



台灣婦產科醫學會
Taiwan Association of Obstetrics and Gynecology

Bridging the Bone Health Gap

Strategies for Women's Health Across the Lifespan

10th, March, 2024

台灣婦產科醫學會, 更年期Symposium

高雄長庚婦產部 主治醫師

王映文



台灣更年期醫學會
THE TAIWANESE MENOPAUSE SOCIETY

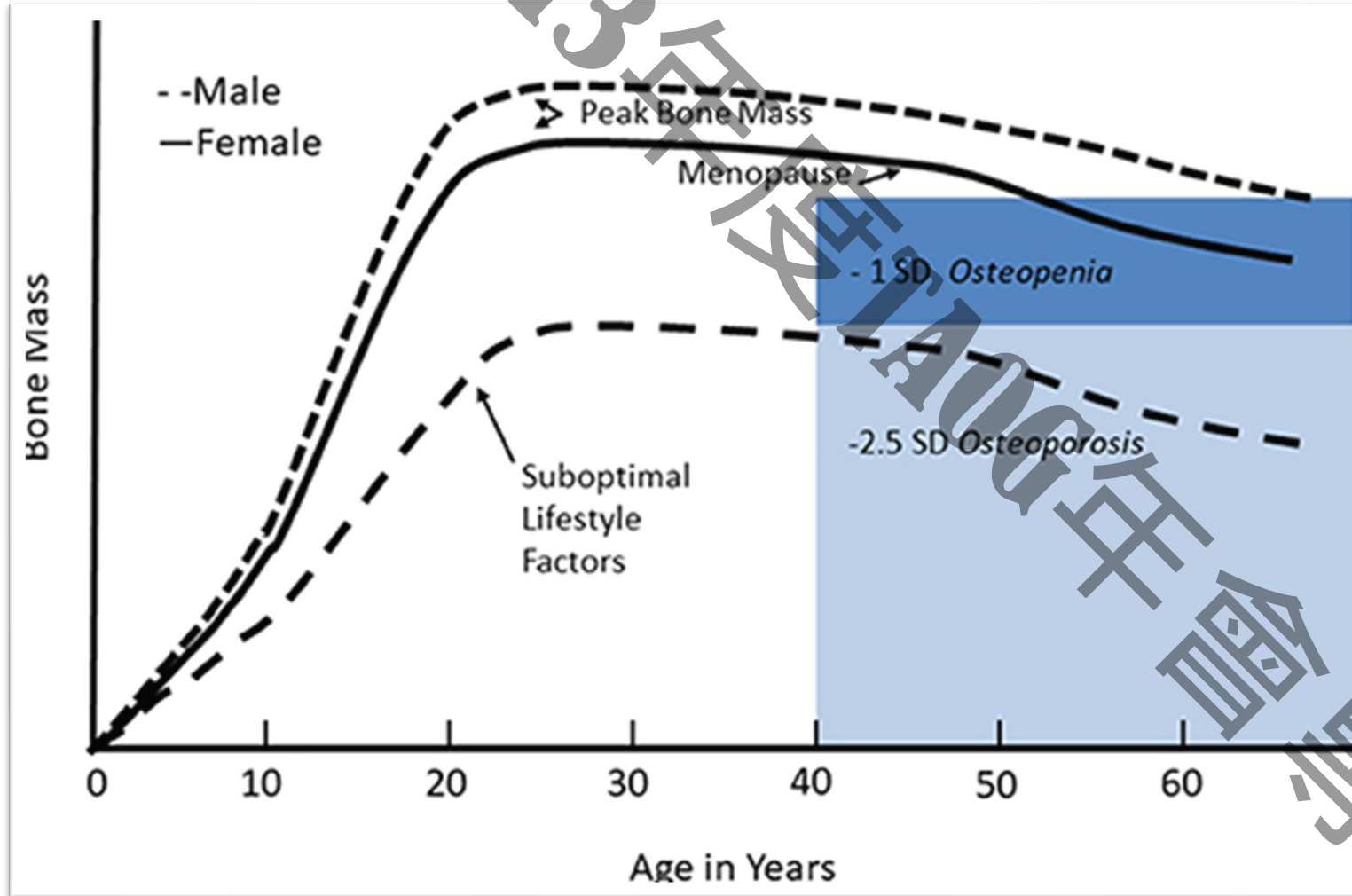


高雄長庚紀念醫院
Kaohsiung Chang Gung Memorial Hospital

Outline

- ① 女性的骨骼健康以及台灣的現況
- ② 找出高風險族群 (Target to treat)
- ③ Bridging the Bone Health Gap: reproductive age women
- ④ Bridging the Bone Health Gap: postmenopausal women
- ⑤ Bridging the Bone Health Gap: women cancer survivor
- ⑥ Bridging the Bone Health Gap: women with premature ovarian insufficiency

Changes in bone mineral mass across the life cycle



- ① Bone mineral mass reach a plateau in young adulthood
- ② Bone loss rapidly in the first few years of the menopausal transition
- ③ Bone loss gradually and continuously in older age
- ④ **With suboptimal lifestyle**
 - → failure to achieve optimal peak bone mass
 - → reduces the age of onset of osteopenia or osteoporosis

關於台灣女性的骨質疏鬆

① 台灣女性髖關節骨折的盛行率

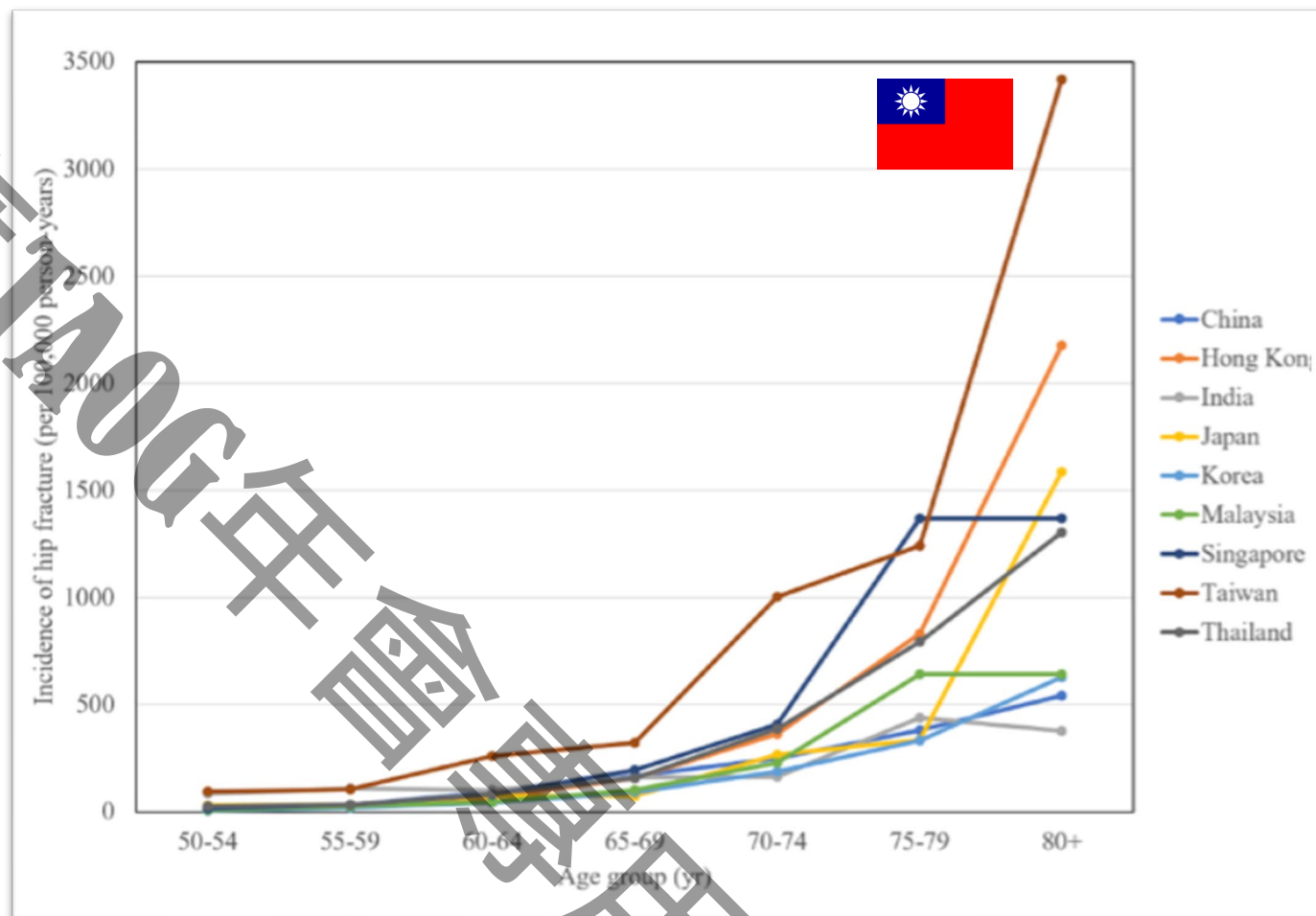
亞洲第一¹ (based on published data in 9 AFOS members: 中國、香港、印度、日本、韓國、馬來西亞、新加坡、台灣、泰國)

② 台灣女性髖關節骨折的盛行率

世界排名第九²

③ TOA study³ (2008-2011): 更年期後的台灣女性

- 罹患osteoporosis的比例：40.7%
- 罹患osteopenia的比例：43.9%³



1. An updated hip fracture projection in Asia: The Asian Federation of Osteoporosis Societies study. Osteoporos Sarcopenia. 2017 Dec; 3(4): 161-163.
2. A systematic review of hip fracture incidence and probability of fracture worldwide. Osteoporos Int. 2012 Sep;23(9):2239-56. doi: 10.1007/s00198-012-1964-3.
3. Underestimated fracture risk in postmenopausal women — application of the hybrid intervention threshold. Osteoporos Int. 2020 Mar;31(3):475-483

Osteoporosis：對健康的衝擊

- ① Osteoporosis導致骨折及其併發症，以「**髌骨**」骨折為甚
 - » 25% increase in mortality within 1 year of the incident²
 - » 20–30% death causally related to the fracture
 - » **Death** most occur in the first 3–6 months following the event¹
 - » 50% of women: long-term loss of mobility after a hip fracture (存活者中約 50% 會有行動不良的後遺症，終身依賴他人照顧)²
- ③ Vertebral fracture : pain, impaired lung function²

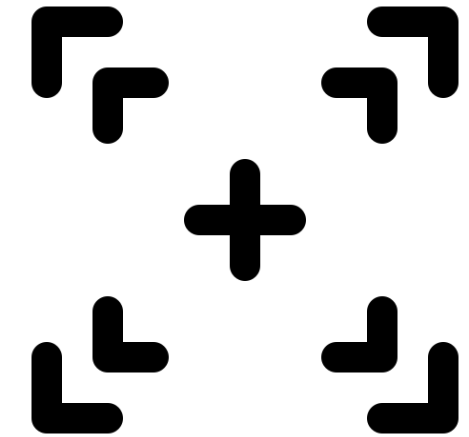


¹European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2019 Jan;30(1):3-44. doi: 10.1007/s00198-018-4704-5. Epub 2018 Oct 15.

²Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society. Menopause. 2021 Sep 1;28(9):973-997. doi: 10.1097/GME.0000000000001831

Low screening rate

1. 美國：**91%** of women > 65 years old with a previous low trauma fracture **not screened** for osteoporosis ¹
2. 台灣-2013國民健康訪問調查報告 ²
 - ① 40-64歲國人，10.9%曾罹患骨質疏鬆症；其中**62.7%從未接受過骨密度檢查**
 - ② 65歲以上國人，26.4%曾罹患骨質疏鬆症(男性: 16.9%，女性34.8%)



¹ Hansen D, Pelizzari P, Pyenson B. Medicare Cost of Osteoporotic Fractures-2021 Updated Report. Milliman, Inc.: Seattle, WA, 2021

² 國民健康署：2013年國民健康訪問調查報告 <https://www.hpa.gov.tw/Pages/Detail.aspx?nodeid=364&pid=6543>

Large gap between risk group and treatment

- ① A large gap between the number treated compared to that eligible for treatment based on their fracture risk ¹
- ② < 1/3 with fragility fracture received a comprehensive osteoporotic evaluation and the proper treatment ²
- ③ 台灣骨折後的醫療現況: 停經後女性若有 fragility fracture , 僅30%接受骨鬆藥物治療 ³



¹European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2019 Jan;30(1):3-44.

²Capture the Fracture: a Best Practice Framework and global campaign to break the fragility fracture cycle. Osteoporos Int. 2013 Aug;24(8):2135-52.

³ Factors influencing diagnosis and treatment of osteoporosis after a fragility fracture among postmenopausal women in Asian countries: A retrospective study. BMC Womens Health. 2013 Feb 14;13:7.

Risk factor for low BMD

Risk factors can be controlled	Risk factors cannot be controlled
Diet	Age
Physical activity	Gender
Body weight	Ethnicity (Black American > Asian American)
Smoking	Family history (Parent fracture history)
Alcohol	
Medications	

1. Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society. *Menopause*. 2021 Sep 1;28(9):973-997.
2. 台灣成人骨質疏鬆症防治之共識及指引 (2020年增修版)

Diseases and drugs adversely affect bone health

Medications	
Medications causing bone loss	
Aromatase inhibitors	Glucocorticoids for >3 mo
Thyroid hormone in excess	Immunosuppressive agents (eg, cyclosporine)
Gonadotropin-releasing hormone agonists or antagonists	Some anticonvulsants (eg, phenytoin)
Cytotoxic agents	Intramuscular medroxyprogesterone
Medications associated with increased fracture risk	
Proton pump inhibitors	Thiazolidinediones
SGLT2-inhibitors	Insulin with hypoglycemia
Selective serotonin-reuptake inhibitors	Selective norepinephrine-reuptake inhibitors
Medical conditions	
Genetic disorders	
Osteogenesis imperfecta	Hypophosphatasia
Thalassemia	Hemochromatosis
Endocrinopathies	
Gonadal insufficiency (primary and secondary)	Type 1 and type 2 diabetes mellitus
Hyperthyroidism	Primary hyperparathyroidism
Hypercortisolism, including Cushing syndrome	
Nutritional disorders	
Eating disorders	Obesity
Disorders of calcium balance	
Vitamin D deficiency	Hypercalciuria
Gastrointestinal diseases	
Malabsorption syndromes (eg, celiac disease)	Inflammatory bowel disease
Gastrectomy	Chronic liver disease
Other disorders and conditions	
Chronic renal disease	Systemic mastocytosis
Rheumatologic diseases (eg, rheumatoid arthritis)	Hematologic malignancies (eg, leukemia, multiple myeloma)
Frailty	Neuromuscular or visual impairment

FRAX[®]骨折風險評估工具：找出高風險族群

國家: 台灣 指名: 有關危險因子

問卷:

1. 年齡 (40至90歲之間) , 或出生日期
年齡: 出生日期: 年: 月: 天:

2. 性別 男性 女性

3. 體重 (公斤)

4. 身高 (公分)

5. 過去骨折史 否 是

6. 父母髖骨骨折 否 是

7. 目前吸菸 否 是

8. 類固醇 否 是

9. 類風溼性關節炎 否 是

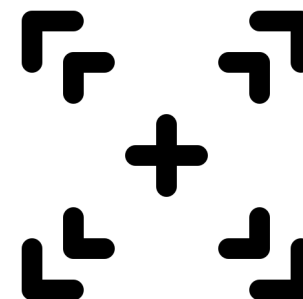
10. 續發性骨質疏鬆症 否 是

11. 每日飲用酒精3單位或以上 否 是

12. 股骨頸骨密度(BMD)
選擇BMD機型

身體質量指數: 19.7
十年骨折機率(%)

無骨密度值	
主要骨鬆性骨折	2.7
髖骨骨折	0.3



FRAX介入治療閾值：台灣

Intervention threshold for Taiwan

FRAX可估算「未來 10 年」的「主要骨鬆性骨折」及「髌骨骨折」的風險

✓ 中度骨折風險：主要骨鬆性骨折 >10% or 髌骨骨折 >1.5%

✓ 高度骨折風險：主要骨鬆性骨折 >20% or 髌骨骨折 >3%

身體質量指數: 19.7
十年骨折機率(%)


無骨密度值

主要骨鬆性骨折	2.7
髌骨骨折	0.3



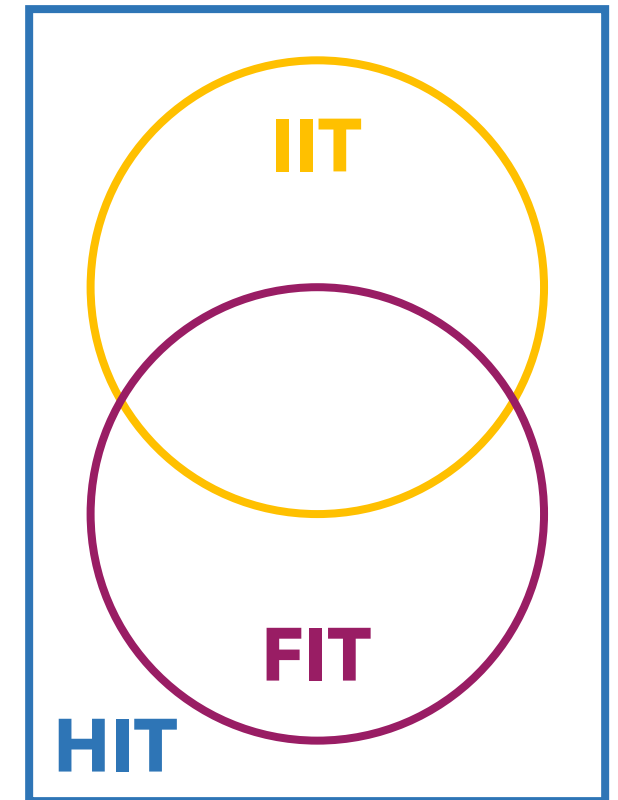
1. FRAX: <https://www.sheffield.ac.uk/FRAX/tool.aspx?lang=cht>
2. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2019 Jan;30(1):3-44. doi: 10.1007/s00198-018-4704-5. Epub 2018 Oct 15.

Underestimated fracture risk in postmenopausal women—application of the hybrid intervention threshold

Y. Wang¹ · S. Yu² · C. Hsu² · C. Tsai¹ · T. Cheng^{2,3} 

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Hybrid intervention threshold (HIT) = Individual intervention threshold (IIT) + Fixed intervention threshold (FIT)

Promoting a bone healthy lifestyle

Peak bone mass achieved in young adulthood: 25-35

提高巔峰骨量

- ⊕ 足量「Ca」和「Vit D3」攝取
- ⊕ 荷重、肌力增強運動和平衡訓練

去除降低骨密度的危險因子

- ⊕ 均衡飲食
- ⊕ 多活動
- ⊕ 戒菸
- ⊕ 戒酒
- ⊕ 不要太瘦 ($BMI \geq 18.5 \text{ kg/m}^2$)

1. 2021台灣成人骨質疏鬆症防治之共識及指引

2. Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society. Menopause. 2021 Sep 1;28(9):973-997

營養該如何補充？

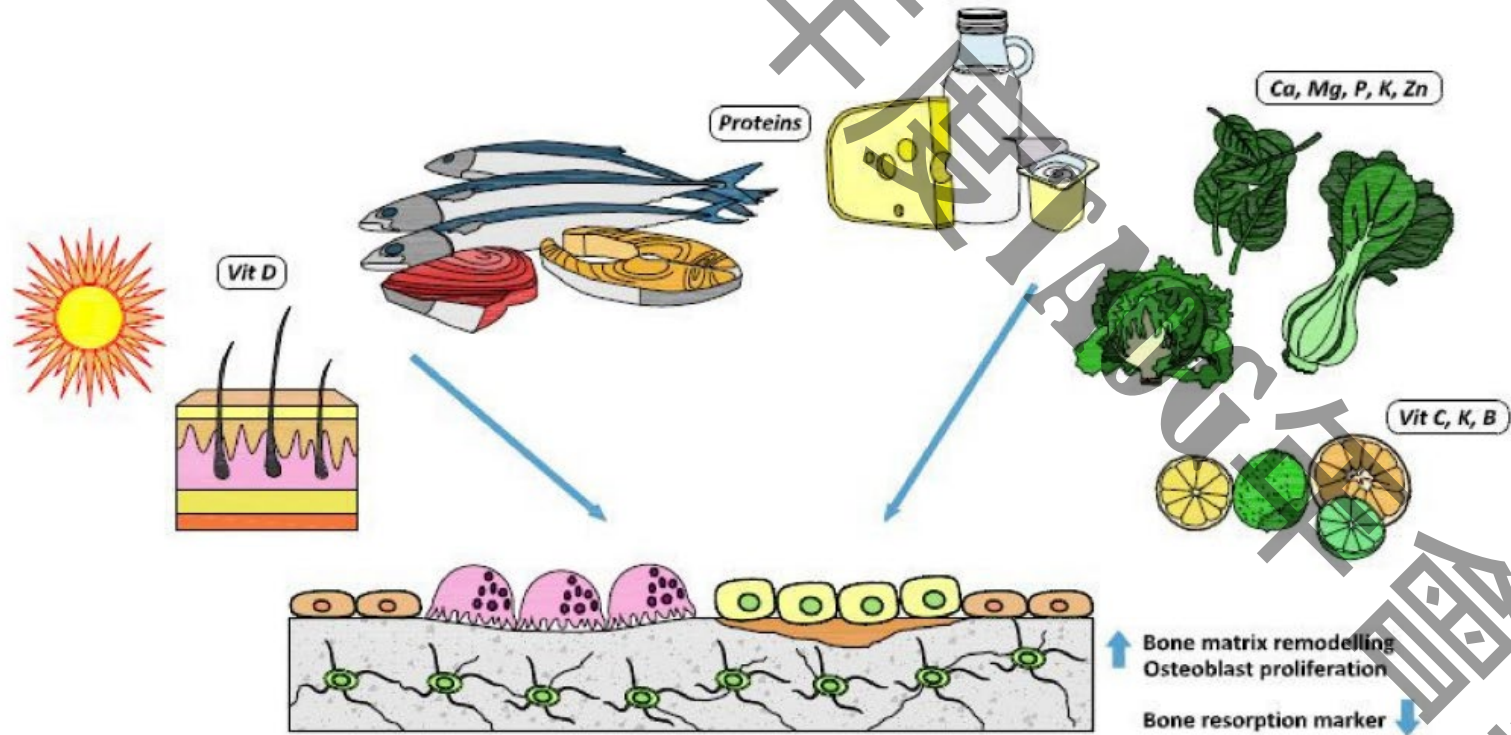


Figure 1. Nutrients and their bone effects.

均衡飲食

- High intake of fruit, vegetables, low-fat dairy products, whole grains, poultry, fish, nuts and legumes
- A positive effect on bone health and directly associated with a better BMD

Weight-bearing and resistance exercises

荷重、肌力增強運動

- ① Weight-bearing physical activity stimulates bone remodeling and is the most positive modifiable intervention for building healthy bone in adolescents ¹
- ② Weight-bearing exercise² :
 - 當腿部和足部支撐身體時，骨骼和肌肉須對抗重力
 - Stairs climbing, jogging, tennis
- ③ Resistance exercise² : weight lifting

¹ J Womens Health (Larchmt). December 2022; 31(12): 1671-1676

² American College of Sports Medicine: [https://www.acsm.org/docs/default-source/certification-documents/img-327023929-0001-\(1\).pdf?sfvrsn=283c5662_0](https://www.acsm.org/docs/default-source/certification-documents/img-327023929-0001-(1).pdf?sfvrsn=283c5662_0)

近100%兒童與青少年及「8成以上成人」鈣攝取不足

建議攝取量：每日1000 mg

實際上多數人只攝取了約 300mg/day



長期久坐



少曬太陽



缺乏運動



少喝牛奶



»每日1-2杯低脂乳品：240 ml的低脂乳品約含240 mg的鈣質

»攝取高鈣食物

»適當的日照

»多運動

»避免過度攝取咖啡因

鈣建議攝取量

1000mg/day

(胃腸道可吸收約35%)

年齡分層	19-30 歲	31-50 歲	51-70 歲	71 歲以上
參考體重男/女 (kg)	男 64/女 52	男 64/女 54	男 60/女 52	男 58/女 50
鈣增積率 (mg/d)	50/10	0	0	0
鈣總流失量 ^a (mg/d)	309/258	309/297	292/288	284/280
尿鈣 (mg/d)	128/104	128/108	120/134	116/130
內因性糞鈣 (mg/d)	141/114	141/119	132/114	128/110
汗鈣 (mg/d)	40	40	40	40
鈣需要量 ^b (mg/d)	359/268	309/297	290	282
EAR 估計值 ^c (mg/d)	800	800	800	800
AI 值	1000	1000	1000	1000

分 300、300、400 mg 攝取時，吸收率以 30%、30%、35% 計算，吸收鈣量為 320 mg/d，可超過各年齡層的需要量

a 尿鈣和內因性糞鈣可依照體重而估算，分別為 2.0 mg/kg/d 與 2.2 mg/kg/d；婦女 51 歲以上年齡層之尿鈣量比停經前增加 30 mg/d。

b 鈣需要量=鈣增積率+鈣總流失量；c 根據國外鈣平衡實驗結果。

EAR: estimated average requirement

AI: adequate intake

TABLE 6. Institute of Medicine recommendations for daily intakes of calcium and vitamin D for women aged older than 50 years

Age range, y	Calcium, mg		Vitamin D, IU	
	EAR ^a	RDA ^b	EAR ^a	RDA ^b
51-70	1,000	1,200	400	600
Over 70	1,000	1,200	400	800

EAR, estimated average requirement; IU, international units, RDA, recommended dietary allowance.

^aExpected to satisfy the needs of 50% of persons in that age group.

^bDaily dietary intake level of a nutrient considered sufficient to meet the requirements of 97.5% of healthy persons in that group.

Institute of Medicine.⁷⁶

鈣如何補充？

高鈣食物

- » 乳酪、高鈣牛奶
- » 小魚乾、深綠色蔬菜(芥藍、青花椰)
- » 髮菜、海帶

富含Vit. C水果

(幫助鈣吸收)

- » 如橘子、柳丁、奇異果、芭樂等

食物	含鈣量 (mg)
Fortified oatmeal, 1 packet (高鈣麥片)	350
Sardines, 3 oz (沙丁魚)	324
Cheddar cheese, 1.5 oz (切達起士)	306
Milk, nonfat, 1 cup (脫脂牛奶)	302
Yogurt, plain, low fat, 1 cup (低脂原味優格)	300
Tofu, with calcium, ½ cup (豆腐)	204
Salmon, 3 oz (鮭魚)	181
Baked beans, 1 cup (豆)	142
Cottage cheese, 1 cup (Cottage 起士)	138
Broccoli, raw, 1 cup (青花椰菜)	90
Ice cream, vanilla, ½ cup (香草冰淇淋)	85

2021台灣成人骨質疏鬆症防治之共識及指引

The 2004 Surgeon General's Report on Bone Health and Osteoporosis: What It Means to You. U.S. Department of Health and Human Services, Office of the Surgeon General, 2004, pages 12-13.

Picture from: <https://www.gq.com/story/the-surprising-health-benefits-of-cheese>



Vitamin D

- 日照是主要來源，但飲食攝取量也與體內維生素D濃度有關
- 體內維生素D濃度充足： $\geq 30\text{ng/ml}$ (75nmol/L)
- **Daily dietary intake: Cholecalciferol 5-10ug/day or Vit D 200-400IU**
- 台灣女性有 70%有充足的Vit D
- 素食者Vit D 攝取量較低，尤其是純素者

1. Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society. Menopause. 2021 Sep 1;28(9):973-997.
2. 衛服部國民健康署：國人膳食營養素參考攝取量」第八版：維生素D

Vit D的來源：陽光

- ① 皮膚經陽光照射之合成是主要的維生素D來源
- ② 估計人體皮膚合成維生素 D可達 $6 \text{ IU vit D/cm}^2/\text{hr}$
- ③ 日曬的方法：
 - 對白皮膚的人，在夏季4-10分鐘日曬便足以產生 1 個 MED 的維生素 D；膚色較深者，曝曬時間則需要延長。
 - 澳洲的研究：未塗防曬的情況下，於10 am-3pm (日照較強的時段)，每週 3-4 次將**臉部、手臂**曬 10-15 分鐘，即可獲得足夠的維生素 D

Evaluating fragility fracture risk

- ① Promoting a bone-healthy lifestyle
- ② Evaluating fragility fracture risk: FRAX[®] + Intervention threshold
- ③ Evaluating bone mineral density (BMD) by DEA for \geq moderate risk

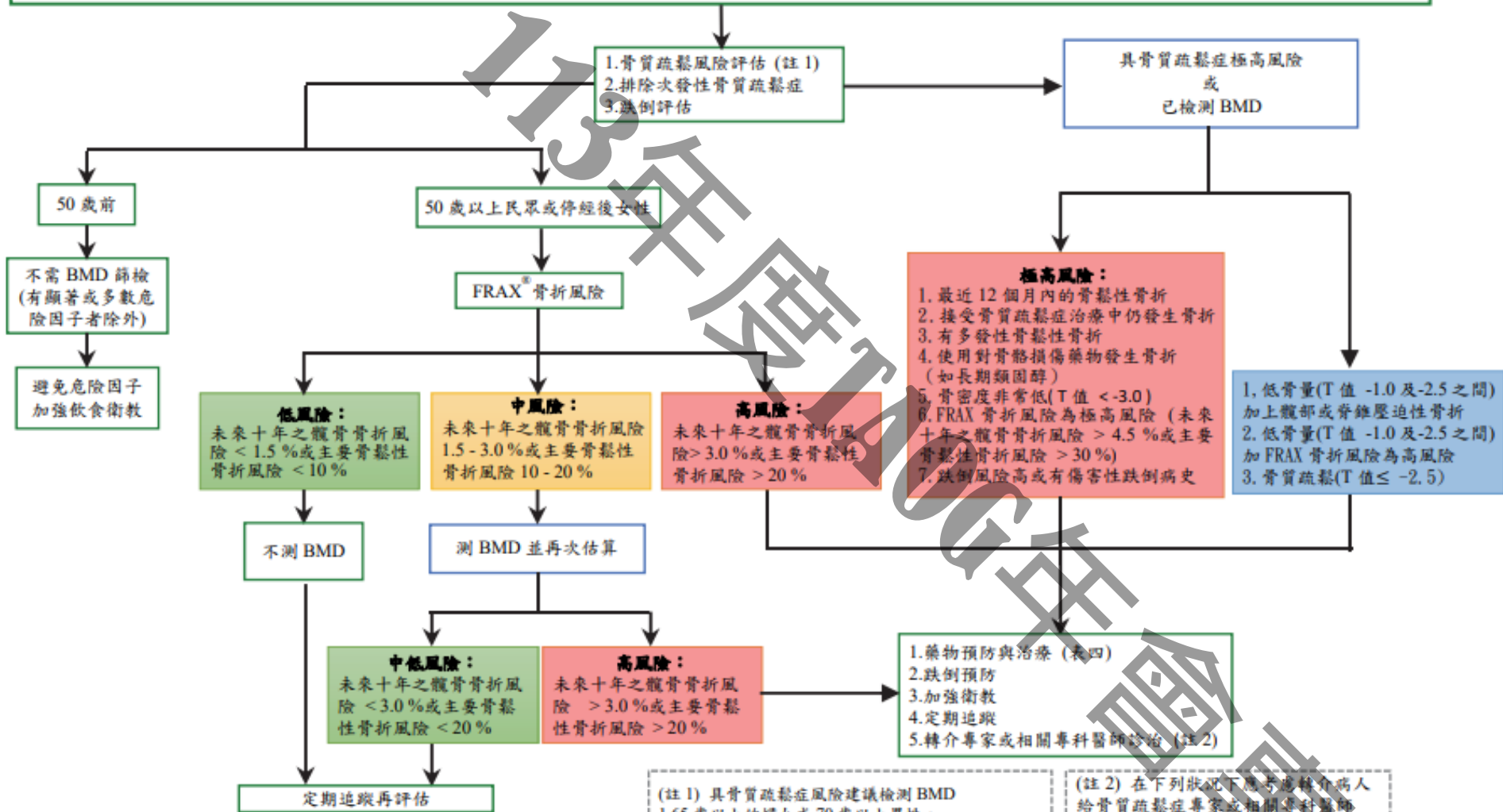
Moderate risk

FRAX fracture risk: Hip 1.5-3% or
Major 10-20%

High risk

- ① Osteopenia (T-score: $-1.0 < T < -2.5$) +
髖部或脊椎壓迫性骨折
- ② Osteopenia (T-score: $-1.0 < T < -2.5$) +
FRAX 骨折高風險
- ③ Osteoporosis: $T \leq -2.5$

所有人都應增加飲食中鈣質與維生素 D₃ 攝取、
保持體重、避免菸酒、規律運動、預防跌倒



(註1) 具骨質疏鬆症風險建議檢測BMD
 1.65歲以上的婦女或70歲以上男性。
 2.65歲以下且具有危險因子的停經婦女。
 3.即將停經並具有臨床骨折高風險因子的婦女，如體重過輕、先前曾經骨折、服用高骨折風險藥物。
 4.50-70歲並具有骨折高風險因子的男性。
 5.脆弱性骨折者(指在低衝擊力下就發生骨折)。
 6.罹患可能導致低骨量或骨量流失之相關疾病者。
 7.所服用藥物和低骨量或骨量流失有相關者。
 8.任何被認為需要用藥物治療骨質疏鬆症者。
 9.接受治療中，用以監測治療效果者。
 10.有骨密度流失證據而可能接受治療者。

(註2) 在下列狀況下應考慮轉介病人給骨質疏鬆症專家或相關專科醫師
 1.次發性骨質疏鬆症。
 2.骨密度正常在低創傷性情況下骨折者。
 3.使用藥物，如：bisphosphonates、鈣片等為禁忌症者。
 4.用藥期間骨密度仍持續明顯下降者。
 5.治療追蹤期間仍有再發性骨折者。
 6.病情複雜者。



Management stratified by risk group

Moderate risk

- » Promoting a bone-healthy lifestyle
- » Calcium and Vit D Supplement
- » Hormone replacement therapy
- » 定期追蹤再評估

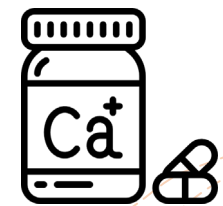
High risk

- » 藥物預防與治療
- » 預防跌倒
- » 加強衛教
- » 定期追蹤
- » 轉介相關專科醫師診治

Calcium supplement

種類	鈣離子含量	吸收率	每1000mg 可補充到的鈣離子	備註
碳酸鈣 (Calcium carbonate)	40%	26%	104	需胃酸協助才能吸收，隨餐或飯後兩小時內服用吸收最好
檸檬酸鈣 (Calcium citrate)	21%	35%	73.5	在體內的吸收就不受胃酸影響，不需隨餐服用 <ul style="list-style-type: none">• Elderly persons decreased stomach acid secretion → Calcium citrate• Persons taking PPI → Calcium citrate

- ✓ **Incomplete calcium absorption from the gut** (even with adequate Vit. D)
- ✓ Calcium absorption from supplements: about 30%





Calcium supplement

常見劑型

- » Calcium carbonate 500mg
- » Calcium Vitamin D3 Stella (鈣立德發泡錠)
 - Ca 1000mg (as calcium carbonate 2469mg) + Vit D3 880IU): 20's/bot
 - 自費600 (1PC QD)
- » Bio-CAL plus 滋骨加強錠
 - Tricalcium phosphate (磷酸鈣) 1203mg (as calcium 450mg) + Cholecalciferol (D3) 330 IU
 - 一次一錠，每日2-3次，飯後使用

過度攝取

- >1200 mg/day: 對身體無益處
- 便秘

MHT for the management of osteoporosis

Statistically significant reduction in the risk of any fracture (including hip and vertebral fracture) for women taking HT

(Cochrane Database Syst Rev. 2017)

JAMA. 2002 288(3):321-33

Reduce hip and vertebral fracture rates by **one third** compared with placebo

Arthritis Rheum. 2006
54(10):3194-204

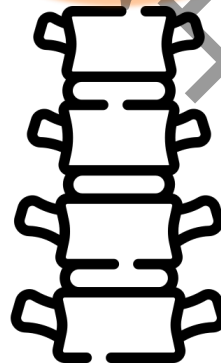
Estrogen lower rates of any **arthroplasty** (HR 0.84, borderline significant for hip and not significant for knee)

JAMA. 2013 310(13):1353-68

CEE ± MPA: **33% reductions** in hip fracture, significant fracture benefit persisted over 13 years

Menopause. 2013 20(6)

Modest but sustained reduction in the frequency of **joint pain**



MHT

Hormone for the management of osteoporosis

Menopausal hormone therapy for the management of osteoporosis. Best Pract Res Clin Endocrinol Metab. 2021 Dec;35(6):101551.

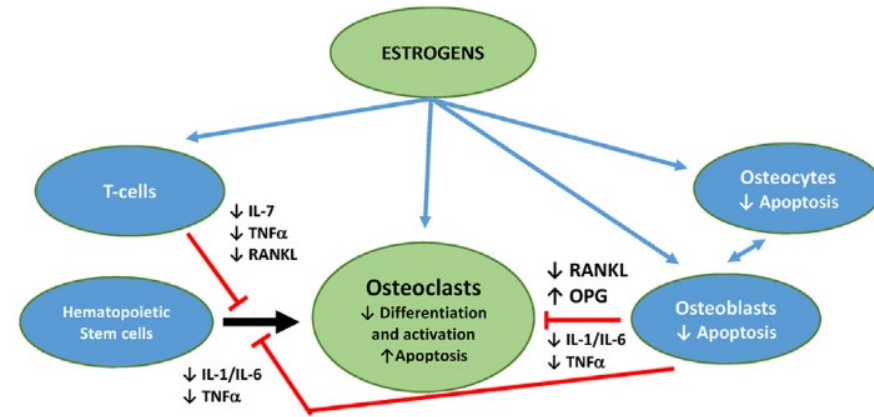
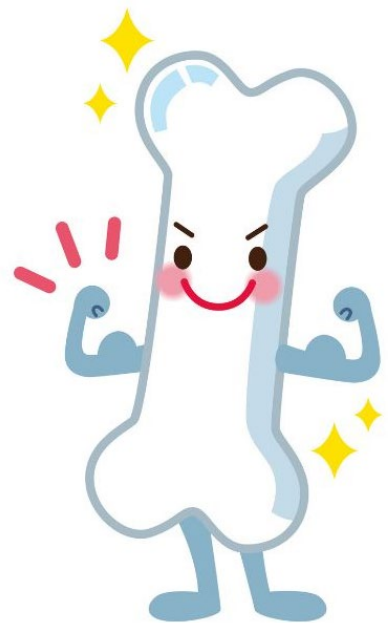


Fig. 1. Impact of estrogens on bone cells.

Practice points

- MHT prevents osteoporosis and reduces the risk of fracture regardless of initial BMD level
- MHT should be considered as a 1st option for the maintenance of bone health in early postmenopausal women with a low to moderate risk of fracture where specific bone active medications are not warranted
- There is a positive risk-benefit balance of MHT in symptomatic early postmenopausal women within the first 10 years after menopause or before the age of 60
- The individual benefit-risk balance of MHT is dependent on whether estrogen is opposed or unopposed as well as the type, doses and duration of MHT together with the individual risk profile in each woman



骨質疏鬆治療

» Fragility fracture high risk

» 需要治療的不一定符合健保給付條件

- ① 健保只給付給已骨折過 + 骨質疏鬆
- ② 未達給付標準都需自費使用

1. 全民健康保險支付及給付之藥品相關法令規定全民健康保險藥物給付項目及支付標準
> 附件六：藥品給付規定 > 5.6. 骨質疏鬆症治療藥物

2. Picture from: <https://www.victoriavn.com/en/health-library/osteoporosis>

Osteoporosis

用藥及其臨床實證

台灣成人骨質疏鬆症防治之共識及指引 (2020 年增修版)

	使用頻率	脊椎骨折	脊椎外骨折	男性骨鬆	類固醇骨鬆	初級骨折預防	骨鬆預防
雙磷酸鹽類							
Alendronate	每週	++	++	++	++	++	++
Risedronate	每週/每月	++	++	++	++	++	++
Zoledronate	每年	++	++	++	++	++	++
Ibandronate	每季	++	+	N/A	N/A	N/A	N/A
RANKL 單株抗體							
Denosumab	每半年	++	++	+	+	+	N/A
雌激素、選擇性激素調節劑							
Estrogen	每天	++	++	不宜	不宜	++	++
SERM (Raloxifene)	每天	++	+	不宜	N/A	++	++
(Bazedoxifene)	每天	++	+	不宜	N/A	N/A	N/A
STEAR (Tibolone)	每天	++	N/A	不宜	N/A	N/A	N/A
維生素							
1 α (OH)D ₃ /1 α ,25(OH) ₂ D	每天	+	+	N/A	N/A	N/A	N/A
副甲狀腺							
Teriparatide	每天	++	++	+	++	N/A	N/A
抑制 sclerostin 單株抗體							
Romosozumab	每月	++	++	+	N/A	+	N/A



Osteoporosis: 治療

減少骨質流失、增加骨密度、減低骨折發生率

抑制骨質流失 Anti-resorptive

- ① 雙磷酸鹽類 (Bisphosphonate)
- ② 選擇性雌激素受體調節物 (SERMs)
- ③ 細胞受體抑制劑 (RANKL)

增加骨質生成 Osteoanabolic

- ① 副甲狀腺素及類似劑
- ② 抑硬素單株抗體(Anti Sclerostin Antibodies)



Bind to hydroxyapatite (absorbed by bone)

- Cytotoxic injury of osteoclasts
- Inhibition of osteoclast attachment to bone
- Inhibition of osteoclast differentiation

Bisphosphonate

雙磷酸鹽類

Human IgG2 monoclonal antibody against RANKL

- inhibits osteoclast formation, function, and survival

RANKL單株抗體

Estrogen regulate the survival of mature osteoclasts via the Fas/FasL system

Raloxifene: estrogen agonist/antagonist

- agonist on bones
- antagonistic on the breasts and GI tract

SERMs (Selective Estrogen Receptor Modulators)

選擇性雌激素接受器調節劑

Mechanism

1. 2021台灣成人骨質疏鬆症防治之共識及指引
2. Molecular Mechanisms and Emerging Therapeutics for Osteoporosis Int J Mol Sci. 2020 Oct 15;21(20):7623. doi:10.3390/ijms21207623.
3. Pharmacological Therapy of Osteoporosis: A Systematic Current Review of Literature. Front. Pharmacol., 07 November 2017

骨密度追蹤檢查

- ① 未接受治療者不建議一年之內重覆測量
- ② 評估治療成效：建議一年以上，最好兩年再測量
- ③ 若治療期間骨密度改變 > 最小顯著差異值，可認為有顯著變化：
腕骨 $\geq 3 \sim 6\%$ or 腰椎 $\geq 2 \sim 4\%$



113 年 研 究 用

Women cancer survivor

Evaluate fragility fracture risk 2 years after treatment completion

Managing high-risk women

Bridging the Bone Health Gap: Strategies for Women's Health Across the Lifespan

女性癌症

1. 女性癌症患者約21.7%在診斷時年齡<50歲¹ (台灣女性平均停經的年齡為50.2歲)
2. 癌症治療可能使女性提早停經
 - Surgery: oophorectomy
 - Radiotherapy: irreversible injury when accumulated dose > 6 Gy
 - Chemotherapy: irreversible injury to germ cell, granulosa cell and theca cell
 - **High risk** (>80% experience infertility): Alkylating agent (ifosfamide, cyclophosphamide)
 - **Intermediate risk** (20- 80% experience infertility): cisplatin, adriamycin
 - **Low risk** (< 20% experience infertility): methotrexate, 5-FU, vincristine, bleomycin, actinomycin D

¹ Health Promotion Administration, M.o.H.a.W. *Cancer Registry Annual Report 2016*. <https://www.hpa.gov.tw/Pages/List.aspx?nodeid=269>

² Fertility preservation in female patients. *Human Reproduction Update*, 2004. 10(3): p. 251-266

³ Fertility preservation options in pediatric and adolescent patients with cancer. *Cancer*, 2018. 124(9): p. 1867-1876

When to evaluate bone health?

1. BSO: 平均術後約29個月後就會面臨骨質流失¹
2. NCCN guideline²
 - If premature menopause after cancer treatment, may evaluate fragility fracture risk by FRAX
 - DEA for risk groups, and follow DEXA every 2 years



¹ Osteoporosis risk and management in BRCA1 and BRCA2 carriers who undergo risk-reducing salpingo-oophorectomy. *Gynecol Oncol*, 2015. 138(3): p. 723-6

² NCCN Task Force Report: Bone Health In Cancer Care. *J Natl Compr Canc Netw*, 2013. 11 Suppl 3: p. S1-50; quiz S51.

哪些藥物適合女性癌症患者？

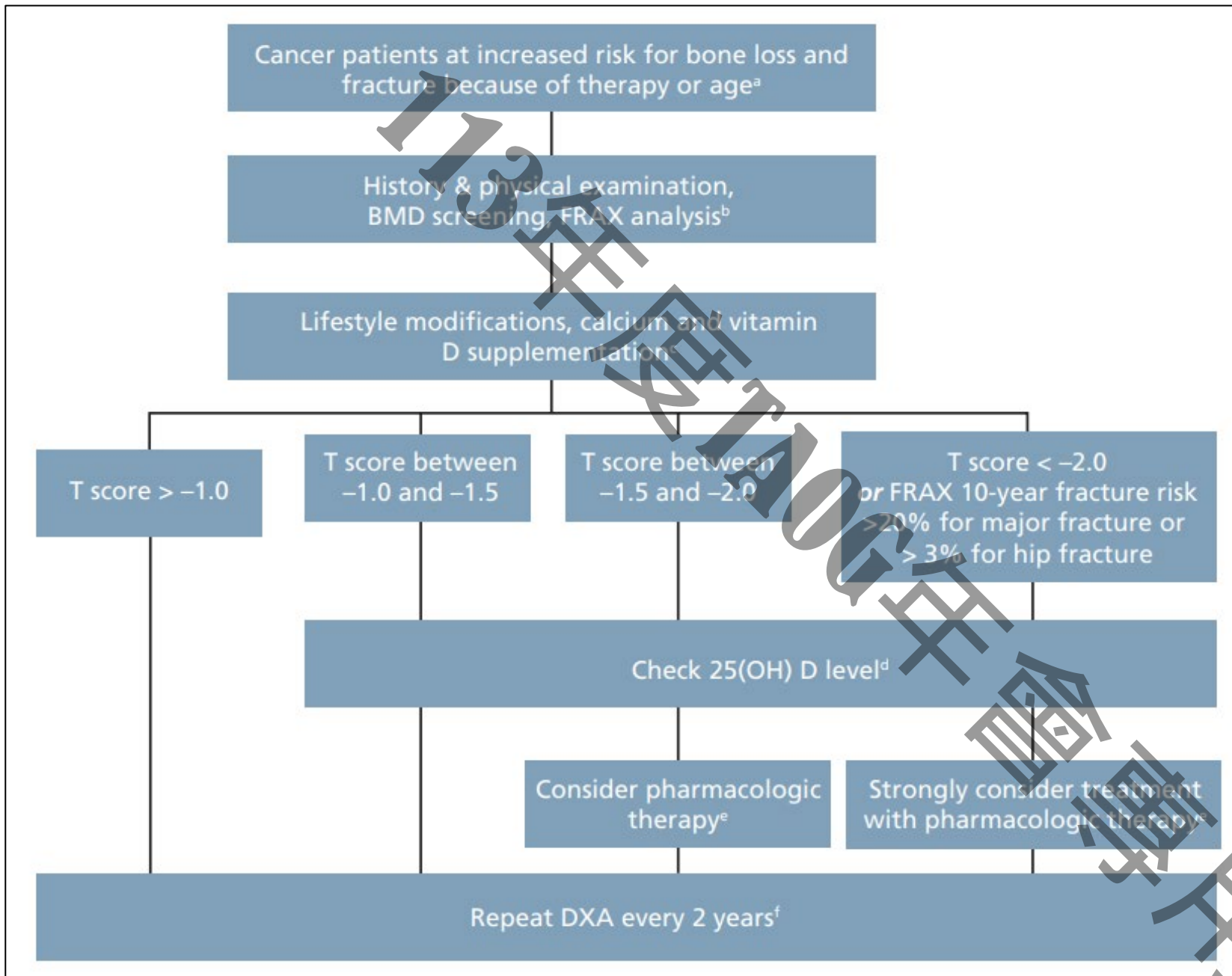
RANKL 單株抗體

- » Denosumab除了可治療骨鬆，也被用於治療bone mets
 - 治療骨鬆劑量: 60mg (every 6 months)
 - 治療骨轉移劑量: 120mg (monthly)
- » 癌症患者身上使用上的安全性也已在臨床試驗中證實
- » 和bisphosphonate相比，Denosumab使用上更為簡單，副作用也較少

雙磷酸鹽類 (Bisphosphonate)

- » Bisphosphonate除了用於osteoporosis，也常用於治療癌症相關的hypercalcemia and bone mets
- » 對於整體乳癌患者的存活以及次分析上，使用bisphosphonate不影響乳癌患者的預後

**NCCN Task Force
Report 2013: Bone
Health in Cancer Care**



藥物	使用方式	頻次	單價	年度預估費用
Alendronic acid (雙磷酸鹽類 · Fosamax 福善美)	口服	每週一次	約150-200	約8000-10000
Ibandronic acid 3mg (雙磷酸鹽類 · Bonviva 骨維壯)	靜脈注射	每三個月一次	約2500-3000	約10000-12000
Risedronate 150mg (雙磷酸鹽類 · Reosteo 瑞骨卓)	口服	每月一次	約800	約9600
Zoledronic acid 5mg (雙磷酸鹽類 · Aclasta 骨力強)	靜脈注射	每年一次	約12000	約12000
Denosumab (單株抗體 · Prolia 保路麗)	皮下注射	每六個月一次	約7000	約14000

Women with premature ovarian insufficiency

Hormone replacement therapy

Evaluating fragility fracture risk when reaching age 50

Bridging the Bone Health Gap: Strategies for Women's Health Across the Lifespan

Strategies for POI: HRT

Loss of ovarian function < age 40; Estrogen deficiency

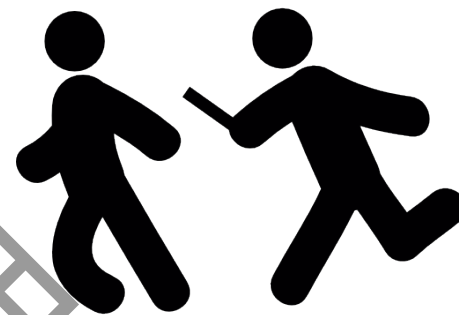


- ⊗ Optimal HRT regimen: still under investigation
- ⊗ POISE study (Premature Ovarian Insufficiency Study of Effectiveness of Hormonal Therapy): aims to find out the most effective HRT for women with POI
- ⊗ Adequate estrogen dose:
 - ✓ Oral estradiol 2mg or 100–150ug transdermal estradiol
 - ✓ Natural 17- β -estradiol (E2) provides superior benefit to synthetic estrogens
- ⊗ HRT initiated at the time of POI onset (*unless contraindicated*) and continued until the natural age of menopause: better skeletal outcomes, menopausal symptoms relief and prevention of cardiovascular morbidity

Osteoporosis 用藥注意事項



- ① 不論任何藥物，治療需1年以上 (最好持續3年)
- ② SERM、Estrogen、RANKL 單株抗體 等藥物在停用後，骨量會快速流失，甚至增加骨折機率。應妥善規劃並銜接其他anti-resorptive drug
- ③ 建議藥物治療期間檢查：鈣、磷、腎功能



長期用藥之副作用

顎骨壞死 (Osteonecrosis of the jaw, ONJ)

上、下顎骨產生骨髓炎及骨壞死

- ⊗ 發生率: $1/10000$ in bisphosphonate，多發生在用藥第三年
- ⊗ 症狀：疼痛、骨頭暴露
- ⊗ 其他症狀：腫脹、麻木感、牙齦撕裂傷、化膿、牙齒鬆動
- ⊗ 使用破骨細胞抑制劑前，至牙科做好檢查及治療
- ⊗ 保持良好口腔衛生：每 6 個月做定期口腔檢查及清除牙結石等口腔照護工作

長期用藥之副作用

非典型骨折 (Atypical Femoral Fracture)



- ① 發生率：1/1000 after 8-10 years of therapy
- ② 藥物種類：主要是「Bisphosphonate」
- ③ 原因：microfracture 之處無法自行重塑
- ④ 位置：股骨中段或轉子下方
- ⑤ 症狀：骨折前一段時間會在大腿處隱隱作痛
- ⑥ X光：反覆性裂痕、骨痂 callus formation、皮質骨增厚

台灣成人骨質疏鬆症防治之共識及指引 (2020年增修版)

Management of osteoporosis in postmenopausal women: the 2021 position statement of The North American Menopause Society. Menopause. 2021 Sep 1;28(9):973-997.

Picture from <https://www.sciencedirect.com/science/article/pii/S240552551630053X#fig1>

Drug Holidays

雙磷酸鹽假期 (bisphosphonate holidays)

雙磷酸藥物會累積且可能在骨骼中作用時間延長，可考慮於治療中
暫停使用雙磷酸鹽藥物

- ① Drug holiday評估時間：注射劑型三年，口服劑五年
- ② 雙磷酸鹽假期是否結束應基於個體患者的情況 (骨折風險、骨密度變化)



Summary 1

1. Current Situation: There are notable gaps in the clinical care for women's bone health across different stages of life.
2. Key Strategies for Improvement:
 - Interventions for High-Risk Women
 - Bone-Healthy Lifestyle
3. Targeted Recommendations:
 - Reproductive Age Women: optimize peak bone mass through bone-healthy lifestyles
 - Postmenopausal Women: assess fragility fracture risk, and provide interventions for those at high risk
 - Women Cancer Survivors: evaluate fragility fracture risk 2 years after treatment completion, and provide interventions for those identified at high risk.
 - Women with POI: Recommend hormone replacement therapy until the age of 50, alongside a bone-healthy lifestyle

Summary 2

1. Medication Selection Rationale: Propose the use of **Denosumab** and **Bisphosphonates** based on individual patient evaluations
 - » Safety of denosumab when long-term use (10 years)
 - » Bridging to bisphosphonate for 3-5 years
 - » Bisphosphonate drug holiday
2. Utilize DEA scans to monitor BMD every 2 years after initiating anti-osteoporotic medication



Thanks for attention on a beautiful Sunday morning!

健保給付條件

使用「抑制骨質流失」的藥物 (anti- resorptive)

(保骼麗、福善美、骨力強、骨維壯、鈣穩)

Osteoporosis (T-score \leq -2.5SD)
+ 一處「脊椎」或「髖部」骨折

Osteopenia (-2.5SD < T score < -1.0SD)
+ 「脊椎」或「髖部」 \geq 2次(處)骨折

使用「增加骨質生成」的藥物 (Osteoanabolic)

(骨穩、益穩挺)

- ① T-score \leq -3.0 SD
- ② 已有脊椎或髖部 \geq 2處骨折
- ③ 無法耐受「抗骨質吸收劑」副作用 or 已使用 \geq 12 個月仍發生至少1 處新的骨折

ESMO 2020

Recommended algorithm for managing bone health during cancer treatment

