New Engine, Lousy Chassis

- *Kick the tires , check under the hood, it's never too late to get the goods.....*

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Cyclosporine and BMD

- in vitro inhibits PTH mediated osteocalst activity (Stewart et al, 1986)
- in vivo rat studies revealed high turnover trabecular >cortical osteopenia (bone Gla, 1,25 OH-D)
- not age dependent; worsened by estrogen and may cause testosterone deficiency; not due to hyper PTH

Cyclosporine and BMD

- bone depleting effects may be T-cell mediated (nude rat resistant)
- increased IL-1 mRNA (?IL-6, TNF)
- similar to post oophrectomy state (Epstein et al 1996)
- similar effects with FK-506 in the rat
- human studies required

Osteoporosis and the Transplant patient

Pre tranplant risk factors by organ group

- **Lung**: corticosteroids, immobility
- **Liver, Pancreas**: malabsorption, Etoh, malnutrition (Vit D), hypogonadal
- **Renal**: HPTH, Vit D deficiency, acid base disturbance
- **Heart**: immobility, anticoag, smoking

Osteoporosis and the Transplant patient

Post Transplant

- high dose corticosteroids
- cyclosporine and analogues
- ?other immunosupressives (MTX, Rapamycin, new agents)
- persistent hyper PTH (renal) and organ failure due to graft rejection

Complications post transplant

- rejection, infection, renal impairment due to CyA (HTN, Hyper UA)
- hyperglycemia, hypogonadism, hyperlipidemia (Gc effects)
- accelerated coronary artery disease

Cardiac Transplants

- relatively few seconadary risk factors pre transplant
- predominantly male, ischemic cardiac disease
- uniform posttx Rx regimen
- BMD maintaine pretx
- among the highest rates of fracture ***early*** post transplant

Homocysteine and cardiac transplants

- homocysteinemia (MTHFR mutants)

-prevalent in CAD

-associated with increased thromboses

- hyperhomocystinuria

-predisposition to CAD

-premature osteoporosis

Homocysteine and Osteoporosis

McKusick's Hypothesis

- inhibits cross linking of type 1 collagen (major constituent of bone matrix)
- reduced solubility
- synthesis normal
- cross links (ICTP) reduced

Fractures / Osteoporsis post Tx

- corticosteroid and CyA - mineral and matrix deficit (**quantity**)
- hyperhomocysteine, other factors - **matrix** deficit

DEXA = Bone Mass (Quantity)

Bone quality ??

>Ultrasound

Fractures and Osteoporosis post cardiac tranplantataion

- Toronto program

>130 living patients

>clinical /lab evaluation

>thoracolumbar Xray

>DEXA

>US

>genetic assessment

(retrospective)

- Columbia program

>clinical evaluation

>prospective biochem parameters

>serial DEXA

>thoracolumabar Xray

>genetic assessment

(prospective)

Fracture & Osteoporosis post cardiac transplant : genetic markers

- Candidate genes

>Vitamin D receptor (haplotype analysis)

>Col 1A1 (Sp1 transcription binding site)

>Estrogen receptor (Exon 2 polymorphism)

>MTHFR (Homocysteine)

"association with fracture"

- lab : 25-OHD, Sprep, Ca/P, intact PTH

Fractures&Osteoporosis post cardiac transplantation

- Muchmore (1991):pre tx BMD 20% lower than age matched controls, no #
- Rich (1992) : 44% # (vert), significant reduced BMD all sites, abnormal lab (OC, PTH) suggest increased turnover state despite Gc
- Shane (1993) : 35% #(vert), elevated OC, osteopenia (women>men, younger)

Fractures&Osteoporosis post cardiac transplantation

- Buerger(1994) : older pt, worse BMD, no relation to Gc total dose, stable after 6 mths
- Sambrook (1994) :serial DEXA post Tx-rapid loss first 6 mths then stabilizes, serum OC only predictor of LSp loss (testoterone, Oc and OHproline [N] at 6 months)
- Lee (1994) : Tx vs CHF- no difference in BMD (LSp[N],FN[r], biochem, Cst, **but** # rate Tx>CHF (28% vs 12%)

Fractures&Osteoporosis post cardiac transplanation

- Shane (1996) : large prospective study (47 patients) with complete clinical, serial lab, Xray and DEXA

-54% women, 29% men fractured (85% within 6 months post Tx)

-absolute FN BMD predictive of # in women only, rate of loss in men

-preTx 1,25OHD(r) and PTH(h) inv with #

-BMD, cumulative Cst not predictive of #

Fractures&Osteoporosis post cardiac transplanation: Treatment

inconclusive results, combination Rx best?

- calcium and Vitamin D
- calcitonin (SQ, nasal)
- sex hormones (estrogen / testosterone)
- bisphophonates (oral, iv)
- Vitamin D analogues (calcitriol)
- PTH analogues (1-34 fragment)
- ER agonists (raloxifene)