Rose[1,] MS
Edward Cole[2], MD

University of British Columbia[1], [2]University of Toronto
American Transplant Congress, Boston - 2009

Study Purpose

- There is limited information regarding hypercalcemia in kidney transplant recipients

- The purpose of this study was:
  - To determine the prevalence and predictors of hypercalcemia after kidney transplantation
  - To identify factors associated with resolution of hypercalcemia
  - To determine association of hypercalcemia with clinical outcomes

Study Population/ Laboratory Parameters

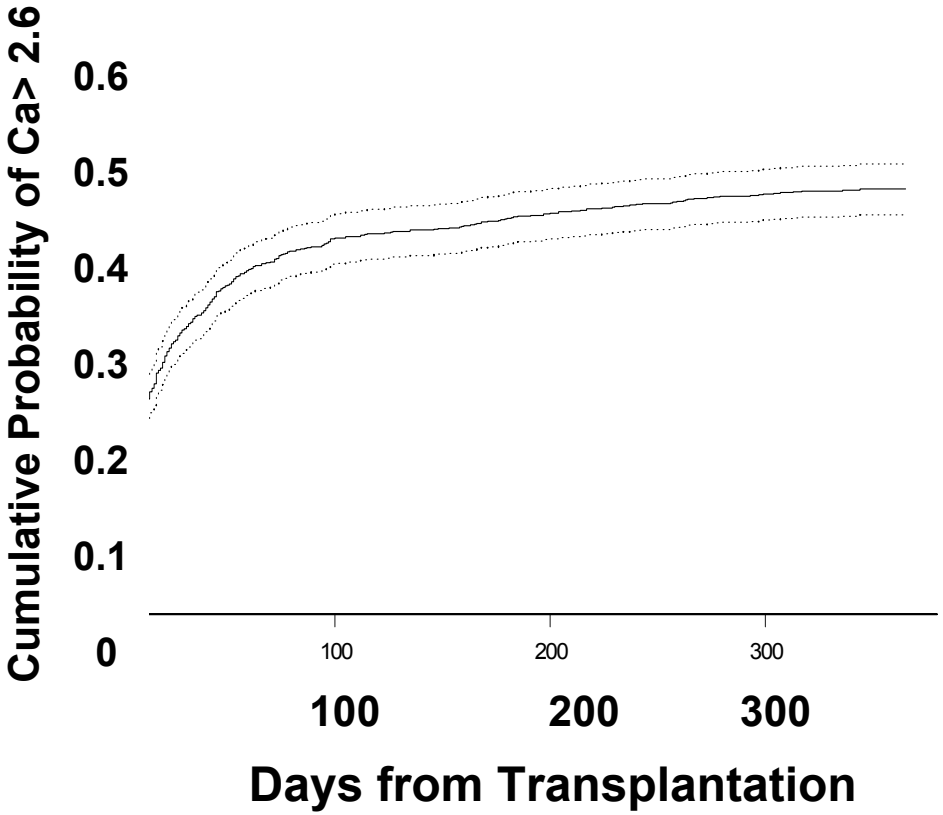
- N = 1352,consecutive, adult (>18yrs), kidney-only transplant recipients at St Paul's Hospital (Vancouver) and Toronto General Hospital between 2000 and 2007

- All serum calcium values were corrected for serum albumin

- Pre-transplant laboratory values obtained within 12 months of transplant date

Transient Hypercalcemia was common

Time to first Ca > 2.6



***Dotted lines represent 95% CI**

Patients had a mean (std) number of 27(11) of calcium measurements in the first post transplant year

40% had at least one Ca>2.6 mmol/L in the first post-tx year

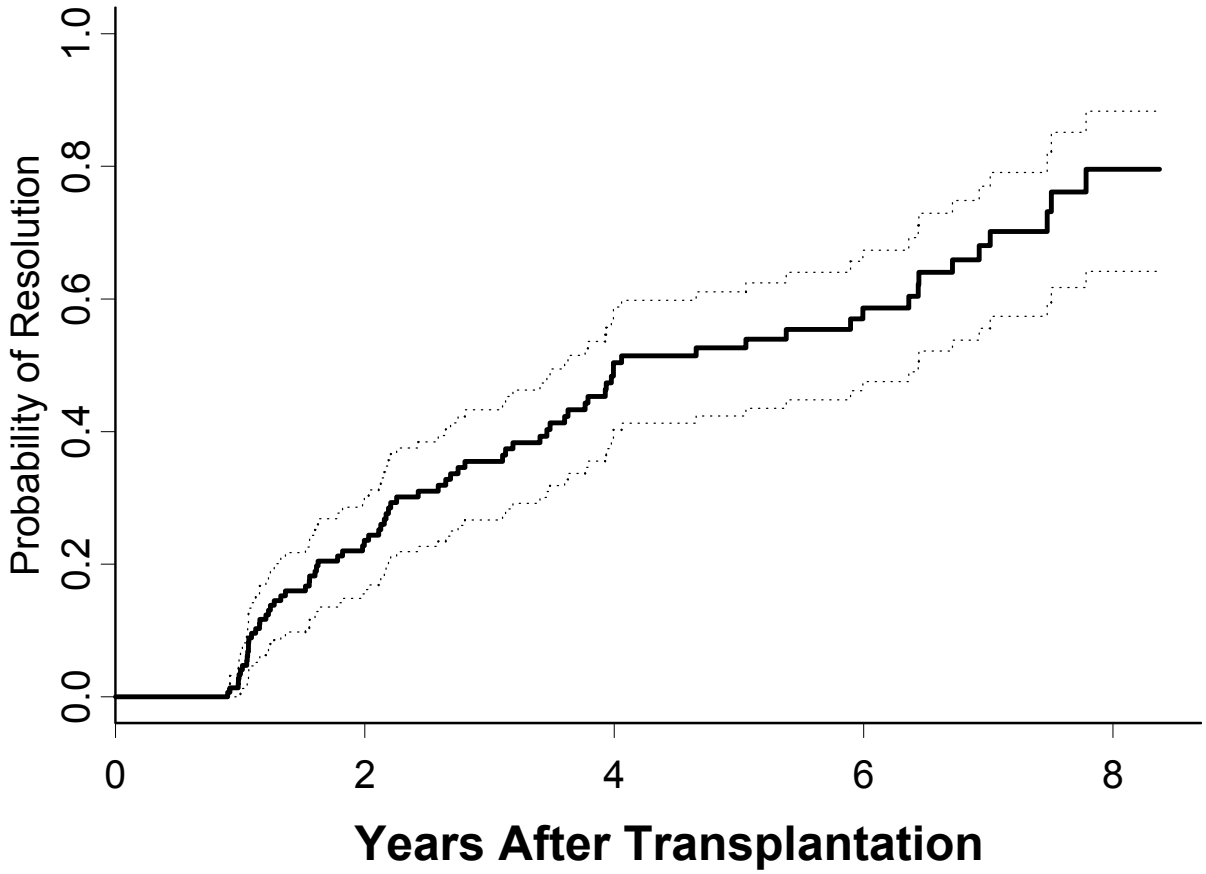
- 108 had only 1 episode
- 52 had 2 episodes
- 386 had 3 or more
- **157(28%) had an average Ca > 2.6 mmol/L in the first post-tx year**

Risk Factors for Hypercalcemia

(mean ≥ 2.6 mmol/L in first year)

Variable	Multivariate Odds Ratio
Age at Tx	
18-39	1.00
40-49	1.89 (1.07, 3.33)
50-59	1.75 (1.00, 3.07)
>=60	2.14 (1.19, 3.86)
Female Sex	1.32 (0.91, 1.92)
Cause of ESRD	
DM	0.78 (0.42, 1.45)
GN	1.00
Other	0.70 (0.45, 1.08)
Living Donor	1.03 (0.62, 1.69)
Pre-Transplant Calcium (mmol/L)	
≤ 2.6	1.00
>2.6	5.77 (3.17, 10.49)
Pre-Transplant iPTH (pmol/L)	
<10.6	1.00
10.6-53	4.11 (1.69, 10.00)
>53	11.18 (4.60, 27.18)
Pre-Tx Dialysis Duration	
<1 year	1.00
1-3 years	0.66 (0.29, 1.50)
3-5 years	1.21 (0.54, 2.71)
> 5 years	2.75 (1.29, 5.86)

Time to resolution of hypercalcemia among patients with mean Ca > 2.6 mmol/L in first post-transplant year

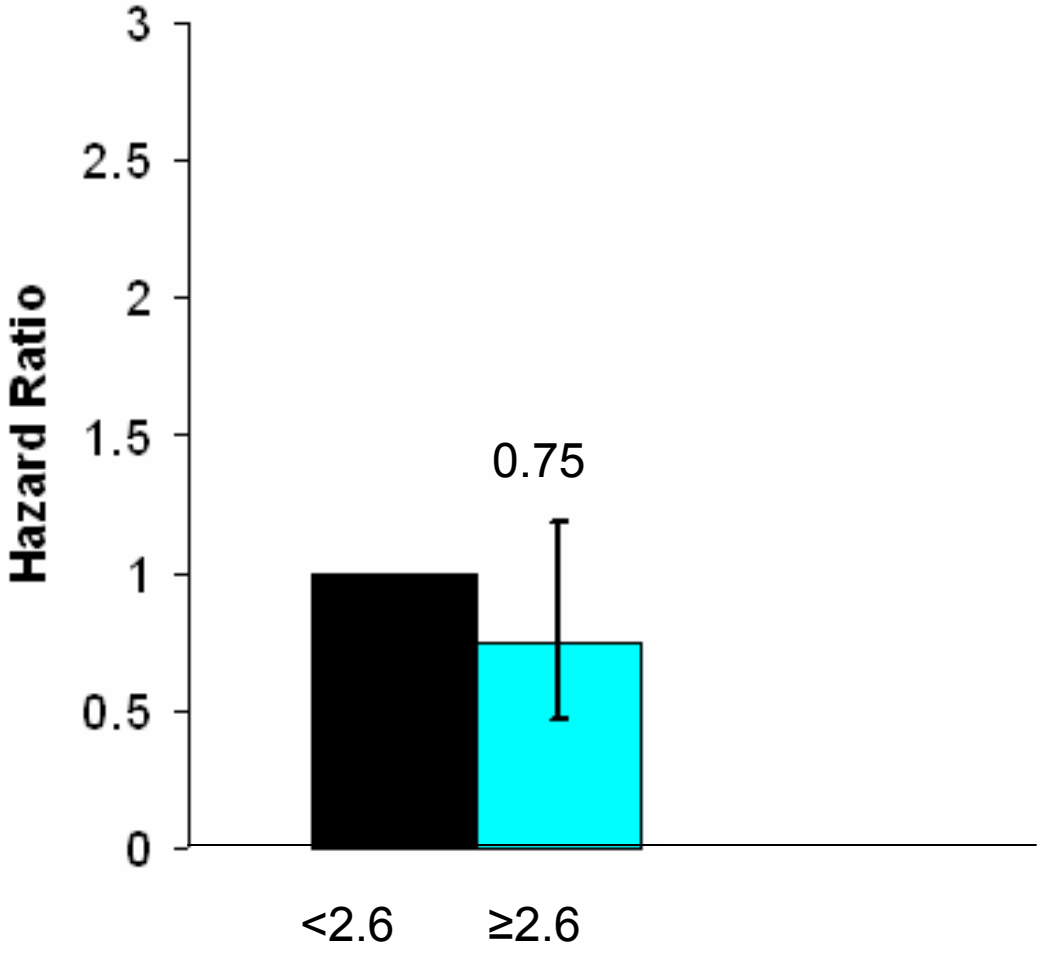


The probability of resolution at 2,3 and 5 years was 25, 36, and 54%

Factors associated with resolution of hypercalcemia In the first year:

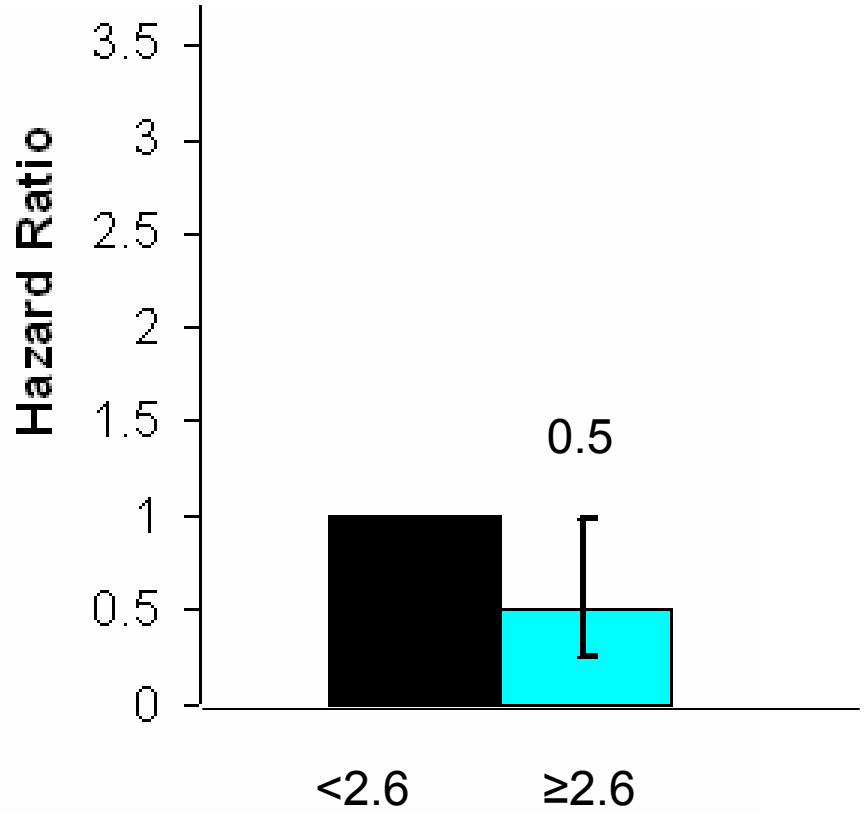
Variable	Odds Ratio
Pretransplant Serum Calcium (mmol/L)	
≤2.6	1.00
>2.6	1.04 (0.69, 1.56)
Pre-Tx iPTH (ng/L)	
<10.6	9.89 (1.93, 50.5)
10.6-53	0.93 (0.53, 1.63)
>53	1.00
Age at Tx	NS
Female Sex	NS
Cause of ESRD	NS
Living Donor	NS
Pre-Tx Dialysis Duration	NS

Post Transplant Hypercalcemia in first year was not associated with graft loss from any cause



Cox MV regression including age, Mean Ca in first year, pretx iPTH
Sex, Cause of ESRD, Donor type, Pre-Tx duration of dialysis

Hypercalcemia in first year not associated with death censored graft loss



Adjusted for: Age, Sex, Cause of ESRD, Donor Type, Pre-Tx duration of dialysis

The rate of GFR decline was similar in patients with and without hypercalcemia

Mean serum calcium in first post transplant year	Annualized change in GFR ml/min/1.73m^2
≤ 2.6	-1.04 (1.17)
> 2.6	-1.30 (1.81)

P-value for difference in slopes p=0.94

Calcium Phosphate Product (Ca x P) Was not tested for association with Graft Survival

- 13,009 lab records for Ca X P were available between 1-12 months post-tx.

- Most transplant recipients had low/normal phosphate values
  - 98% of 13,009 phosphate values were within normal laboratory range (0.8-1.6 mmol/L)
  - Median value was 0.95 (0.80, 1.11)

- In only n = 50 records (23 patients) was CaxP ≥ 4.5 $mmol^2/L^2$

  - Only 2/23 patients had an average CaxP ≥ 4.5 in the first year

Hypercalcemia -Summary

- **40% had at least 1 high calcium in first yr**
  - **28% will had average calcium > 2.6 in first year**
- **12% have average Ca > 2.6**
  - **Risk factors were age > 50, Pretx Ca> 2.6 , Pretx iPTH > 10.6 and dialysis exposure > 5 years**
- **Hypercalcemia not associated with increase of graft loss from any cause, DCGL or change in GFR**
- **Most patients do not have elevated phosphate levels and thus testing for associations with calcium phosphate product was not indicated**

Bone Disease After Transplantation Is Not an Indication for PreTX -Parathyroidectomy

- Risk of fractures after Tx is high
- Etiology is MULTI-FACTORIAL
- BMD does not predict fracture risk in TX
- NO RCTs examining specific therapies with hard outcomes
- It is unclear how to identify patients who would benefit from specific therapies
- The absence of RCTs that show fracture prevention and heterogeneity of bone disease prevents generalization from NON TX Setting

Vascular Calcification
Is NOT an indication for PreTX Parathyroidectomy

- Only one cross sectional study using plain films rather than CT
- Correction of Uremia may reverse vascular calcification
  - Small studies suggesting reversability

These are the facts (and they are indisputable)

- Indications for para-thyroidectomy in dialysis patients are poorly defined
- Pre-transplant identification of patients who will develop tertiary hyperparathyroidism after transplantation is difficult
- Potential consequences of tertiary hyperparathyroidism are rarely serious or too poorly understood to recommend pre-transplant parathyroidectomy
  - Hypercalcemia is common, usually transient, rarely serious and is not associated with long-term outcome
  - Bone disease is poorly understood
  - Vascular calcification is poorly understood
- **Medical options exist for treatment of tertiary hyperparathyroidism after transplantation**
- If required parathyroidectomy after transplantation can be safely performed

Medical therapy for tertiary hyperparathyroidism exists

- Cinacalcet can be safely used in patients after transplantation – multiple studies showing this

These are the facts (and they are indisputable)

- Indications for para-thyroidectomy in dialysis patients are poorly defined
- Pre-transplant identification of patients who will develop tertiary hyperparathyroidism after transplantation is difficult
- Potential consequences of tertiary hyperparathyroidism are rarely serious or too poorly understood to recommend pre-transplant parathyroidectomy
  - Hypercalcemia is common, usually transient, rarely serious and is not associated with long-term outcome
  - Bone disease is poorly understood
  - Vascular calcification is poorly understood
- Medical options exist for treatment of tertiary hyperparathyroidism after transplantation
- **If required parathyroidectomy after transplantation can be safely performed**

Parathyroidectomy Post Transplant Can Be Performed Safely

- Hypocalcemia (more common with total vs sub-total or total plus autotransplantation)
- Injury to recurrent laryngeal nerve
- Acute decrease in GFR
  - PTH is vasodilates preglom vessels- acute hemodynamic deterioration is possible but transient effect
  - No differences in graft survival between those with/without parathyroidectomy after transplantation

These are the facts (and they are indisputable)

- Indications for para-thyroidectomy in dialysis patients are poorly defined
- Pre-transplant identification of patients who will develop tertiary hyperparathyroidism after transplantation is difficult
- Potential consequences of tertiary hyperparathyroidism are rarely serious or too poorly understood to recommend pre-transplant parathyroidectomy
  - Hypercalcemia is common, usually transient, rarely serious and is not associated with long-term outcome
  - Bone disease is poorly understood
  - Vascular calcification is poorly understood
- Medical options exist for treatment of tertiary hyperparathyroidism after transplantation
- If required parathyroidectomy after transplantation can be safely performed

Parallels with Pre-tx Coronary Revascularization

Cardiac Disease	Hyperparathyroidism
• Risk factors but limited value in individual patients	• Risk factors but limited value in individual patients
• Poor non-invasive tests (echo MIBI)	• PTH mass on U/S
• Surgical risk +++	• Surgical risk +
• May improve post tx	• May improve post tx
• Medical therapy exists	• Medical therapy exists
• Consequences if no pre tx intervention+++	• Consequences rarely serious, not life or graft threatening