Parathyroidectomy:

Is it really necessary pre-transplant?

Background

- HyperPTH a common problem with CKD
- Begins when GFR approx 50% normal (ie early; often before renal disease recognized)
- Poor compliance with therapy
- Secondary begets tertiary hyperPTH after many years

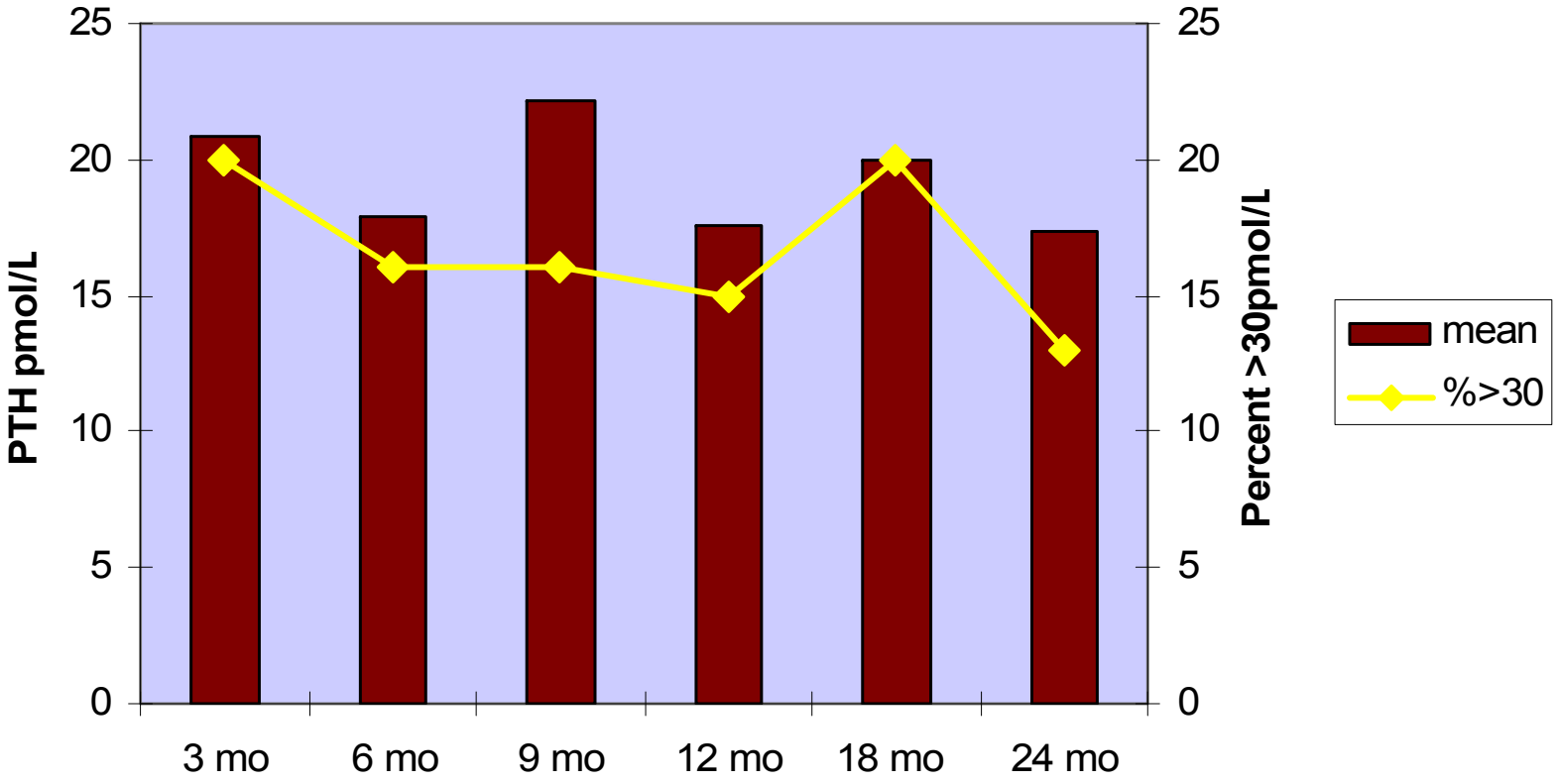
Background cont'd

- Our patients exist with ESRD for many more years prior to transplantation compared to previously
- At time of tx, may have unrecognized tertiary hyperPTH
- Following tx, may develop significant hypercalcemia (>2.9 mmol/L), prompting decision re medical vs surgical therapy

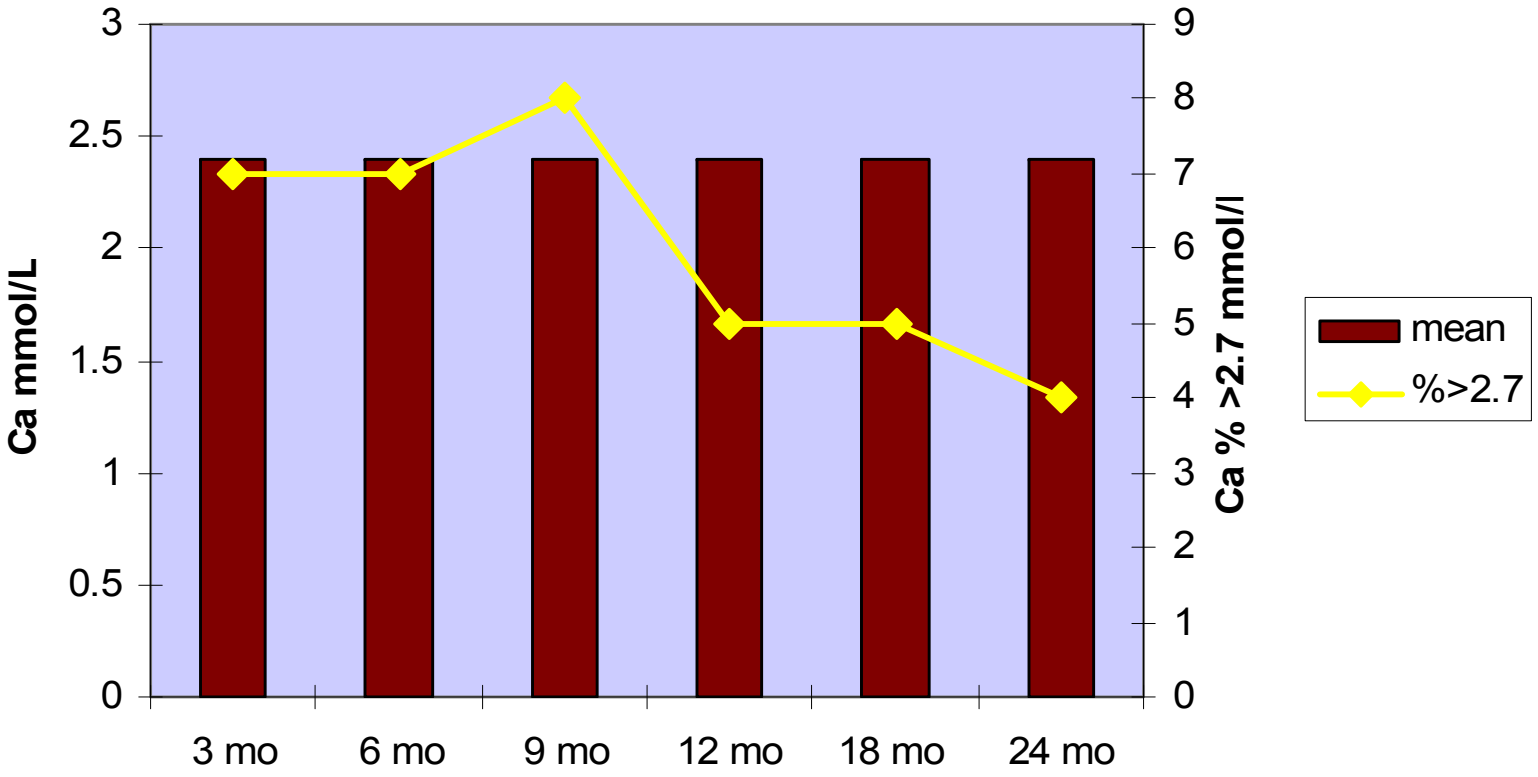
Natural History

- Hypercalcemia post renal tx significant, varies between 9 and 65%
- Evolution is for hypercalcemia to peak between 2 and 10 months post tx and then to gradually resolve
- Reflects involution of hyperplastic PTH glands
- Critically dependent on normalization of GFR

PTH Post Transplant BC Data



Serum Calcium Post Transplant BC Data



Thesis

- Multiple associations between abnormal mineral metabolism, vascular calcification, and mortality
- In transplantation, additional concerns:
    - i) graft dysfunction, calcification and premature graft loss
    - ii) loss of marrow space compounding the risk for cytopenias in setting of immunosuppression

Progression of Coronary Artery Calcification post-transplant

- Prospective single centre Italian study examining CAC scores by CT over 2 years in stable renal tx recips and a matched wait-listed HD cohort (age, cause of renal disease, time on HD)
- Measured Cr, alb, Ca, PO4, PTH, fetuin, osteoprotegerin

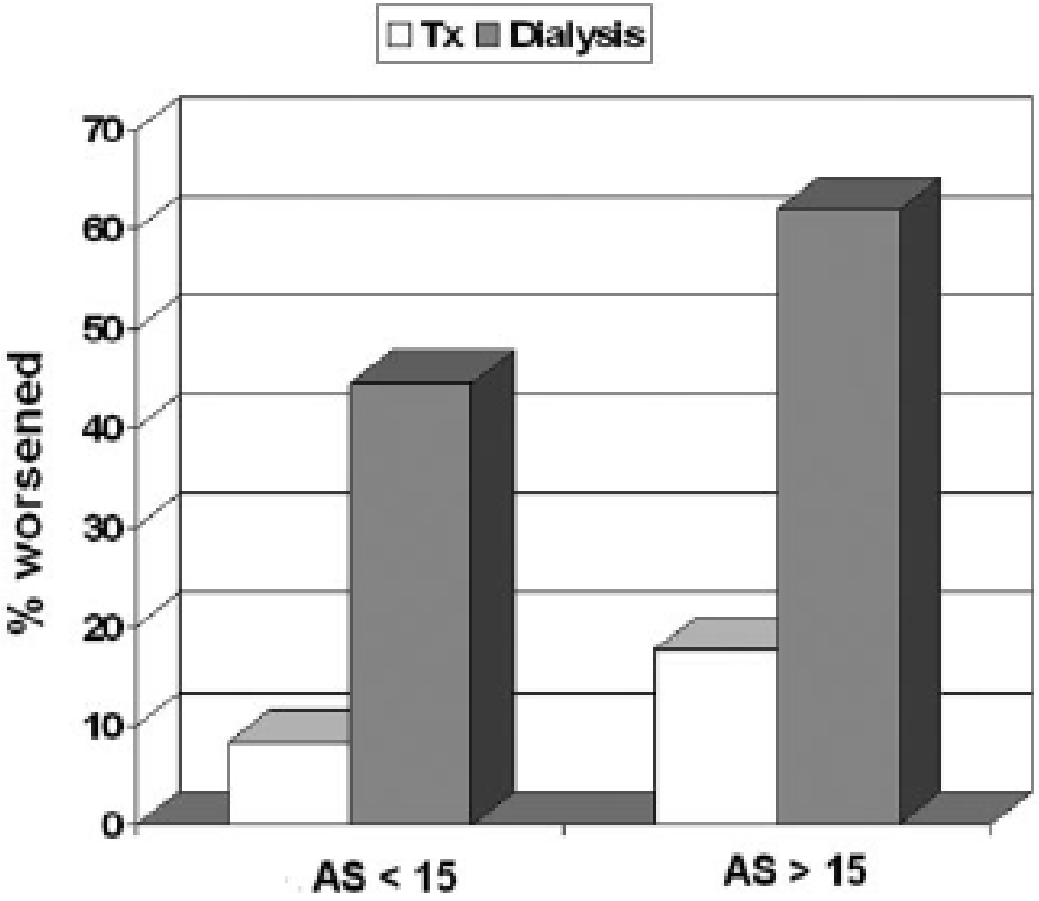
Mazzaferro et al CJASN 2009

CAC progression

	Transplant (41)	Dialysis (30)
Age , years	48 ± 13	51 ± 14
M:F	25:16	20:10
Dialysis duration, years	4.8 ± 4.3	5.7 ± 5.4
Tx duration	6.2 ± 5.5	0
Increase in calcification score over 2 years	5/41 (12.2%)	17/30 (56.6%) * P<0.0001

NB: no patients in the tx group had reduction in CAC score (ie at best, stabilization)
PTH fell close to normal and Ca remained normal in tx group

CAC progression



Mazzaferro et al CJASN 2009

Concerns

- How to make the diagnosis of hyperPTH?
- Medical therapy vs Surgical therapy
- Timing of intervention

Questions

1. Is persistent hyperPTH deleterious to graft function and longevity?
2. Is parathyroid surgery deleterious to graft function and longevity?
3. When is the optimal timing for parathyroidectomy?
4. Who should be considered for parathyroidectomy?

Question 1

- Is persistent hyperparathyroidism deleterious to graft function and longevity?

Risk of graft and vascular calcification

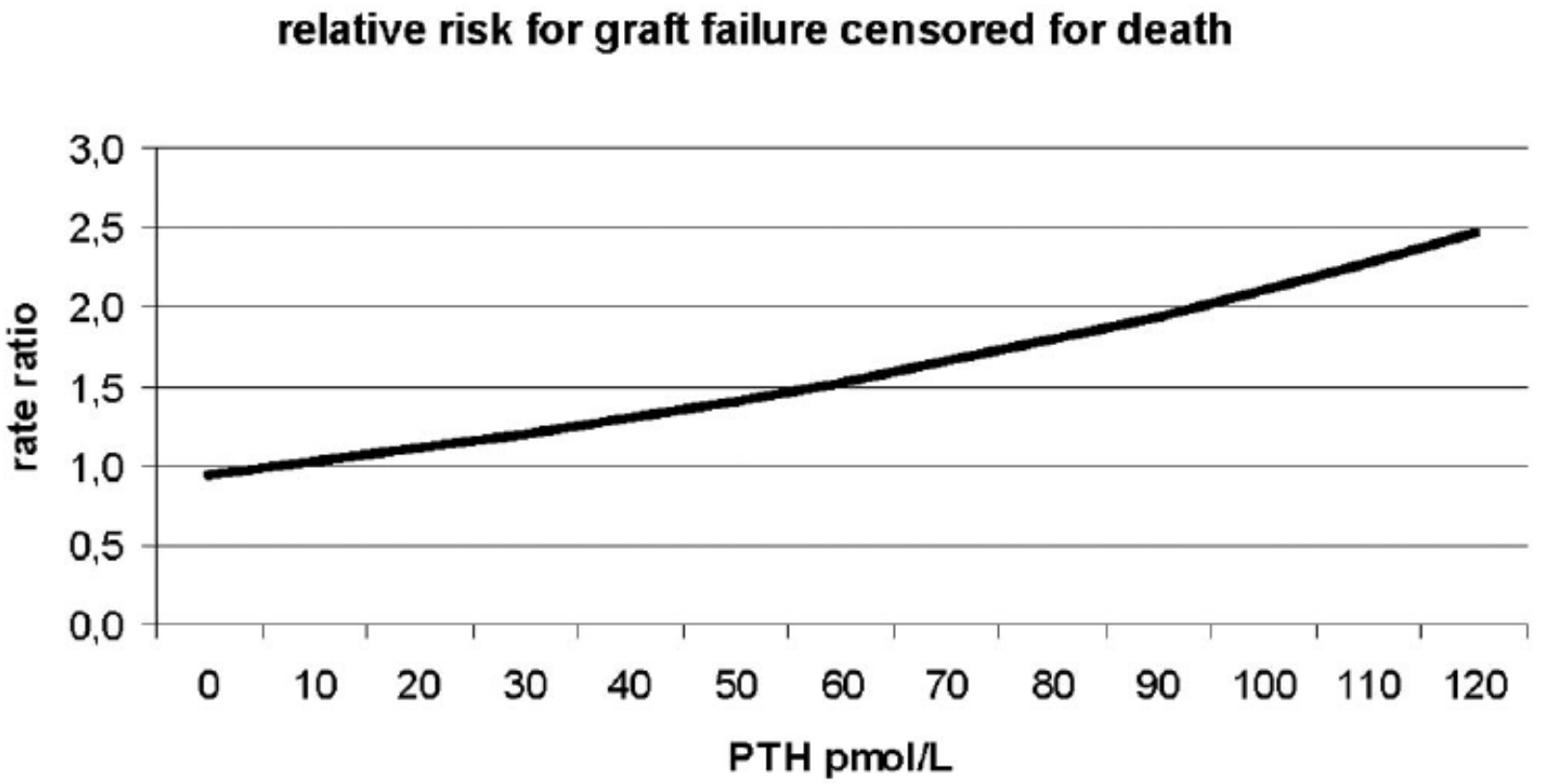
- Some evidence that hyperparathyroidism pre-transplant increases the risk of graft calcification and graft loss

I Risk of graft loss

- Single centre retrospective analysis out of Rotterdam
- n=407 with data at one year post tx
- Identified pre-tx PTH as a risk factor for graft loss

Roodnat et al Tx 2006

PTH and graft loss



Roodnat et al Tx 2006

II Graft calcification

- Review of protocol biopsy data from RTR in Hanover 2001-?2003
- Biopsies at 6 wk, 3 mo, 6 mo; clinical data at 1 year as well
- N=213 with full clinical and biopsy data

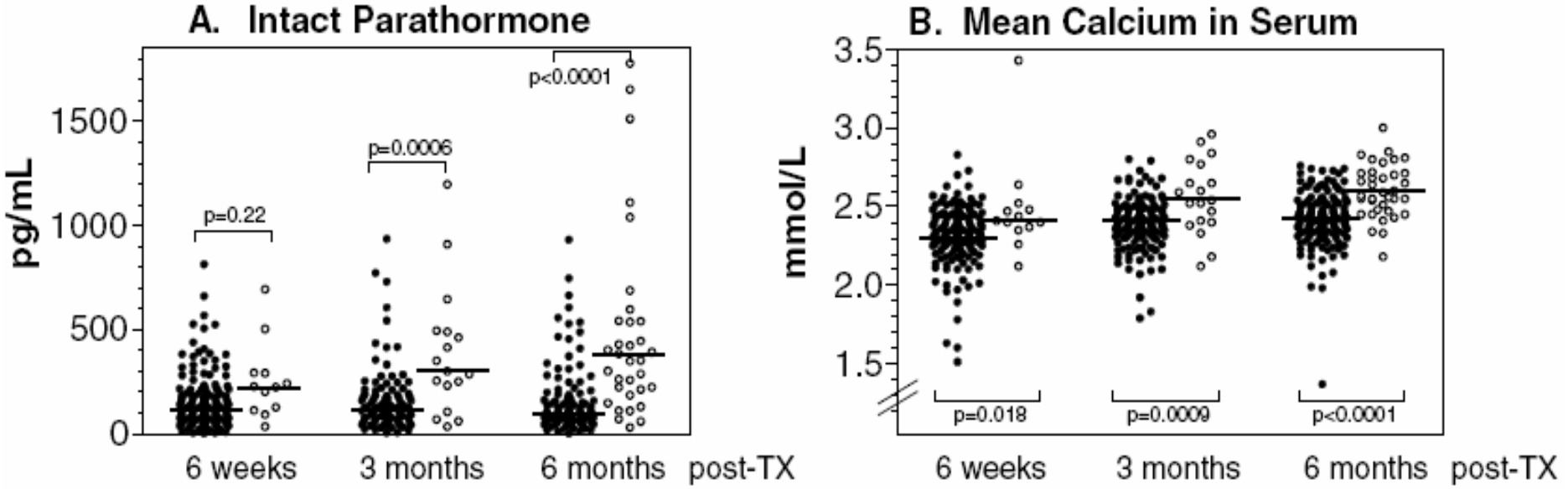
Gwinner et al AJT 2005

Graft calcification

- 56/213 had calcification in one or more biopsies
- Increased rate of calcification over time, with 18% by 6 months
- For analysis, patients divided into 2 groups: Those never calcified

  Those with any calcification
- Groups not different in any other parameters

PTH and Ca levels

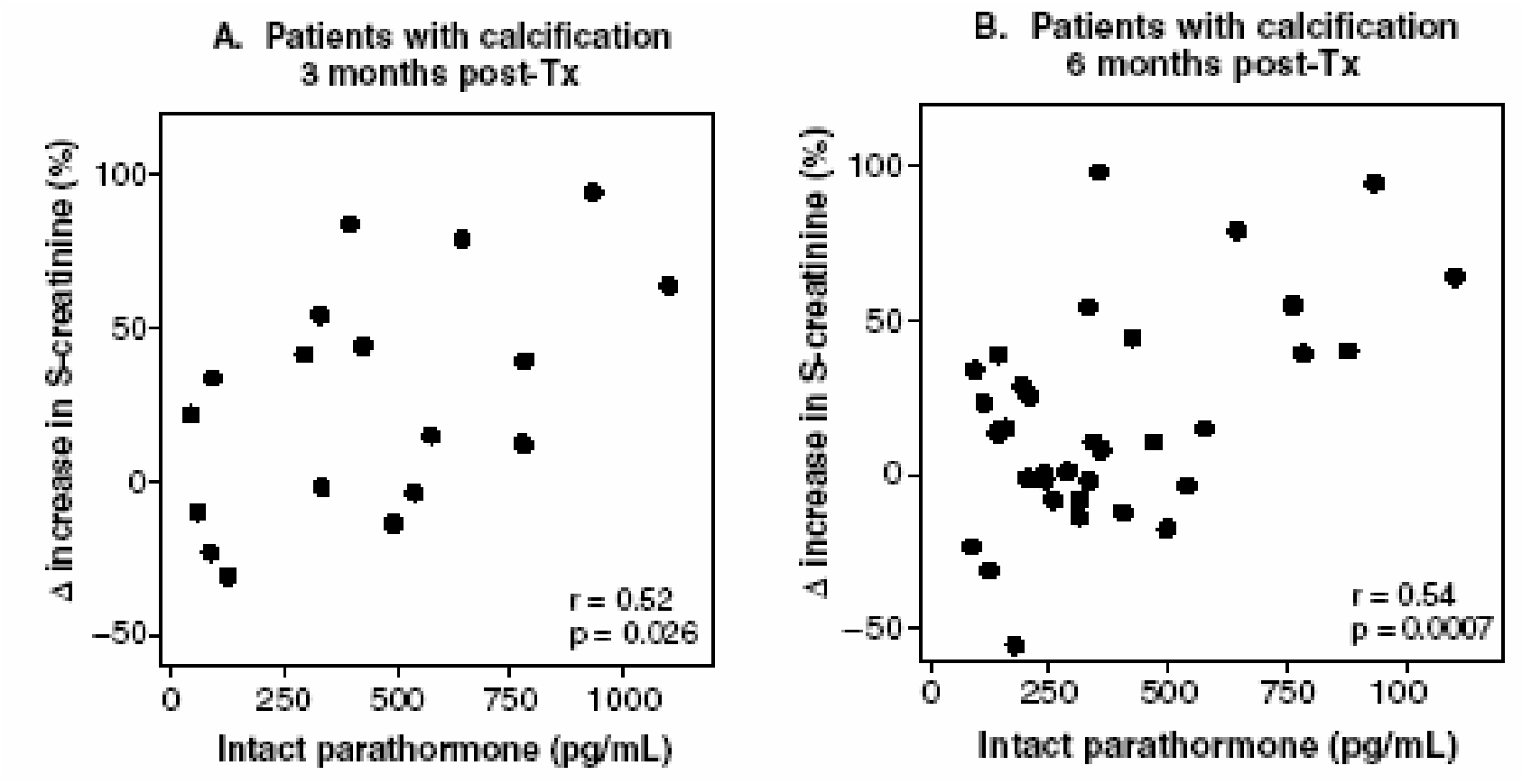


● = without calcification

○ = with calcification

Gwinner et al AJT 2005

Correlation between ΔCreat and PTH



For patients without calcification, no such correlation

Gwinner et al AJT 2005

Graft Calcification

- Calcifications more often in lumen; less often in interstitium
- Contributory role of Vit D and Pi supplementation (greater use in those with calcification); serum Pi levels not different
- Possible to identify early (ie pre-tx) since those with 6 wk PTH >400 pg/ml did not regress by 6 months

Question 2

- Is parathyroid surgery deleterious to graft function and longevity?

Medical vs Surgical Rx?

Medical Therapy

Medical options:

- Pre-transplant, cornerstones are Pi binders and Vit D
- Often unsuccessful; compliance issues, escape from efficacy over time

Medical Therapy

- New agents = calcimimetics
- Shown to be very effective in both dialysis and transplantation
- Major obstacle is $$$ (gatekeeper issues in BC)

Calcimimetics

- Now several studies examining safety and efficacy of calcimetics post-transplantation
- Study numbers small (n= 9-12); drug often introduced late post-tx (years vs months)
- Shown to be safe and effective, but effects not durable; problems recur with drug cessation
- Potential issue with increased urinary Ca excretion

Surgical Treatment

Schwarz et al

- Retrospective chart review from a single centre in Germany
- Patients transplanted between Jan 1997 and June 2003
- 78/2192 patients underwent PTHX post tx
- Arbitrarily divided into 2 groups based on decline in GFR:
    i) Deteriorating group (n=36)
    ii) Non-deteriorating group (n=40)

Schwarz et al: NDT 2007

Schwarz et al

- Mean age 48
- 46 male; 30 female
- Mean time on dialysis 79.4 ± 37.6 months
- Mean time post transplant 29.4 ± 28.9 months (range 2.5-154.8 months)

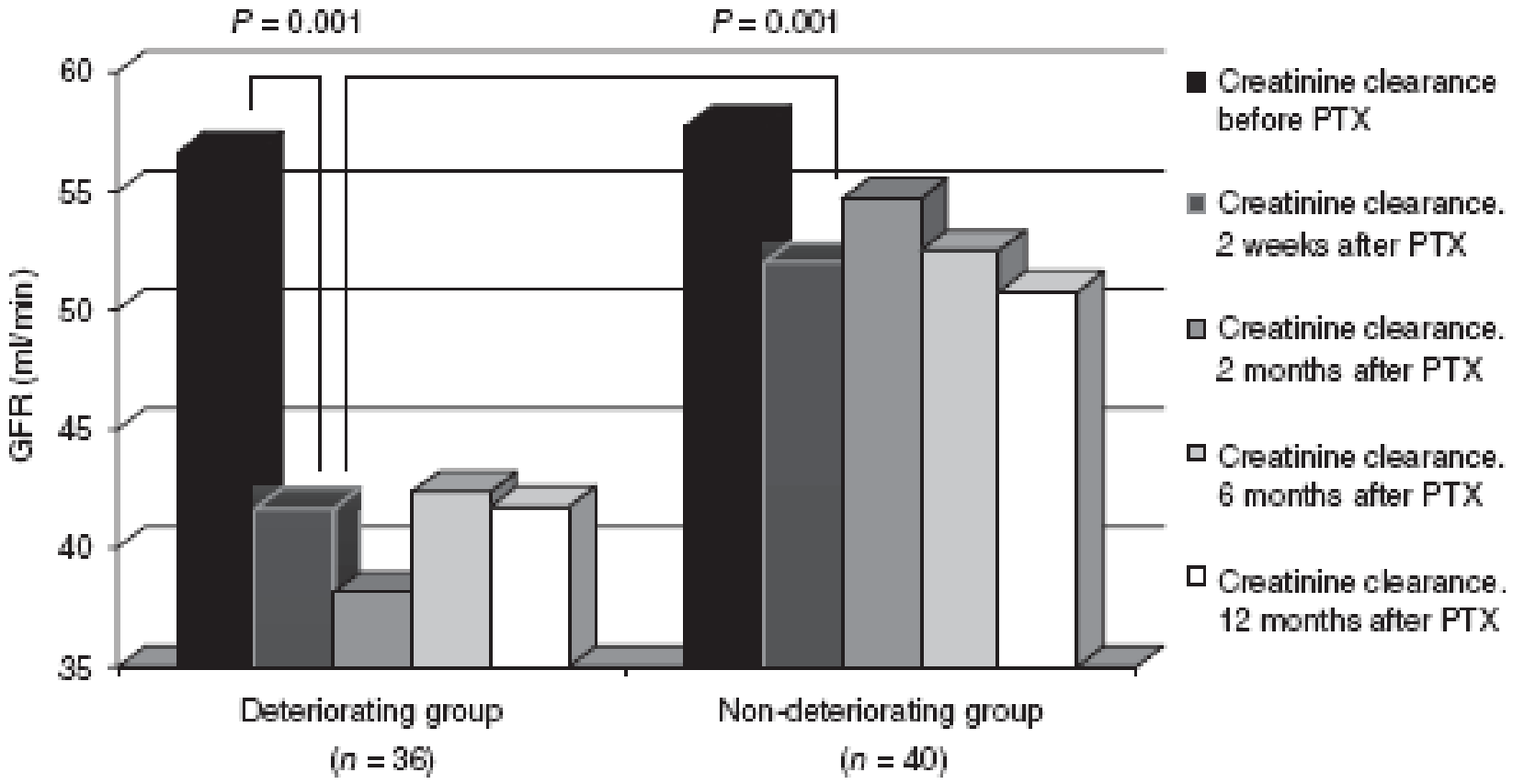
Schwarz et al: NDT 2007

Schwarz et al

- All patients had parathyroids scanned by MIBI
- Surgery: 29 patients subtotal
  47 total with re-implant
  13 re-operated
- 46/76 had biopsy: 70% showed tubulo-interstitial calcification

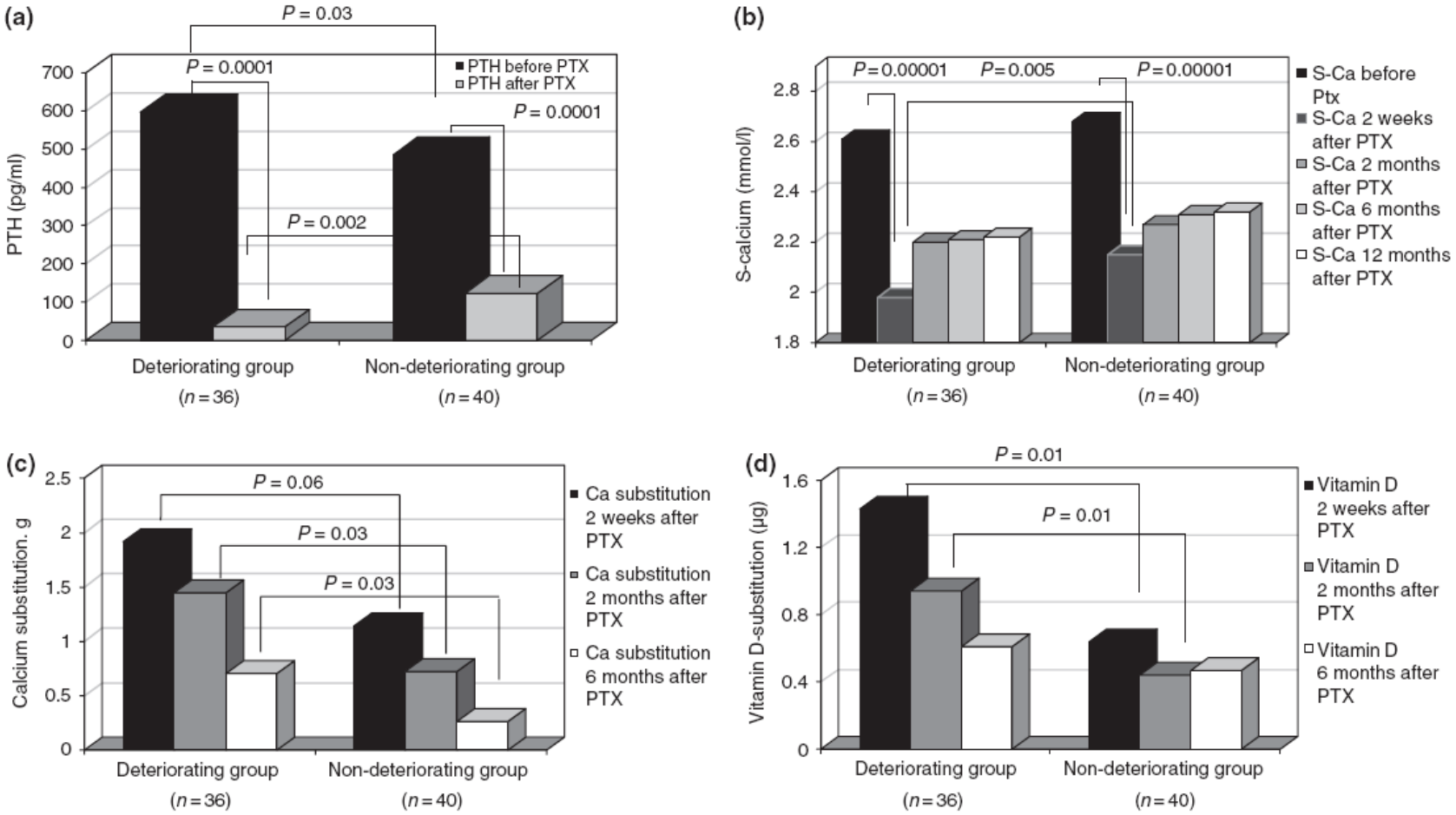
Schwarz et al: NDT 2007

Change in GFR



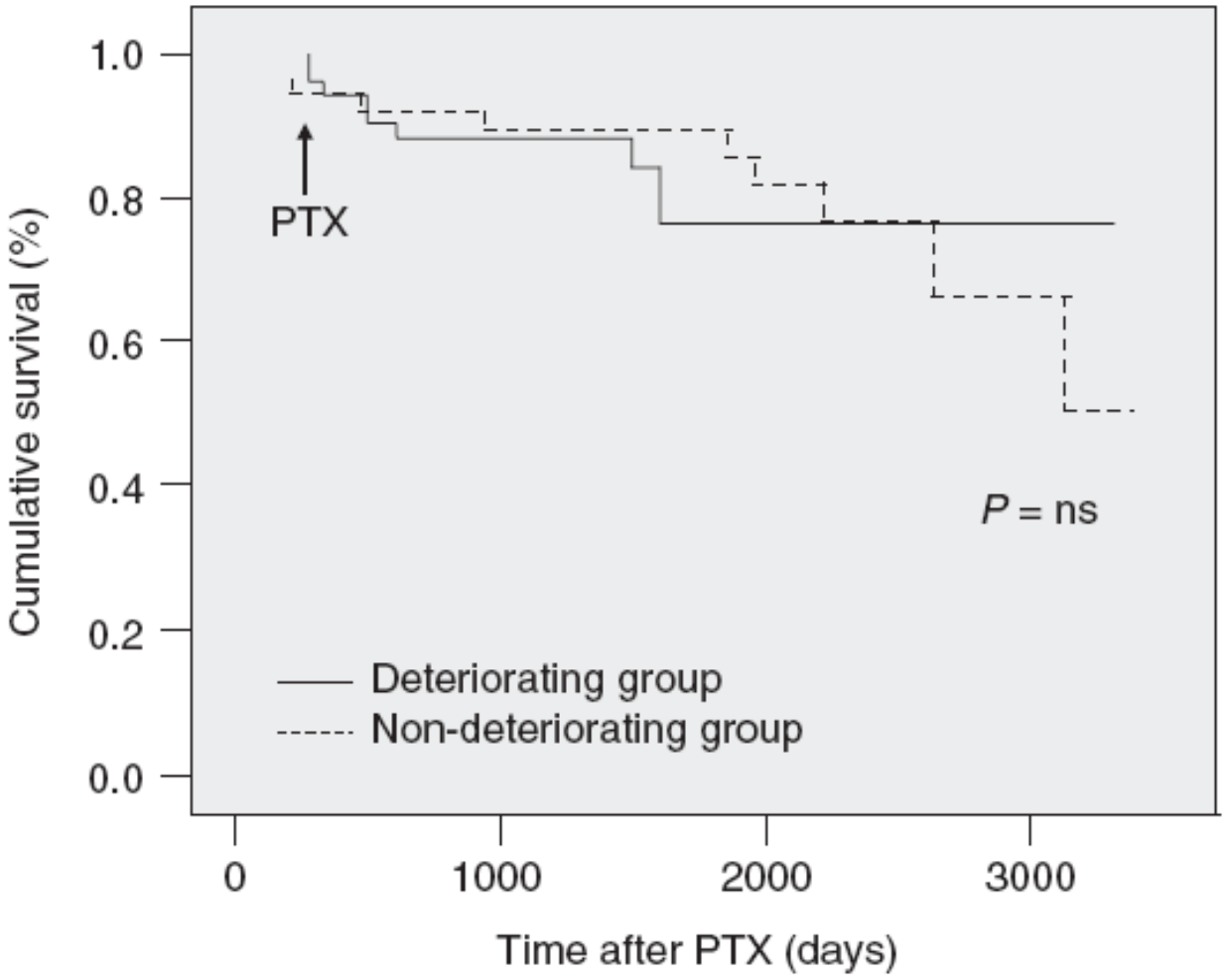
Schwarz et al: NDT 2007

Changes in PTH, SCa, supplements



Schwarz et al: NDT 2007

Graft Survival



Schwarz et al: NDT 2007

Evenepoel et al

- Retrospective case-controlled study from a single centre in Belgium
- 1647 patients transplanted 1989-2004
- n = 88 PTHX: excluded 56; final n = 32
- 16:16 male:female; average age 51
- Average time to PTHX post tx 29 months
- Compared this cohort to matched group

Impact of PTHX

	Case		Control	
	Period 1 Pre-PTHX	Period 2 Post-PTHX	Period 1	Period 2
Creat mg/dl	1.75	2.13 *	1.76	1.74
CrCl ml/min	46.8	41.0 *	55.1	52.6
% with ⇩ Cr Cl		65.6		12.5
SBP mm Hg	149.9	141.7 *	144.4	142.9
PTH ng/L	106.4	8.5 *	37.0	51.6
Ca mg/dl	10.7	9.2 *	9.9	10.0

Evenepoel et al NDT 2005

* **p≤0.001**

Complications

- Other complications post PTHX
- Increased mortality (Foley) short term
- Need for surgical re-exploration
- Failure of auto-transplant to secure blood supply (hypoparathyroid)
- Hungry bone syndrome long hospitalization
- Local surgical complications (hoarseness etc)

Question 3

- When is the optimal timing for parathyroid surgery and which surgical approach should be used?

Timing

- Ideally, prior to transplantation to avoid risk to graft
- If post tx, controversial: most centres recommend observation for at least one year to see if resolves spontaneously
- More difficult decision if persistant hypercalcemia, especially after one year

Surgical approach

- No head-to-head comparisons between subtotal and total PTHX with re-implant
- In general, tendency(?) for total PTHX in more severe cases
- Risk of subtotal is that miss an adenoma
- Risk of total is that become functionally hypoparathyroid
- Implant sites are neck and forearm

Question 4

- Who should be considered for parathyroid surgery?

Surgical candidates

- Persistent hyperPTH (>2.5ULN) by one year post tx
- Persistent hypercalcemia >2.9 mmol/L
- Anticipated patient survival > 6 months (ie minimal co-morbidities)

Summary I

- Persistent hyperPTH impacts on graft function; impact on graft survival less certain
- PTHX post-tx may be deleterious (transient vs permanent?)
- No head-to-head comparison of medical vs surgical therapy for hyperPTH
- Optimum surgical approach unclear

Summary II

- Preferable to perform PTHX pre-tx to avoid potential decline in GFR
- Advantages outweigh risks
- Avoid risk of graft calcification and graft loss
- Improve overall cardiovascular risk profile for pts with ESRD