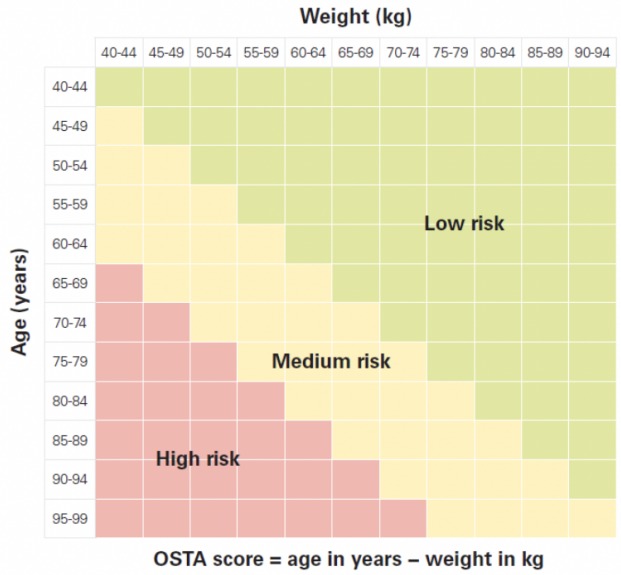
Osteoporosis – Dr Andre Tan

Who should be screened for osteoporosis? 00:14

- **Generally post-menopausal women, men > 65yo**
- Consider earlier screening especially in the context of risk factors like family history, low body weight, height loss, early menopause (<45yo), comorbidities, low calcium intake, alcohol/smoking, prolonged immobility, history of falls
- Steroid use – > 5-7.5mg of prednisolone/day for 3 months

Tools for screening?

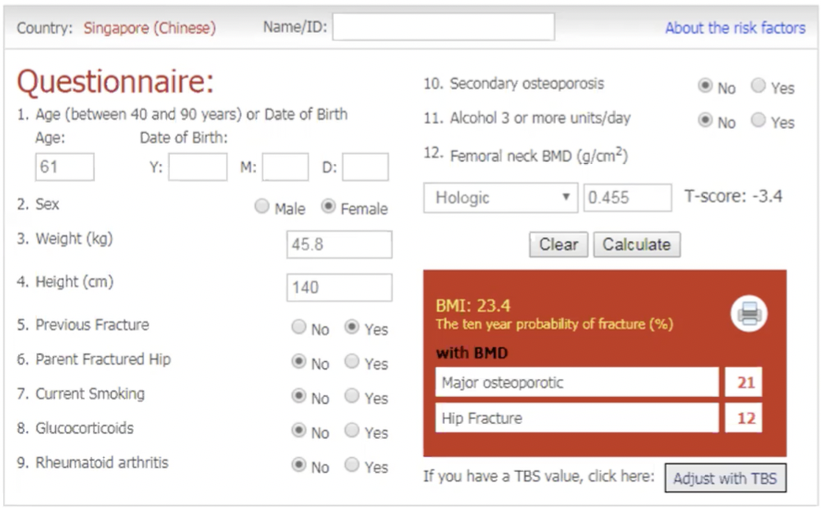
- OSTA: Osteoporosis Self-Assessment Tool for Asians



- **High-risk (>20)** ⟶ consider DXA scan as the chance of finding osteoporosis (low BMD) is high in this group
- **Medium-risk (0-20)** ⟶ consider DXA scan if any other risk factor(s) (Table 1) for osteoporosis is present
- **Low-risk (<0)** ⟶ consider deferring DXA

In patients initially deemed low risk, reassess risk if there has been significant weight loss or any clinical risk factor development since the last visit, or if last assessment was five or more years ago.

- FRAX Tool – Can be calculated with or without DEXA



>20%

>3%

  - Risk stratify patients in osteopenic range
  - In context of osteopenia at higher risk, may consider therapy early
  - >20% for major osteoporotic fracture and > 3% for hip fracture considered high risk
- DEXA Bone Density Scan

How is osteoporosis diagnosed? 06:25

- Presence of fragility fracture: Low energy injury (fall from standing height) involving hip/pelvis, vertebrae, proximal humerus. Distal radius controversial
- T score < -2.5 SD (-1.5 to -2.5 defined as osteopenia) – For diagnosis, take the lowest reading from the various regions
- Trabecular bone (vertebra) affected before cortical bone (e.g. hip)
- BMD
    - Areas: Neck of femur, total hip, vertebrae
    - T score: Compares against the same race, gender, age 20-29. E.g. Singaporean Chinese women will be compared against the Singaporean Chinese women reference data – Used to define osteoporosis
    - Z score: Compares against same age and gender – Abnormalities suggest secondary causes in younger women and older men
    - Looking for osteophytes/aortic calcifications which may falsely increase density on BMD scan
- In context of acute compression fracture, still can do BMD to look at other unaffected areas

Evaluation of Secondary Etiologies? 18:33

- When is it needed?
    - Pre-menopausal, men < 65yo, treatment failure despite medication compliance
    - Z-score is below -2.0
    - In post-menopausal patients, while it may not be absolutely necessary to perform secondary work up, one can consider at least excluding the common secondary causes at the outset
- Investigations
    - FBC – anaemia, abnormal blood counts
    - Renal function – renal impairment
    - Calcium / phosphate – hyperparathyroidism, osteomalacia
    - 25OH vit D – vit D deficiency
    - Liver panel – liver dysfunction, elevated ALP (bone source)
    - Thyroid function – hyperthyroidism
    - ESR – myeloma, connective tissue disease, chronic inflammation
    - Testosterone level – male, less than 70 years of age

Timing for Treatment Initiation 21:22

- No concern about fracture healing with initiation of anti-resorptives – however if there is surgical instrumentation, discuss with surgeons before initiation
- Incident fracture admission is the best time to discuss and initiate osteoporosis treatment because the perceived need for treatment would be highest at that point
- Generally 30-50% risk reduction (highest with vertebral fractures) with treatment initiation

Optimising Calcium and Vitamin D status prior to treatment? 24:15

- Calcium replacement
    - Aim for 1000-1200mg/day
    - Advise on calcium rich food: Milk, soy milk, cheese, taukwa, green leafy veg
    - Supplements: Calcium/Vit D 2 tab ~ 360mg of elemental calcium, calcium carbonate (1250 ~ 500mg of elemental calcium), Caltrate (600mg of elemental calcium)
    - Exercise/physical activity
- Vitamin D
    - Generally, aim for 25OH Vit D of > 30ug/L (at least 20ug/L)
    - Pre-treatment
    - Supplementation: Cholecalciferol
        - Maintenance: 1000 units daily

§ Loading (If < 20ug/L): 25,000 units weekly x 8 weeks

- Pre-Treatment Targets
  - § PO Bisphosphonates: Ideally 25OH vit D > 15; can start loading Vit D and start PO bisphosphonates concurrently
  - § IV Zoledronate/SC Denosumab: Aim for 25OH Vit D > 25-30 ug/L (in view of hypocalcemia risk); would generally recheck Vit D levels pre-initiation of treatment
  - § Anabolic Agent: Aim to optimize calcium and Vit D in long term, but pre-initiation levels less essential

Dental Clearance? 30: 51

- Depends on baseline dental status and choice of agent (lower threshold for dental review if starting IV zoledronate and SC denusomab in view of higher risk of osteonecrosis of jaw)

Choice of Initial Treatment? 34:13

	ALN / RIS	ZOL	DMAB	TPTD	RAL
Mode of admin	PO	IV	SC	SC	PO
Frequency	Weekly	Yearly to q18mths	6-mthly	Daily	Daily
Fracture risk reduction	Hip + Vert	Hip + Vert	Hip + Vert	Vert + Non-vert	Vert only
GI side effects					
Adherence					
Positive BMD effect beyond 3-5 yrs					
Residual effect after stopping tx					
Risk for ONJ/AFF					
Risk for VTE					
CrCl < 35ml/min					
Cost		$$	$$	$$$$	$$$

- Generally, PO bisphosphonates first choice given favourable cost profile
- If concerns about GI side effects, can consider IV bisphosphonates or SC denusomab
- If renal dysfunction, consider desnosumab
- In severe osteoporosis, consider more potent agents (Teriparatide > SC Denosumab > IV bisphosphonates > PO bisphosphonates)

Bisphosphonates 39:12

- PO
  - Dosing: Alendronate: 70mg once/week, Risedronate: 35 mg once/week or 150mg once/month
  - Side Effects: Mainly GI side effects – Contraindicated in documented esophagitis/Barrett's esophagus or definitive reflux symptoms; if mild dyspepsia can consider PPI (but give the night before away from the dosing of bisphosphonate)
  - Administration Instructions: Taken on empty stomach with no other interfering medications/food – drink lots of water, stay upright for at least 30 minutes, medication cannot be crushed
  - New buffered aldendronate where the pH is less acidic – May have better GI side effect profile
  - Consider drug holiday after 5 years given limited BMD gains after
- IV
  - Dosing: IV 5mg once a year
  - 2 formulations: Aclasta 5mg and Zometa 4mg - only the 5mg one is indicated for osteoporosis. Zometa is for cancer-related bone disease and hypercalcaemia of malignancy.

- Indications: GI issues/swallowing dysfunction, ease of administration (can last a year to 18 months)
- Side effects: Prominent acute phase reaction (flu-like symptoms for a few days to a week) – may consider pre-medicating with paracetamol
- Consider drug holiday after 3 years given limited BMD gains after

Denosumab 45:00

- Indications: Renal impairment (CrCl < 35), severe osteoporosis, patients not responding to bisphosphonates, compliance preferences
- Dosing: 60mg SC every 6 months
- Advantage: Sustained BMD gains over time (compared to bisphosphonates which stops at 3-5 years)
- Side Effects: Risk of hypocalcemia (can consider giving low dose short course of calcitriol after administration), small risk of worsening eczema
- Compliance is key because BMD loss occurs quite rapidly after cessation

Teriparatide 48:00

- Dosing: SC 20mcg once daily
- Indications: Severe osteoporosis (especially multiple vertebral fractures), treatment failure, atypical femoral fractures/ON of jaw under treatment of anti-resorptives
- Main effect on vertebral fractures
- Cap of 2 years – because of theoretical risk of osteosarcoma

SERMs? 50:40

- Role: Mainly in perimenopausal period (50-60yo age group) – may have a role given concerns of long-term bisphosphonate use, especially in younger patients
- Generally will transit to other agents beyond 60 yo
- Only reduces risk of vertebral fractures (and not other fractures)
- Side Effects: Hot flushes, cramps, VTE

Romosozumab 53:06

- Osteoanabolic agent – Blocks sclerostin (an inhibitor of bone formation)
- Studies have shown bone formation than teriparatide
- Cost profile currently prohibitive
- Recent trials: ARCH 2017, FRAME 2016

Cost Profile of Treatment Agent 54:11

- PO Bisphosphonates: Alendronate ~$50/year, Risedronate ~200-250/year
- IV Bisphosphonates: Zoledronate ~$700/year
- SC Denosumab: ~$700/year
- Teriparitide: $700/month (~$8000/year)
- SERMs: ~$1000+/year

How do we assess treatment response? 55:23

- Repeating BMD: Post initiation – 1 year later, if stable on treatment – repeat every 2 years
- What to look at?
    - BMD Change – Compares against baseline and most recent
    - Compare BMD change with least significant change to determine whether change is significant (different value for hip and lumbar spine)
    - Compare the BMD values and not the T-scores alone, as the T-scores may be different for the same BMD values if we use different reference population to get the T-scores

- Expected response:
    - Small rise in BMD to stable readings with treatment (usually better response at lumbar spine compared to hip)

Treatment Failure: 01:00:35

- Definition: New fractures, significant deterioration (>4-5%) in BMD over 2 years, bone turnover markers not responding as expected (although not commonly done)
- What to do:
    - If on PO bisphosphonate, can switch over to IV bisphosphonate/SC denusumab/anabolic agent
    - If on IV bisphosphonate, can switch over to SC denosumab/anabolic agent
    - If on SC denosumab, can switch over to anabolic agent

How to transit between agents? 01:03:52

- Drug Holidays
    - Only for bisphosphonates – PO (after 5 years), IV (3 years); not denosumab/anabolic agents
    - Basis: Bone density continues to have sustained maintenance, reduced risk of complications (atypical femoral fractures, osteonecrosis of jaw)
    - To consider re-initiation if BMD worsens (can do yearly BMD when off treatment); usually expect BMD to be stable for 1-2 years usually
- Transiting between agents
    - No current guidelines to continue bisphosphonates/denusomab while switching to teriparatide
    - Some data shows that BMD gains for anabolic agents tend to be more in treatment naïve patients
    - If teriparatide is stopped, then change to antiresorptive on cessation
    - If denosumab stopped, switch to bisphosphonate (if renal function okay) – can start ~ 6months from last denosumab injection (for IV zoledronic, may consider only ~ 8 months later)

Osteoporosis in CKD? 01:10:25

- Issue of concomitant CKD mineral bone disease – If anti-resportives given without understanding of bone disease status, there is risk of adynamic bone disease if bone turnover is already low
- TMV model: Turnover, mineralization, volume
- Generally, management will involve endocrinologist and nephrologist, especially in CKD 4-5

Take Home Points? 01:12:55

- Don't forget non-pharmacological management and addressing risk factors
- Contextualise osteoporosis management based on patients overall medical status/functional status
- Individualise treatment based on drug and patient characteristics

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Other Questions

- Should oral bisphosphonates be stopped during dental procedures
  https://www.aaoms.org/docs/govt_affairs/advocacy_white_papers/mronj_position_paper.pdf
    - PO bisphosphonates <4 years: recommend no need to stop beforehand
    - >4 years - can consider stopping 2 months before dental procedure