BoneCast

CSA Edition

Bone Health in Hematologic Stem Cell Transplant Patients

Prof David Kendler

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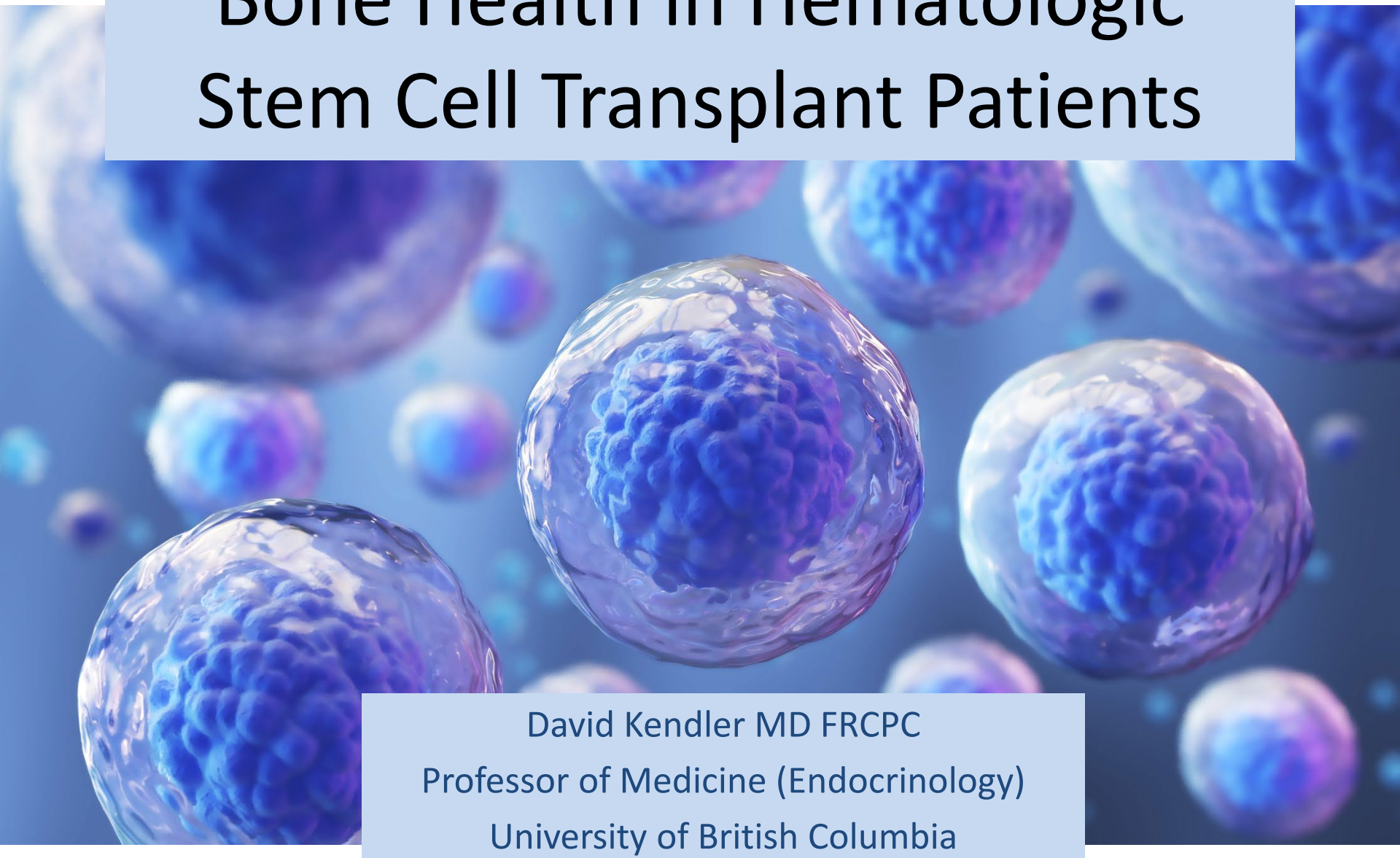
Bone Health in Hematologic Stem Cell Transplant Patients



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Agenda

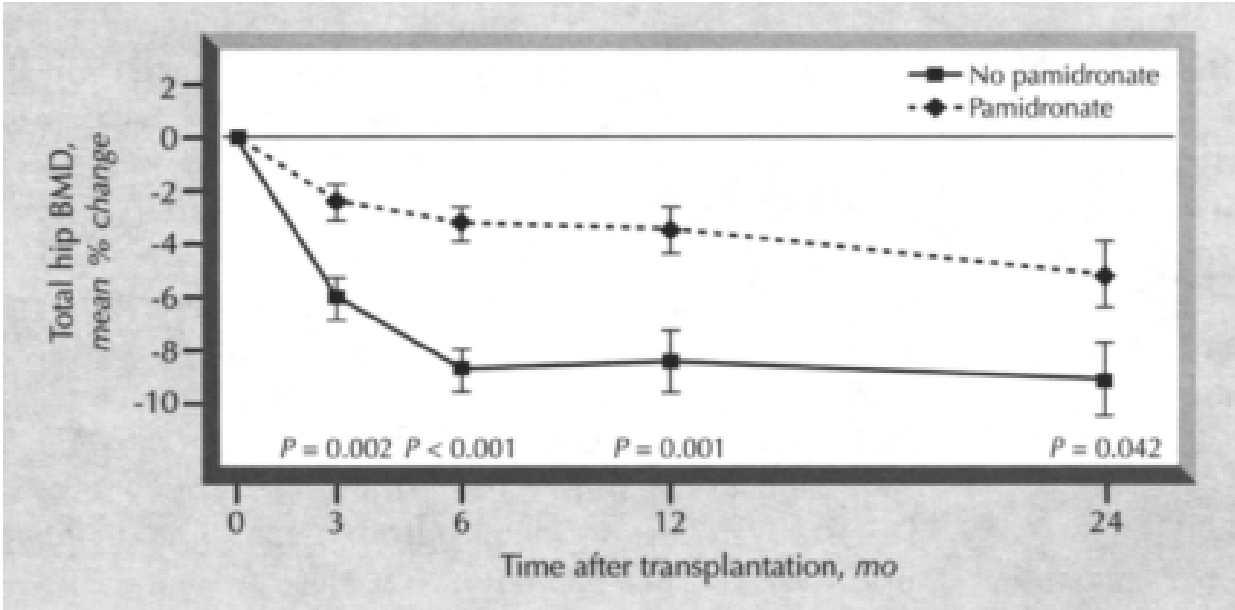
- Epidemiology of bone health in hematologic stem cell transplant (HSCT) patients
- Risks for bone loss in HSCT patients
- Bone protection in HSCT patients
- An algorithm for bone health management

Introduction

- Increasing numbers of allogeneic stem cell transplant patients
- Increased survival from improved acute and chronic care
- Bone loss is most rapid in the 1st 3 to 6 months after stem cell transplant with greatest loss at the hip suggesting cortical bone loss
- Fragility fractures remain a long-term serious complication of allogeneic stem cell transplant.

Osteopenia in patients with HSCT

- 29% of HSCT survivors had osteopenia at spine and 52% osteopenia femoral neck (Cohen A et al. JBMR 2004 19:1919 – 1932)
- Early rapid bone loss more so at hip and spine, incompletely recovered at hip
- Cortical bone loss predominates



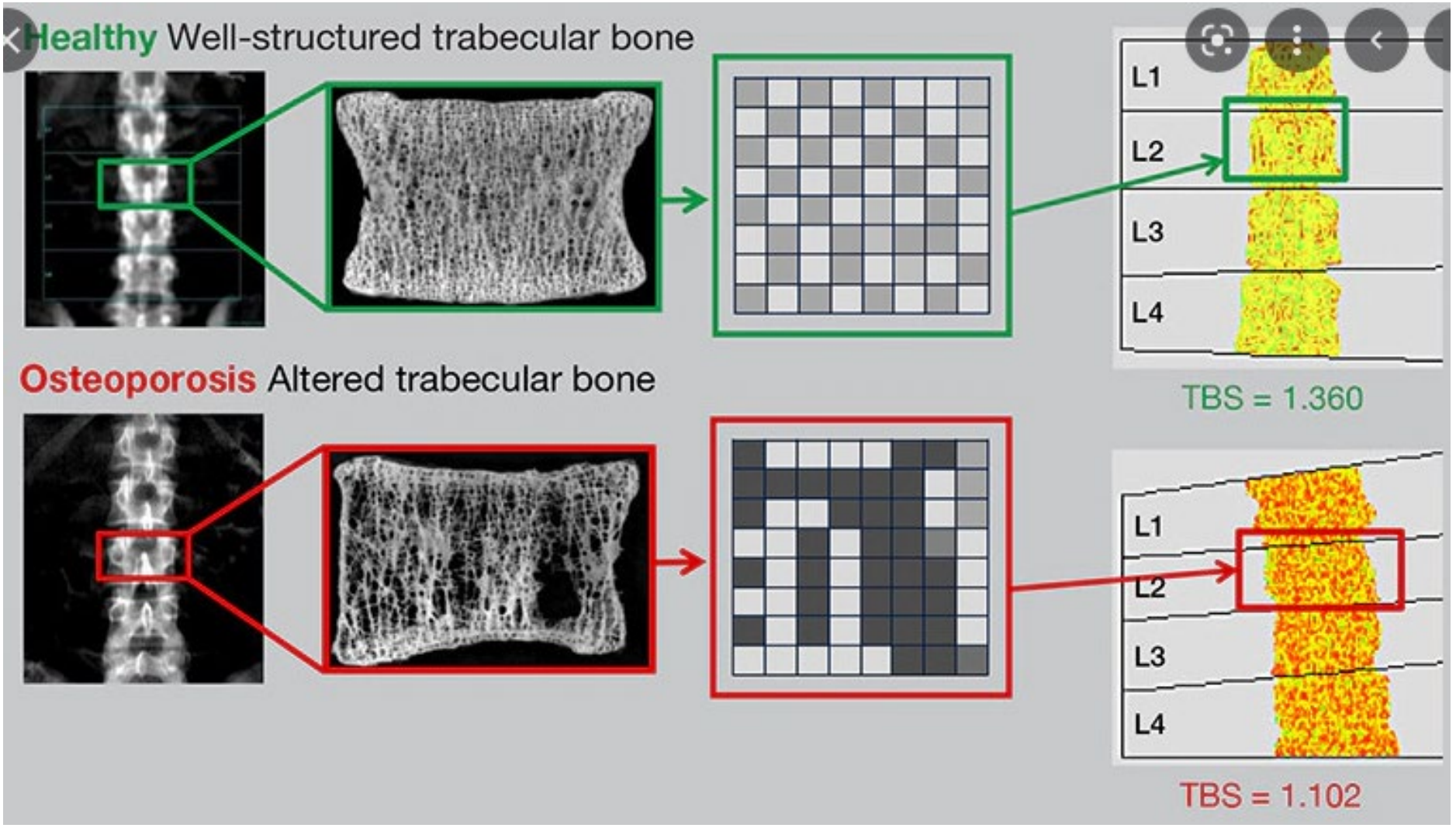
Grigg AP et al. JCEM 2006, 91:3835 - 3843

Early decreases in BMD in HSCT patients

- 137 HSCT patients between 2011 and 2014 with baseline and day 100 DXA
- Mean lumbar spine day 100 decreases of 3%, total hip of 4.6%, and femoral neck 4.7%. Incidence of osteoporosis increased from 12% to 18% and osteopenia increased from 41% to 50%
- Women have greater loss than men; glucocorticoid was associated with bone loss at total hip
- Day 100 trabecular bone score (TBS) was significantly lower than baseline and lower in patients with glucocorticoid exposure.

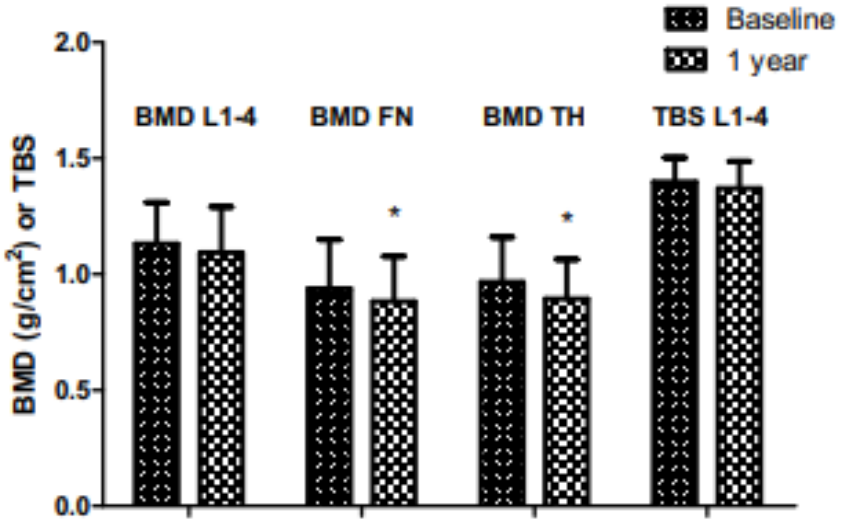
Pawlowska M et al. Bone marrow transplantation 2016, 51, 738 – 740

Trabecular bone score; an indicator of trabecular bone architecture



BMD and TBS changes after HSCT

- Seoul patients 2009 to 2015
- Decreases in femoral neck (5.48%) and total hip (6.84%) between transplant and twelve-month; TBS stable.
  - 24 patients
- Small increases in lumbar spine and total hip BMD in patients between 12 months and 24 months; TBS stable.
  - 44 patients



Lim Y et al. Bone 124 (2019) 40 – 46

Osteoporosis in HSCT patients

- 258 French patients between 2005 and 2016 with baseline, 6 month, and 3 year BMD
- DXA diagnostic of osteoporosis in 17% at baseline, 22.8% at 6 months, and 17.5% at 3 years.
- Incident fractures in 4.1% patients at 6 months and 5.7% of patients at 3 years
- Improvement at spine at 3 years superior to improvements at hip at 3 years.

Leguy et al. Joint Bone Spine. Volume 89, Issue 5, October 2022

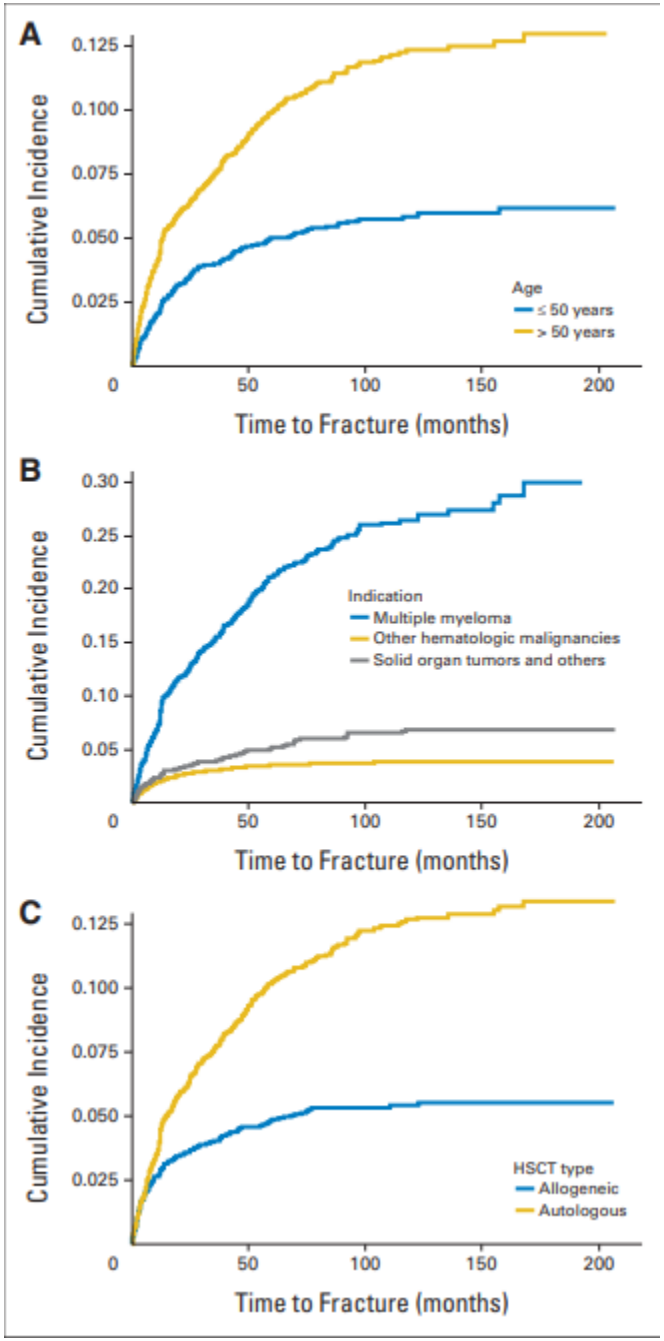
HSCT and fractures

- 15 year MD Anderson study of 7620 HSCT patients showed 8% incident fractures
- Relation to age, malignancy type, and allogeneic versus autologous transplant
- Fracture risk 8 fold higher than age and sex specific fracture incidence rates from the US population

Age

Tumor type

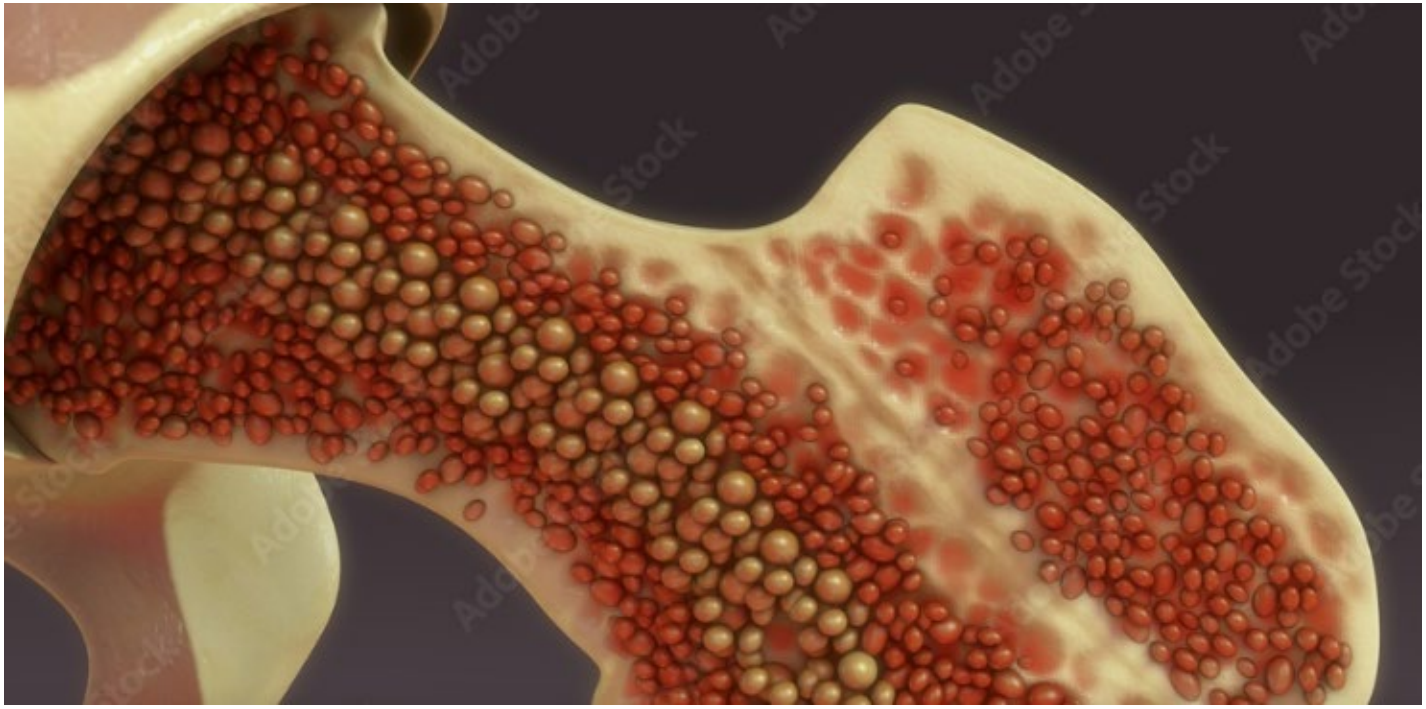
SCT type



Pundole X et al. J Clin Oncol 2016; 33 1364 - 1370

HSCT and fractures

- In 4160 Taiwanese cancer patients without HSCT and 1040 patients with HSCT
- Relative risk of fracture 1.4 in the HSCT group
- Vertebral fractures 68% of the fracture events



Risks for bone loss in HSCT

Table 1 Risk factors for bone loss pre- and post-stem cell transplantation

Pre-HSCT risk factors	Post-HSCT risk factors
Advanced age [5]	Graft-versus-host disease [6]
Female sex [5]	Calcium and vitamin D insufficiency leading to secondary hyperparathyroidism [7]
Chemotherapy [8]	Glucocorticoids [9]
Hypogonadism [10]	Renal dysfunction [11]
	G-CSF treatment [12]
	Renal wasting of calcium or magnesium [13]

- Calcineurin inhibitors
- Interactions between transplant stem cells and bone cells
- Decreased osteocyte viability
- Avascular necrosis in 10% to 20% HSCT survivors

Kendler D et al. Osteoporos Int (2018) 29:2597–2610

Osteo- immunology

- Crosstalk between the immune system and bone cells
- RANK RANKL OPG responsible for osteoclast formation, function, survival.
  - TNF alpha stimulates RANKL and inhibits osteoblast formation and function
  - IL1, IL7, IL23 also implicated in stimulating osteoclasts
- Trials of mesenchymal stem cells systemic infusion
  - may have benefits to GVHD and directly or indirectly to bone health
- GM-CSF support after chemotherapy and its use to mobilize hematopoietic stem cells
  - may increase the number of osteoclast precursors, enhancing posttransplant bone loss

Hypogonadism

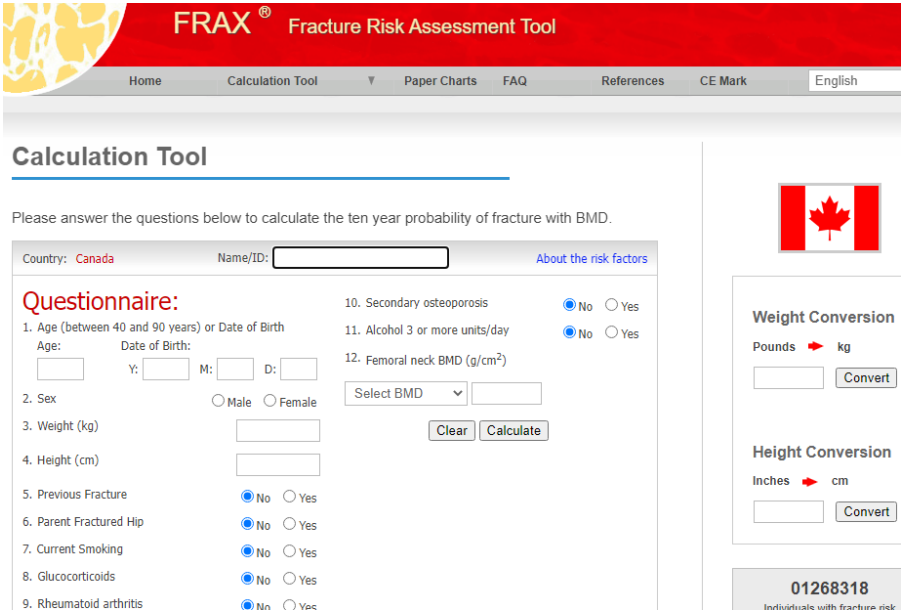
- Ovarian failure occurs in 70% to 90% of young women after HSCT
- Male hypogonadism less common
- Glucocorticoid can lead to central suppression of gonadotropin with secondary hypogonadism

Evaluation of bone health in HSCT patients

- Clinical risk factors
- BMD hip and spine
- Spine radiographs
- Evaluation of secondary cause of bone loss

Risks for bone loss and fracture: pre-existing

- Menopause
- Age
- Prior fracture
- Parental hip fracture
- Smoking
- Alcohol
- Rheumatoid arthritis
- Bone density
- Falls



FRAX has a moderate ability to predict fractures in the HSCT population (Pundole X et al. Arch Osteoporosis 2018. 13:38)

Treatment of HSCT patients: calcium, vitamin D, menopausal hormone therapy

- General nutritional support
- Calcium 1200 mg elemental from combination diet and supplement
- Vitamin D3 2000 IU by supplement, consider loading dose
- Exercise (walking type)
- Menopausal hormone therapy in appropriate patients

Vitamin D deficiency in HSCT patients

- Decreased sun exposure
- GI GVHD may impair vitamin D absorption
- Glucocorticoid, calcineurin inhibitors, renal insufficiency can interfere with vitamin D metabolism
- Median pre-transplant 25 hydroxy vitamin D 40 nmol per litre (16 ng/mL),
  - 70% of patients vitamin D insufficient.
  - (Joseph R. et al 2011 American Journal of Hematology 86:954 – 956)

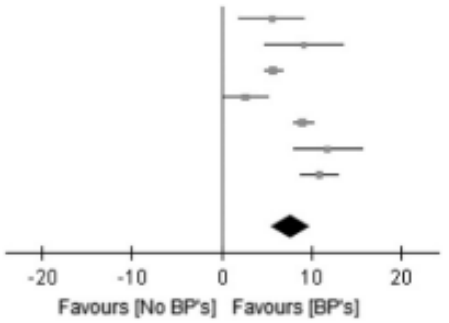
Bisphosphonates post HSCT

- Pamidronate stabilized spine BMD and attenuated femoral neck bone loss (5.1% versus 7.8%) in 99 HSCT patients at 12 months(Kananen K et al. JCEM 2005, 90:3877 – 3885)

Meta-analysis of bisphosphonate in HSCT

Table 3a. Mean differences comparing bisphosphonate with no bisphosphonate therapy for bone mineral density of the lumbar spine at 12 months

	Bisphosphonates			*No bisphosphonates*				*Mean difference*	*Mean difference*
Study or subgroup	*Mean*	*s.d.*	*Total*	*Mean*	*s.d.*	*Total*	*Weight*	*IV, Random, 95% CI*	*IV, Random, 95% CI*
Grigg *et al.*[19]	2.3	8	49	−3.3	8	30	12.2%	5.60 (1.97, 9.23)	
Hari *et al.*[23]	4.1	7	11	−5.14	3	19	10.7%	9.24 (4.89, 13.59)	
Jang *et al.*[25]	−0.7	1.7	16	−6.46	1.4	20	17.5%	5.76 (4.73, 6.79)	
Kananen *et al.*[27]	−0.25	1.5511	33	−2.9	7.3826	33	14.6%	2.65 (0.08, 5.22)	
Tauchmanova *et al.*[14]	5.7	1.7	15	−3.4	1.4	16	17.4%	9.10 (8.00, 10.20)	
Tauchmanova *et al.*[29]	9.8	7	15	−2.1	3	15	11.7%	11.90 (8.05, 15.75)	
Tauchmanova *et al.*[16]	7.2	5.2737	30	−3.7	1.9678	30	15.8%	10.90 (8.89, 12.91)	
Total (95% CI)			169			163	100.0%	7.77 (5.56, 9.98)	

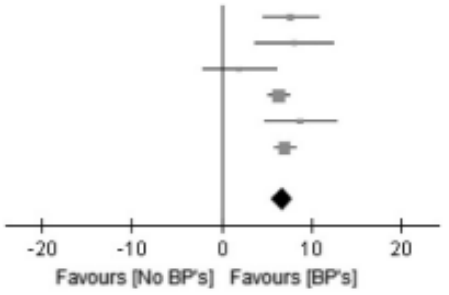


Abbreviation: CI = confidence interval. Test for overall effect: $Z = 6.90$ ($P < 0.00001$). Heterogeneity: $Tau^2 = 6.97$; $\chi^2 = 50.24$, d.f. = 6 ($P < 0.00001$); $I^2 = 88\%$.

Spine

Table 3b. Mean differences comparing bisphosphonate with no bisphosphonate therapy for bone mineral density of the femoral neck at 12 months

	Bisphosphonates			*No bisphosphonates*				*Mean difference*	*Mean difference*
Study or subgroup	*Mean*	*s.d.*	*Total*	*Mean*	*s.d.*	*Total*	*Weight*	*IV, Random, 95% CI*	*IV, Random, 95% CI*
Grigg *et al.*[19]	−2.8	6.9	49	−10.5	6.6	30	10.8%	7.70 (4.65, 10.75)	
Hari *et al.*[23]	2	7	11	−6.1	3.5	19	5.7%	8.10 (3.67, 12.53)	
Kananen *et al.*[27]	−4.2	6.6616	33	−6.2	9.8339	33	6.7%	2.00 (−2.05, 6.05)	
Tauchmanova *et al.*[14]	1.3	1.2	15	−5.1	2	16	34.7%	6.40 (5.25, 7.55)	
Tauchmanova *et al.*[29]	6.47	7	15	−2.3	3.5	15	7.0%	8.77 (4.81, 12.73)	
Tauchmanova *et al.*[16]	3.3	2.7557	30	−3.75	1.5911	30	35.0%	7.05 (5.91, 8.19)	
Total (95% CI)			153			143	100.0%	6.74 (5.62, 7.86)	



Abbreviation: CI = confidence interval. Heterogeneity: $Tau^2 = 0.59$; $\chi^2 = 7.63$, d.f. = 5 ($P = 0.18$); $I^2 = 34\%$. Test for overall effect: $Z = 11.79$ ($P < 0.00001$).

Femoral neck

Pundole et al Bone Marrow Transplantation (2017) 663 – 670

Pretransplant zoledronic acid randomized trial

- 80 HSCT patients receiving pretransplant ZOL with subsequent day 100, day 180, day 270 infusions according to glucocorticoid or >5% bone loss protocol
- Less bone loss compared to historical controls

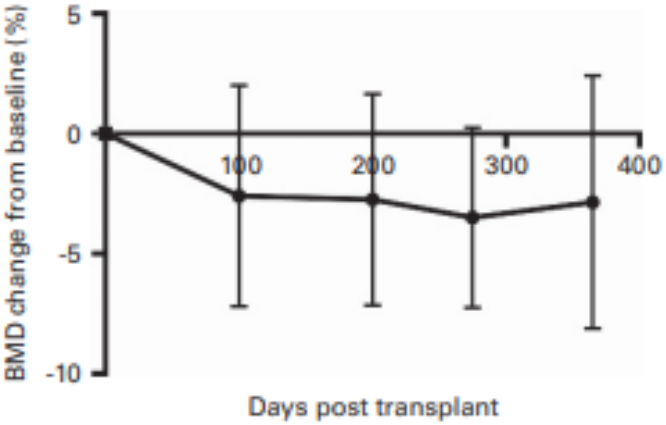
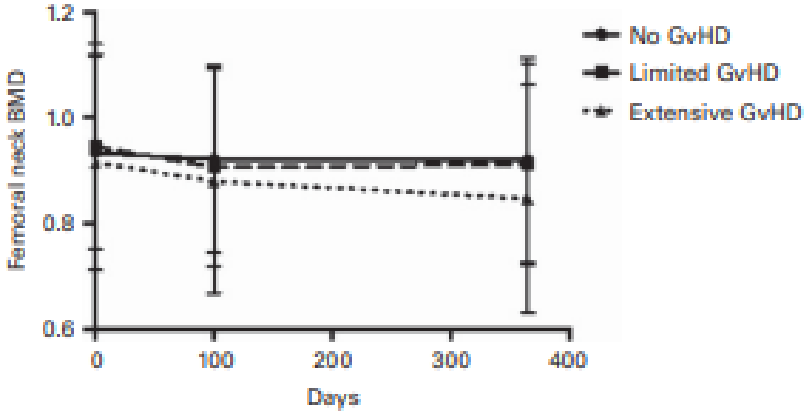


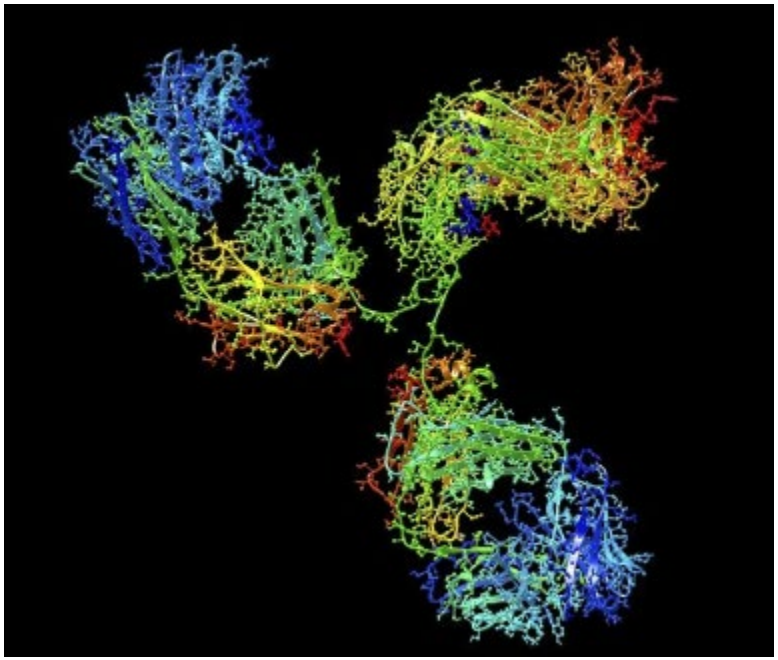
Figure 2. Post-transplant change in femoral neck bone mineral density. Values expressed as mean ± s.d.



Grigg A et al. Bone Marrow Transplantation 2017. 52, 1288 – 1293

Denosumab post HSCT

- 33 female HSCT patients (within 3 years of HSCT) with osteoporosis mean age 52.6 given denosumab 60 mg 6 monthly for 12 months
- Increased spine bone density 4.39%, femoral neck bone density 3.11% and total hip bone density 1.97%



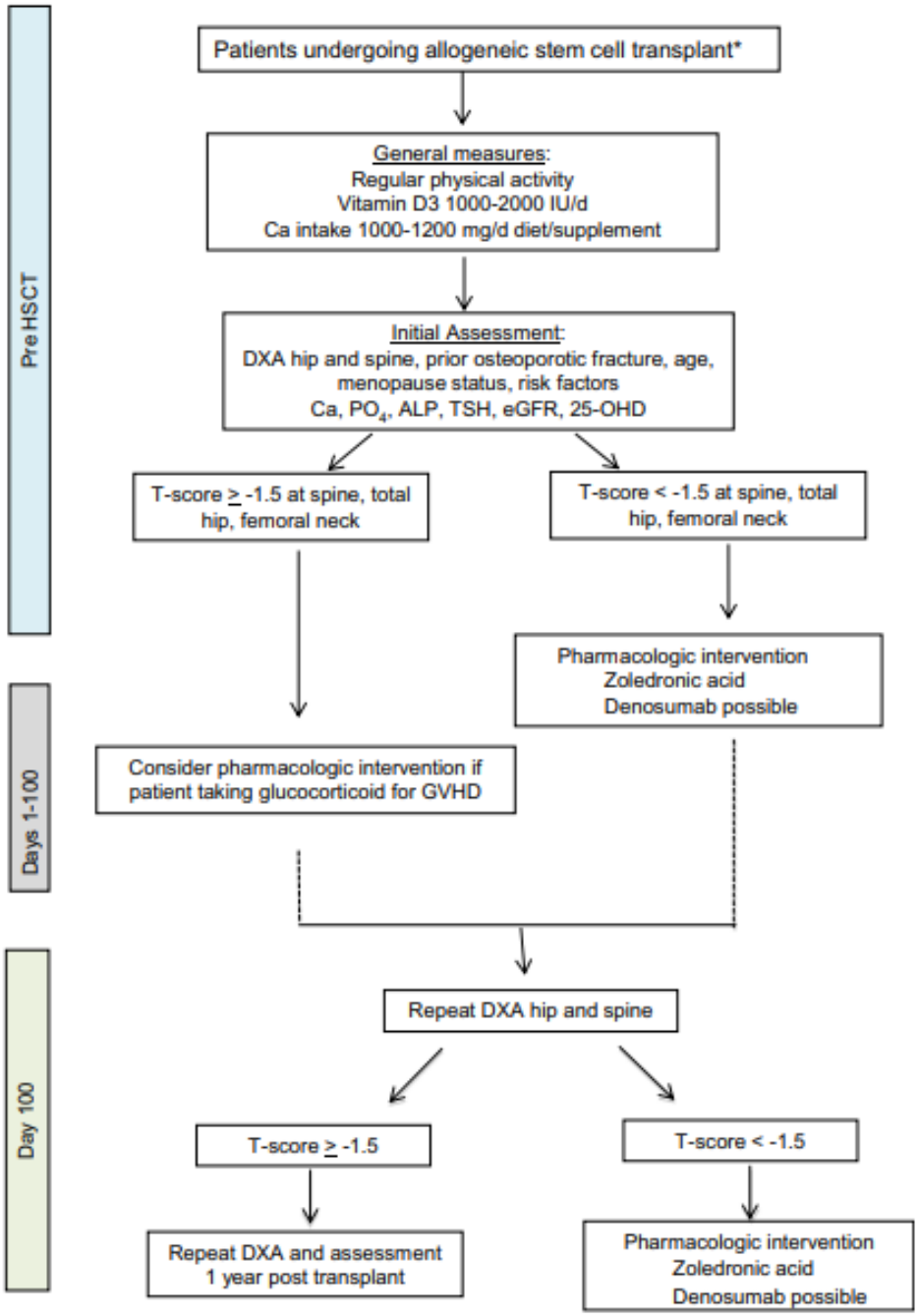
Jeong C et al. Int J Endo 2020 3410921

Other therapies

- Estrogen: trials have consistently shown an attenuation of posttransplant bone loss
- SERM: milder antiresorptive activity but no studies in HSCT patients
- PTH and derivatives: stimulation of bone resorption may release growth factors retained in bone.

  Teriparatide contraindicated in patients with prior skeletal irradiation or malignant disorders of the skeleton.
- Romosozumab has dual action stimulating bone formation and inhibiting resorption. Trials are required.

Management algorithm for HSCT patients



Kendler D et al. Osteoporos Int (2018) 29:2597–2610

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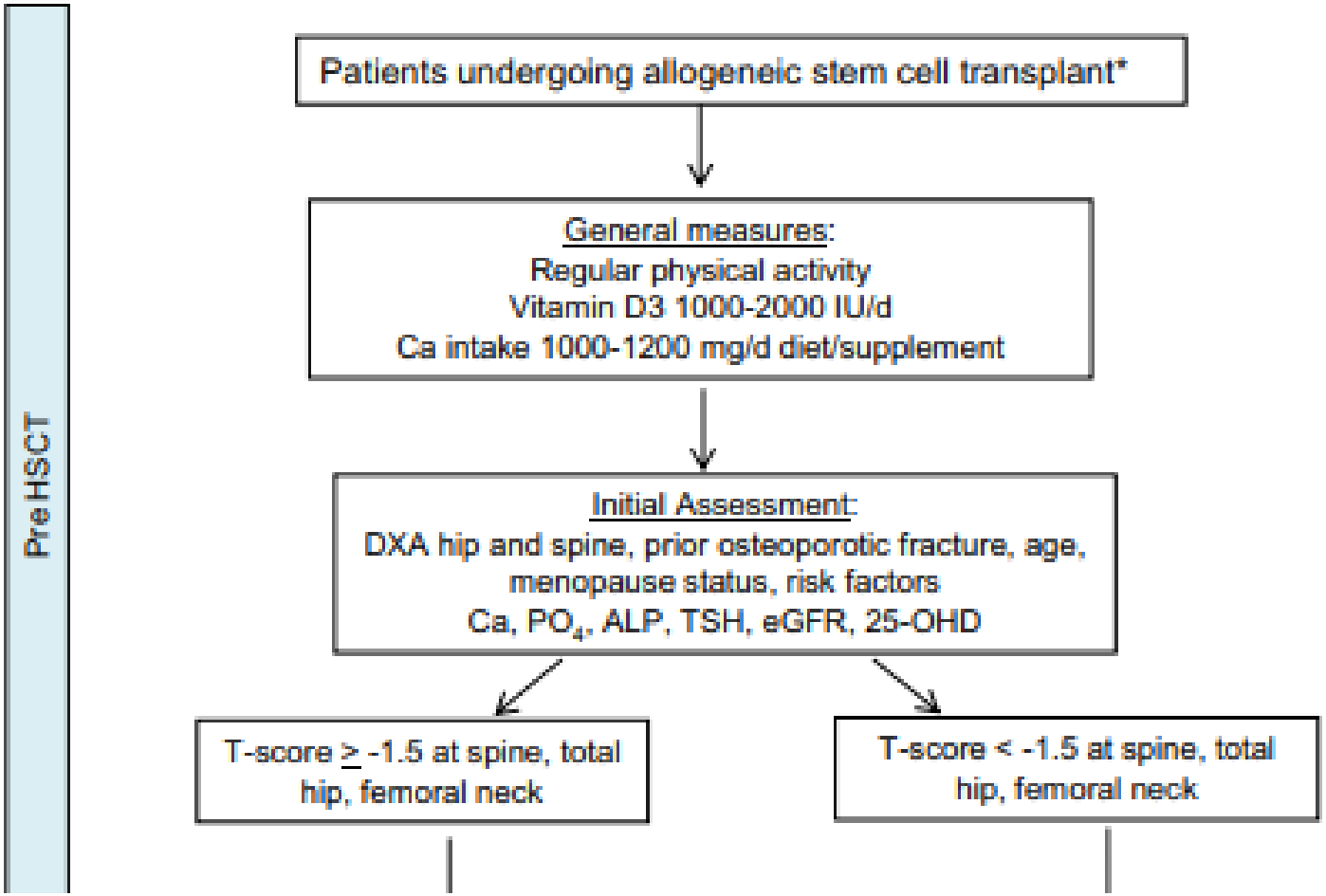

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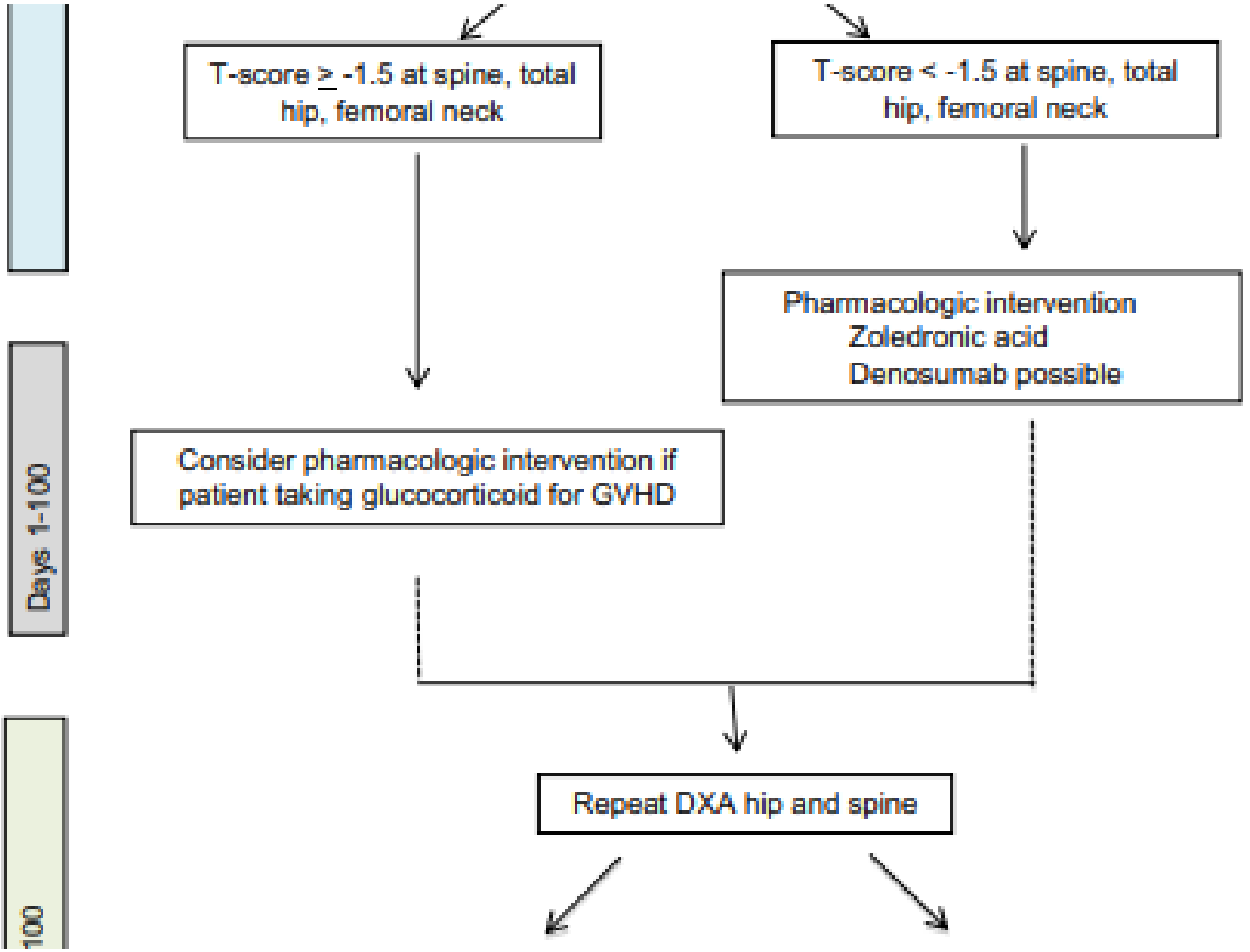

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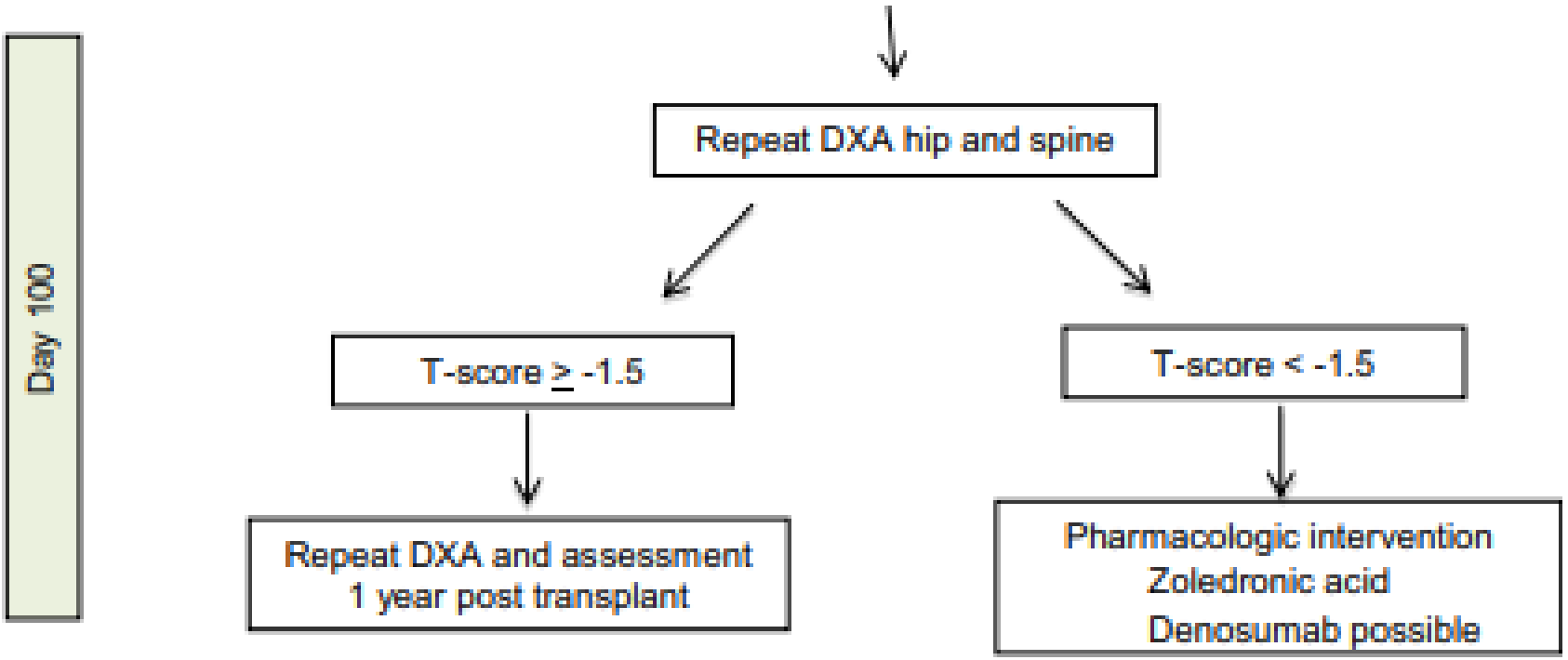

Kendler D et al. Osteoporos Int (2018) 29:2597–2610

Summary

- There is increased utilization of HSCT for a variety of hematologic malignancies
- Improvements in acute and chronic care leads to more long-term survivors.
- Bone health is one of the more significant morbidities post HSCT.
- Consistent and more aggressive monitoring and treatment of bone health in HSCT patients is required to improve long-term outcomes

Q&A

Prof David Kendler

THANK YOU

On behalf of IOF, we thank you for your participation in this webinar

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CSA Edition Webinar

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Our vision is a world without fragility fractures,
in which healthy mobility is a reality for all.

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