Vitamin D and Bone Disease etc...

• Part I
  – Osteoporosis
  – Bone turnover markers in the management of osteoporosis
  – Vitamin D
    • Its importance for bone health
    • Blood level monitoring

• Part II
  – Vitamins D's role in extraskeletal diseases
    • Cancer
    • Immune mediated
    • Other
  – The promise
  – The evidence
  – Current reality

Bone Composition

• Matrix
  – Predominantly type I collagen fibres

• Mineral
  – Calcium phosphate
    • Hydroxyapatite
      – $Ca_10(PO_{4})_6(OH)_2$

• Cells
  – osteocytes
  – osteoclasts
  – osteoblasts

Bone Remodeling

Osteocyte (mineralized bone tissue)
Osteoblast (forms bone matrix)
Osteogenic cell (stem cell)
Osteoclast (resorbs bone)
Bone Remodelling

- Osteoclasts
  - Resorption of bone
  - Life span
    - 2 weeks
- Osteoblasts
  - Formation of bone
    - mineralisation of new bone matrix
  - Life span
    - 2 – 3 months

Bone Remodelling

- Regulation
  - Mechanical stress
  - Systemic hormones
    - PTH
    - Estrogen
  - Local paracrine factors
- Mechanism of up-regulation
  - Increase in bone turnover
  - Increase in the surface area undergoing active remodelling

Calcium Homeostasis
Osteoporosis

• **Characteristics**
  – Low bone mass
  – Deterioration of bone tissue
  – Enhanced bone fragility
  – Increase in fracture risk
  – Most common metabolic bone disease

• **Definition**
  – **Who 1994**
    • Bone mineral density > 2.5 SD below a normal young adult mean

Osteoporosis

• **Screening**
  – Bone mineral density determination

• **Diagnosis - X ray**
  – osteopenia
  – Fracture

• **Biochemistry (rule out secondary causes)**
  – Ca++
  – Phosphorus
  – PTH
  – Estradiol
Osteoporosis Risk Factors

- Genetics
  - Polygenic
  - Vit D receptor
  - Collagen
  - Estrogen receptor
  - Cytokine variants
    - IL-6
    - TGF β

Osteoporosis and Thyroid Disease

- Environment
  - Reduced calcium intake
  - Reduced vitamin D intake
  - Liver conversion
    - 25-OH cholecalciferol
  - Renal conversion
    - 1,25-dihydroxycholecalciferol

- Lifestyle
  - Smoking
  - Alcohol excess, low physical activity and a low BMI

- Physiological
  - Menopause
  - Reduced estrogen
Osteoporosis - Estrogen Effect

- Lifetime risk of fractures at 50 years of age
  - Female
    - Femur 17.5%
    - Vertebra 15.5%
    - Forearm 16%
  - Male
    - Femur 6%
    - Vertebra 5%
    - Forearm 2.5%

Secondary Osteoporosis

- Unexplained fractures
- More severe disease than expected for age
- Iatrogenic
  - Corticosteroids
Osteoporosis - Treatment

• Lifestyle
  – Diet
  – Smoking
  – Exercise

• Therapeutic intervention
  – Calcium and vitamin D
    • With/without magnesium
    • Limited effectiveness
    • Are adequate serum levels being achieved?
  – Bisphosphonates
    • Alendronate
    • Known to be effective
  – Selective Estrogen receptor modulators (SERM)
    • Tamoxifen

Osteomalacia

• Impaired mineralisation
  – Calcium deposition in newly formed bone
    • Rickets in children
  – Excess unmineralised bone matrix (osteoid)

• Calcium Deficiency
  – Calciopenic
  – Often vitamin D deficiency (active form)

• Phosphate Deficiency
  – Phosphopenic
  – Phosphate binding antacids
  – ↓ Renal Tubular reabsorption

Biochemical Markers of Bone Turnover

• Bone Components
  – Collagen
  – Mineral
  – Osteoclasts and Osteoblasts

• Physiological/Pathological Targets
  – Formation
  – Resorption
Bone Turnover Markers

**Formation**
- Alkaline phosphatase (bone isoenzyme)
  - Osteoblastic activity
- Osteocalcin
- Procollagen peptides
  - Collagen synthesis
- Bone Sialoprotein
  - Collagen synthesis

**Bone Turnover Markers**

**Resorption**
- Collagen breakdown
  - Hydroxyproline
  - Galactosyl hydrolysine
  - Free crosslinks
    - Deoxypyridinoline (Dpd)
    - Pyridinoline (Pyr)
  - Peptide-bound crosslinks
    - NTX, CTX
- Osteoclast Activity
  - Tartrate resistant acid phosphatase

**Collagen**
- Pyridinoline crosslinks
  - pyridinoline
  - deoxypyridinoline
Crosslinks

- Pyridinoline crosslinks
  - pyridinoline
  - deoxypyridinoline

- Attached to telopeptides
  - C-terminal
  - "CTX"
  - N-terminal
  - "NTX"

Marker Comparison

- Bone Mineral Density
  - Slow response to therapeutic intervention
  - High cost

- Bone Turnover Markers (BTM)
  - Cannot determine bone status
  - Rapid ↓ in response to
    - Hormone Replacement Therapy
    - Bisphosphonate
  - Low Cost
  - Independent predictor of fracture

BTM Problems

- Biological variability
  - cyclical hormonal changes
  - seasonal changes in vitamin D
  - circadian rhythms
  - Less for Telopeptides (NTX, CTX)

- Imprecision
  - Variability due to urine concentration
    - Pyridinoline
  - Urine results corrected for creatinine
  - Serum assays available for NTX and CTX
Bone Turnover Marker Guidelines

• Measurement of **Absolute Value** of Serum Bone Turnover Markers (BTM) is of **no clinical use**
  - Since the gold standard for osteoporosis is DEXA the lack of BTM correlation implies poor diagnostic efficiency for BTM's

• The change from a baseline level in BTM's can provide more immediate indication of the effectiveness of therapy
  - Physician users should think in terms of least significant change

• Resorption markers are useful in this context
  - The Telopeptides NTX and CTX are good
    • Less diurnal and dietary variation
    • Serum CTX is best

Bone Turnover Marker Guidelines

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  **BUT**

  - BTM's may provide an independent risk factor for development of fractures

Other BTM Applications

• **Osteonecrosis of the Jaw**
  - Dentists need to detect this to avoid complications
    • Complication of Bisphosphonate Therapy
    • BTM's are sensitive markers for osteonecrosis

• **Bisphosphonate “Holidays”**
  - Patients on long term bisphosphonates may benefit from discontinuing therapy
    • Mitigates complications
  - Rise in BTM indicates Bisphosphonates need to be restarted.
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Vitamin D3 vs D2

Cholecalciferol (aka: vitamin D3) - a form of vitamin D found in animal tissues.

Ergocalciferol (aka: vitamin D2) - a form of vitamin D found in plants.

Vitamin D Metabolism
Vitamin D Metabolism

Vitamin D Testing

- Serum 25 Hydroxy Vitamin D (25 OH - Cholecalciferol)
  - Measured by Direct Immunoassay
  - Ranges
    - Ideal 70 – 150 nmol/l
    - Subotimal 50 – 70 nmol/l
    - **Increased risk for Osteoporosis <50 nmol/l
  - Toxicity is rare
  - Insufficiency** is common
    - ~20 % of British Columbians tested at LifeLabs

- So is vitamin D deficiency an epidemic or not? **
  - Put simply, it depends on how you define your terms:
    - what blood level constitutes vitamin D insufficiency in an otherwise healthy population.
  - IOM and NCHS
    - reports rest on defining insufficiency as 25-hydroxyvitamin D blood levels below 20 ng/mL (<50 nmol/L)
  - the Endocrine Society and the National Osteoporosis Foundation
    - define insufficiency as 25(OH)D ≤30 ng/mL (<75 nmol/L).
    - seems like a small difference but
      - It has huge public health ramifications, essentially in defining the difference between sickness and health in 50% of the population.

**National Osteoporosis Foundation. February 2012**
25 Hydroxy Vitamin D
To Test or Not to Test

• “Don’t test for Vitamin D just give Vitamin D”
  – Vitamin D3 is cheap the test is expensive
• Problems with this philosophy
  – Compliance
  – Variable response to therapy
    • Some patients need 100 IU/day
    • Some patients need 2000 IU/day
• Bottom Line
  – 20% of BC patients are Vitamin D insufficient in 2012

Vitamin D Metabolism

1,25 Di Hydroxy Vitamin D Testing

• Serum 1,25 Di Hydroxy Vitamin D (1,25\ diOH -Cholecalciferol)
  – Measured by extraction then Radioimmunoassay
  – Concentration in pmol/l
• Not a good measure of Vitamin D status
  – Imprecise/Inaccurate methods
    • Competitive binding
    • Many interferences
  – Short half life
• However: it IS the active form
New Immunoassay Strategy for 1,25 Di Hydroxy Vitamin D

1,25 Di Hydroxy Vitamin D Testing
- Used for patients with
  - Severe renal disease
  - Suspected Sarcoidosis
  - Patients receiving 1,25 diOH – Cholecalciferol therapeutically
    - Tubular toxicity is a risk

Vitamin D and Cancer
- Many Publications Showing a relationship between Vitamin D levels (25 OH D) and Cancer prevention
  - Cancers showing the relationship include
    - Breast
    - Colorectal
    - Prostate
    - Pancreatic
    - ...etc
Vitamin D and Cancer

- Animals studies
  - VDR are in cancer cells
  - inhibition of proliferation by $1,25(OH)_2D_3$
  - rats fed diets low in vitamin D and calcium develop significantly more mammary tumors when treated with DMBA than rats fed control diets with adequate vitamin D and calcium
  - NMU breast cancer model
    - inhibition of the progression of mammary tumor growth observed in rats treated with $1,25(OH)_2D_3$ or analogs

Evidence for Effectiveness

- Relationship of $25 \text{ OH D}$ levels and cancer risk
  - Relationship does not imply cause
    - Cancer patients aren’t healthy
    - Healthy people tend to be outside in the sun
    - 30 minutes of Sun Exposure => thousands of units of Vitamin D
  - Paradoxical upturn at high levels
    - Cancer Risk

Dosing Studies Mostly Negative

- Compliance???
  - Negative: Not actually taking the study medication
  - Positive: Those on placebo may be taking supplements
- Dosing levels too small
  - Women’s Health initiative
    - 400 IU/day
- Short Duration of Followup
Other Vitamin D Claims

- Autoimmune Disease
  - Multiple Sclerosis
    - Correlation of 25 OH D levels and disease progression
    - Shows an association but is not causal
    - Healthy people get more sun exposure?
  - Systemic Lupus Erythematosus
  - Rheumatoid arthritis

Vitamin D and the Immune System

- Early studies indicate the presence of VDR in activated T cells
- \(1,25(\text{OH})_2\text{D}_3\) inhibits lymphocyte proliferation
  - activation of IL-2 and interferon (IFN)\(\gamma\) are decreased after activated T cells are exposed to \(1,25(\text{OH})_2\text{D}_3\)
  - \(1,25(\text{OH})_2\text{D}_3\) shown to inhibit the differentiation and survival of dendritic cells
    - decrease in IL-12 and an increase in IL-10 secretion

Vitamin D and the Immune System

- IL-17 is inhibited by \(1,25(\text{OH})_2\text{D}_3\)
  - pathogenesis of autoimmune inflammation
  - implicated in autoimmune diseases
- animal studies
  - \(1,25(\text{OH})_2\text{D}_3\) can protect against
    - experimental autoimmune encephalomyelitis
      - the murine model of multiple sclerosis
    - systemic lupus erythematosus
    - inflammatory bowel disease (IBD)
    - autoimmune thyroiditis
Other Vitamin D Claims

- Cardiovascular Disease
  - Animal studies
  - Epidemiological studies
  - Large scale interventional trials have not been completed
- All cause mortality
  - Epidemiological studies only

Vitamin D Receptor Polymorphisms

- Associations with VDR Polymorphisms exist for cancers of:
  - Prostate
  - Colorectal
  - Breast
  - Skin

Significance is unknown

Future Vitamin D Studies

- Vitamin D/Calcium Polyp Prevention Study
  - Vitamin D +/- Calcium
  - 2200 patients
  - Completion December 2017
- Vitamin D and Omega-3 Trial (VITAL)
  - Various cancers
  - 20,000 patients
  - Completion June 2016
Conclusions

• Part I
  – Bone turnover markers have a role to play in the management of osteoporosis
  – Vitamin D monitoring still has a place in minimizing risk of fractures

• Part II
  – Vitamins D’s role in extraskeletal diseases is promising
  – However it is not yet established