Bone Disease in Anorexia Nervosa

Yael Levy-Shraga

Pediatric Endcrinology Unit, The Edmond and Lily Safra Children's Hospital, Chaim Sheba Medical Center, Tel-Hashomer

Ophir megnazi

Osteoporosis in Children

2013 Pediatric Position Development Conference

Fracture Prediction and the Definition of Osteoporosis in Children and Adolescents: The ISCD 2013 Pediatric Official Positions

Nick Bishop,[*,1,2,a,b] *Paul Arundel,*[1,2,c] *Emma Clark,*[3,c] *Paul Dimitri,*[1,2,c] *Joshua Farr,*[4,c] *Graeme Jones,*[5,c] *Outi Makitie,*[6,c] *Craig F. Munns,*[7,c] *and Nick Shaw*[8,c]

2013 Pediatric Position Development Conference

Dual-Energy X-Ray Absorptiometry Interpretation and Reporting in Children and Adolescents: The Revised 2013 ISCD Pediatric Official Positions

Nicola J. Crabtree,[*,1,a] *Asma Arabi,*[2,b] *Laura K. Bachrach,*[3,b] *Mary Fewtrell,*[4,b] *Ghada El-Hajj Fuleihan,*[2,b] *Heidi H. Kecskemethy,*[5,b] *Maciej Jaworski,*[6,b] *and Catherine M. Gordon*[7,c]

1. Definition

Table 1. Summary of Official Pediatric Positions of 2013 International Society of Clinical Densitometry on the Skeletal Assessment in Children From Infancy to Adolescence.

Fracture Prediction and Definition of Osteoporosis

- The diagnosis of osteoporosis should not be made on the basis of densitometry alone.
- Osteoporosis is defined as:
  - One or more vertebral compression fractures in the absence of local disease or high energy trauma

OR

  - BMD Z-score ≤ -2.0 and clinically significant fracture history
    - Clinically Significant:
      - Two or more long bone fractures by age 10
      - Three or more long bone fractures at any age up to 19 years

2. Differential diagnosis

Table 1. Causes of Primary Osteoporosis

	Condition	Genetic mutation or enzyme deficiency	Mechanism	Inheritance
(1)	Osteogenesis imperfecta	COL1A1, COL1A2 and other non-collagen mutations	Quantitative or qualitative defect in collagen, post-translational modification	AR/AD
(2)	Bruck syndrome	PLOD2	Impaired collagen cross-linking	AR
(3)	Osteoporosis pseudoglioma syndrome	LRP5	Impaired Wnt signalling and osteoblast functioning	AR
(4)	Ehlers-Danlos syndrome	COL5A1, COL5A2, TNXB, and COL3A1	Defects in connective tissue	AD
(5)	Marfan syndrome	FBN1 and TGBR2	Defects in connective tissue	AD
(6)	Cleido-cranial dysplasia	RUNX2	Impaired bone formation	AD
(7)	Calvarial doughnut lesions	Unknown	Unknown	AD
(8)	Spondylo-ocular syndrome	Unknown	Unknown	AR
(9)	Hajdu-Cheney syndrome	NOTCH2	Abnormal bone remodelling	AD
(10)	Primary osteoporosis	LRP5 and LRP6	Impaired Wnt signalling and osteoblast functioning	AD
(11)	Idiopathic juvenile osteoporosis	Unknown	Unknown	Unknown

AR = Autosomal recessive; AD = autosomal dominant.

Table 2. Causes of secondary osteoporosis

Category	Aetiological causes
Reduced mobility	Prolonged immobilisation, cerebral palsy, Duchenne muscular dystrophy, spinal cord injury, and Rett syndrome
Pubertal delay	Chronic illness, primary hypogonadism, and induction by drugs
Chronic illnesses	Haematological: leukaemia and childhood cancers, thalassaemia, and post-bone marrow transplant Renal: chronic renal failure and post-renal transplant Gastrointestinal: inflammatory bowel disease, coeliac disease, and chronic liver disease Rheumatological: SLE and JIA Others: anorexia nervosa, cystic fibrosis, severe burns, and HIV
Endocrine causes	Hypogonadism, diabetes mellitus, hyperthyroidism, hyperprolactinaemia, and metabolic bone disease of prematurity
Drug-induced	Glucocorticoids, methotrexate, GnRH analogues, cyclosporine, L-thyroxine therapy, anticonvulsants, heparin, and radiotherapy
Inborn errors of metabolism	Glycogen storage disorder, lysinuric protein intolerance, galactosaemia, Gaucher disease, homocystinuria, and Menke's disease

SLE = Systemic lupus erythematosus; HIV = human immunodeficiency virus; GnRH = gonadotropin-releasing hormone.

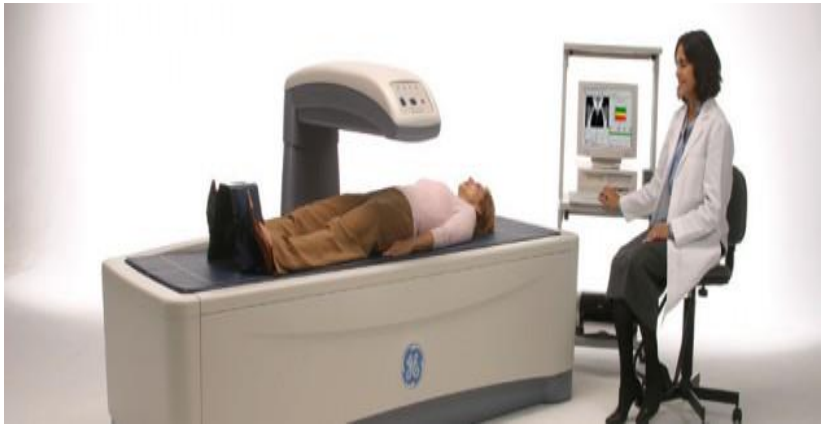
3. Assessment of bone density

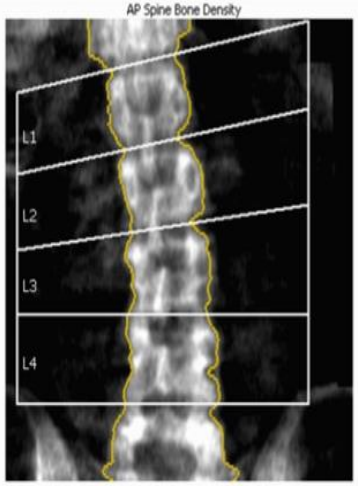
The preferred method of assessing bone health in clinical practice is DXA because of its precision, availability, reproducibility, speed, ease, low radiation exposure, relatively low cost and reference data. **BUT**…

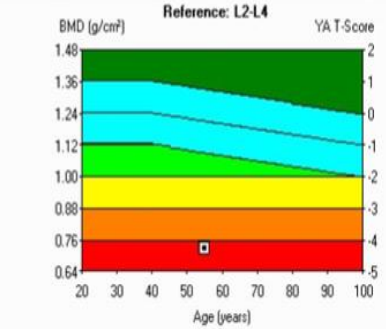
TABLE 1. Methods of assessing bone health in anorexia nervosa

μSv = microSievert	DXA	QCT	pQCT	HR – pQCT
Site Measured	Lumbar Spine Hip Total Body	Lumbar Spine Hip Distal Radius	Distal Radius Distal Tibia	Distal Radius Distal Tibia
Radiation Dose	5–6 μSv	30–7,000 μSv	<3 μSv	<3 μSv
BMD	Areal BMD	Volumetric BMD	Volumetric BMD	Volumetric BMD
Differentiates Cortical from Trabecular Bone	No	Yes	Yes	Yes
Bone Geometry	No	Yes	Yes	Yes
Bone Microstructure	No	No	No	Yes

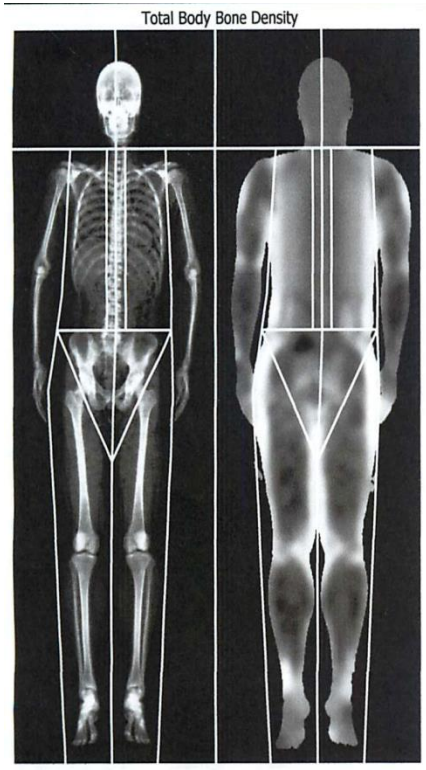
Misra at el, Int J Eat Disord 2016; 49:276–292

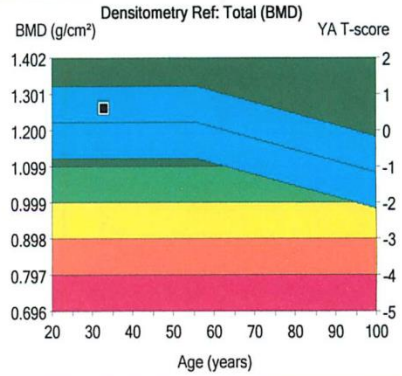




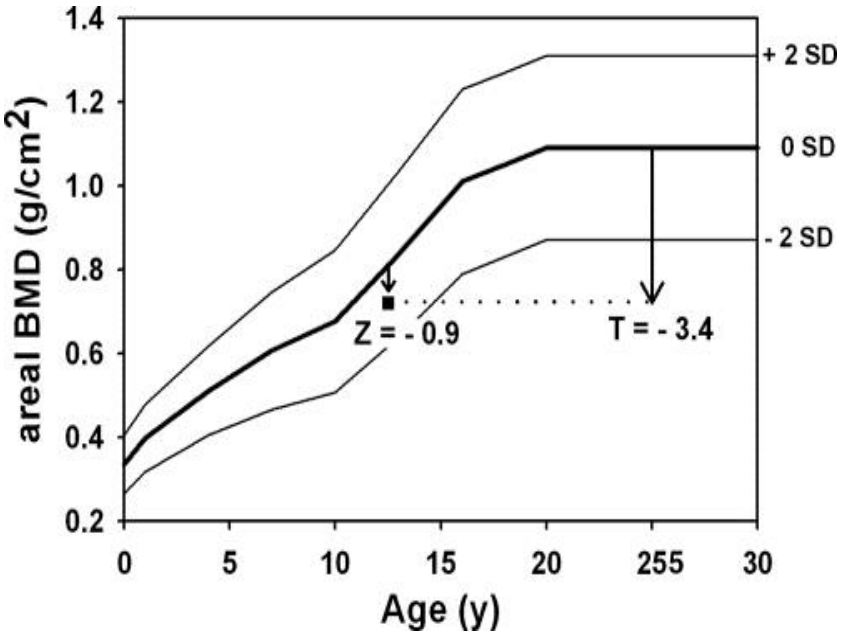


Region	BMD [1] (g/cm²)	Young-Adult [2] (%)	Young-Adult [2] T-Score	Age-Matched [3] (%)	Age-Matched [3] Z-Score
L1	0.670	58	-4.1	59	-3.9
L2	0.738	60	-4.2	61	-4.0
L3	0.726	59	-4.3	60	-4.1
L4	0.725	58	-4.3	60	-4.1
L2-L4	0.729	59	-4.3	60	-4.0



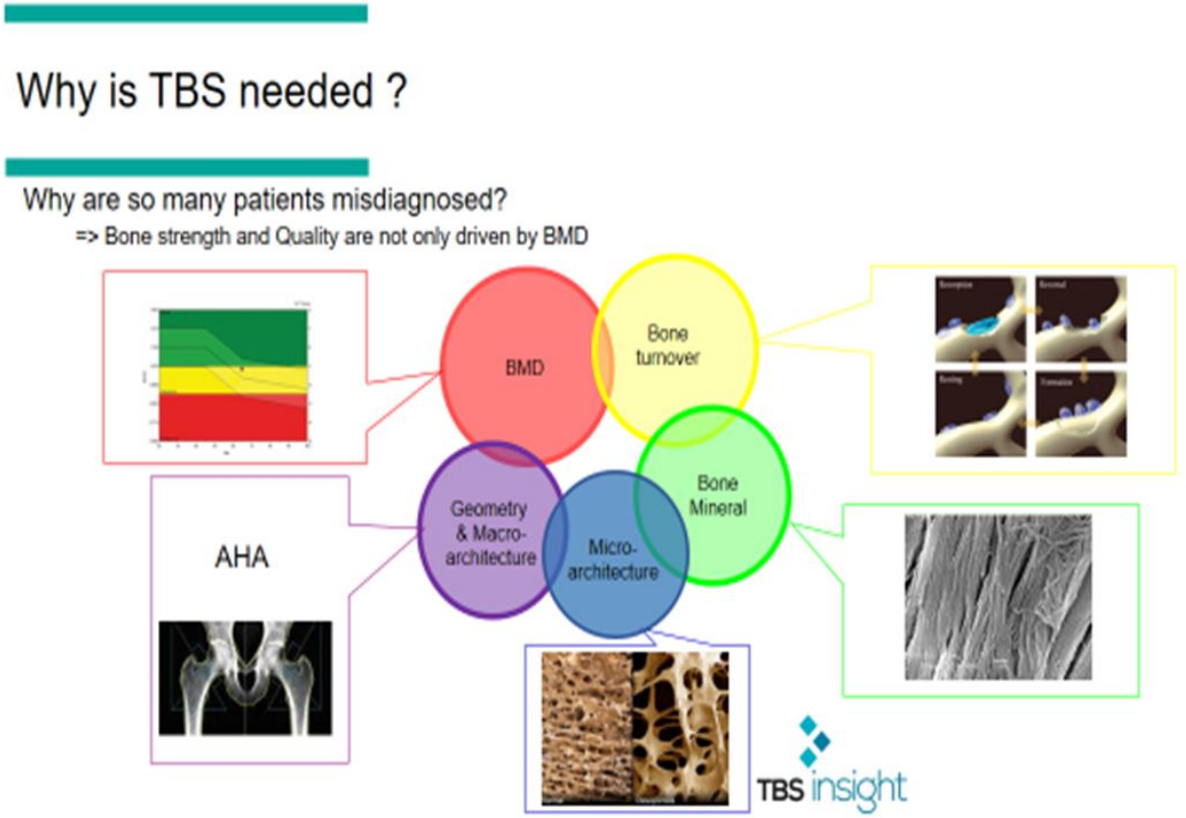


Region	BMD [1] (g/cm²)	Young-Adult [2] T-score	Age-Matched [3] Z-score
Head	2.002	-	-
Arms	1.064	-	-
Legs	1.333	-	-
Trunk	1.075	-	-
Ribs	0.998	-	-
Pelvis	1.076	-	-
Spine	1.199	-	-
Total	1.264	0.6	0.4



4. Bone strength

- Many individuals with fragility fractures have BMD above the osteoporosis range. BMD explains only 60-80% of bone strength.



WHAT IS TBS?

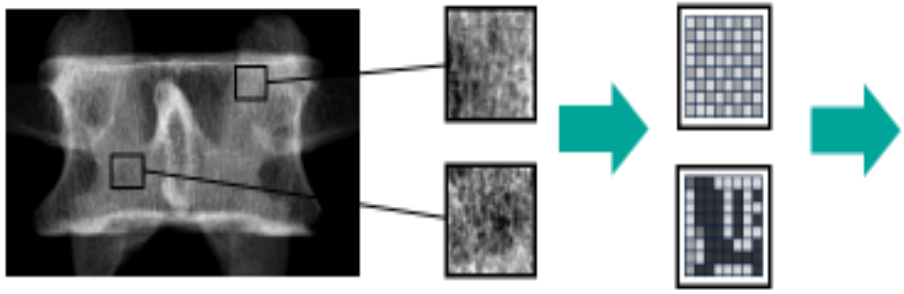
- TBS stands for Trabecular Bone Score.
- It is not a direct measurement but a texture analysis, related to bone microarchitecture.
- It is computed from data contained in **AP Spine** DXA scan **only**.
- TBS iNsight uses patient data (age, gender, weight, height) and scan data to compute TBS.

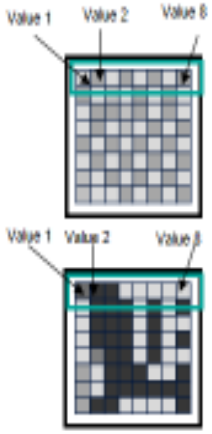
WHAT IS TBS ?

- **TBS** algorithm explores the spatial variability of the pixels brightness in the image. It subtracts neighboring pixels brightness and squares the result.

Image of the projection of a vertebra in 2D

Interpretation of bone picture for a DXA system



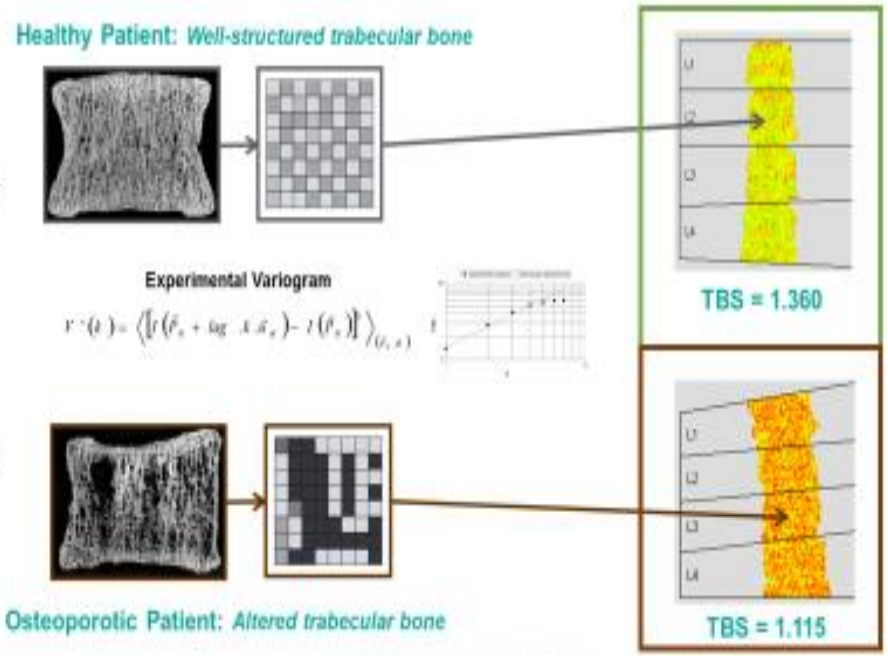


TBS calculation for 1 line: sum of the brightness differences

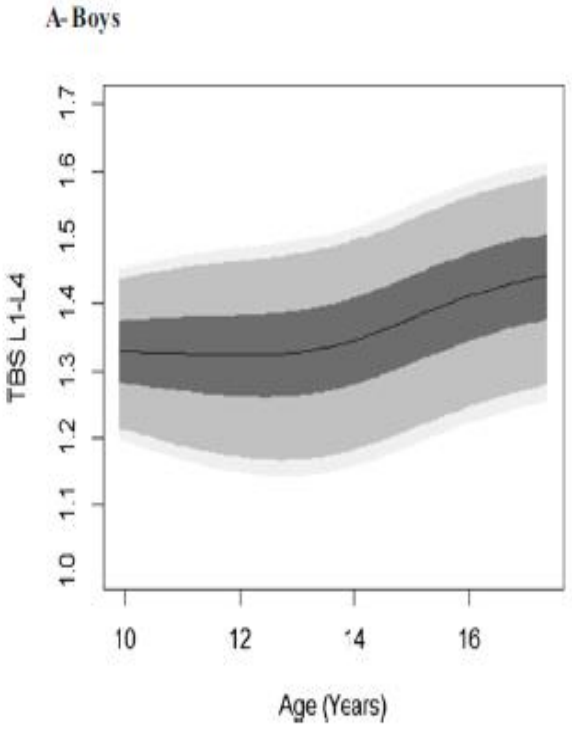
$(\text{value } 2 - \text{value } 1)^2 + \ldots + (\text{value } 8 - \text{value } 7)^2$

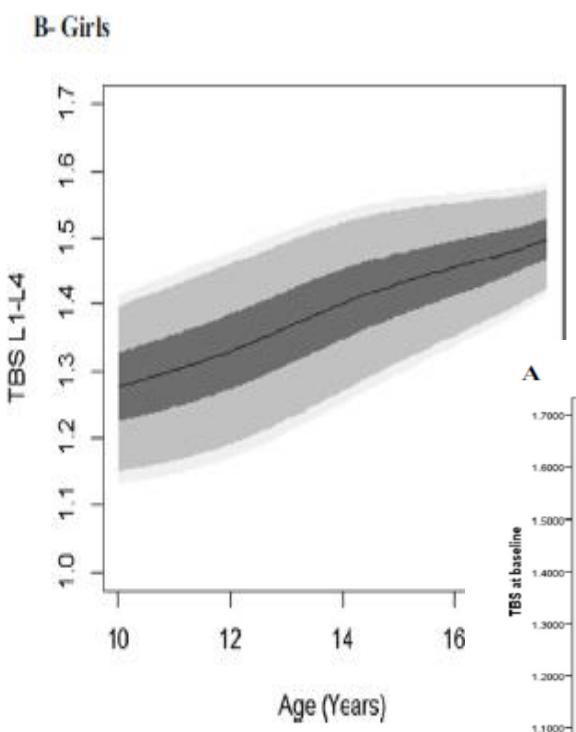
WHAT IS TBS?

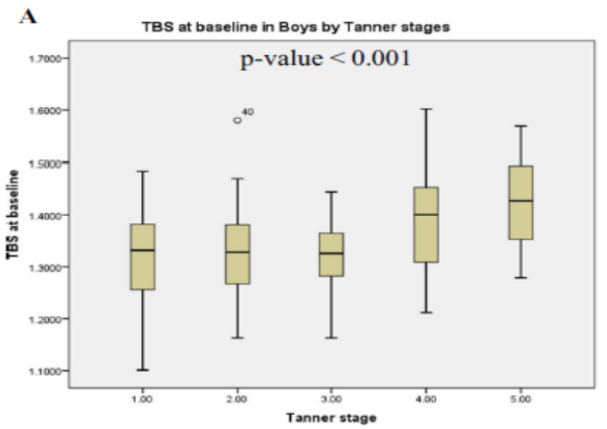
An **healthy patient** with good microarchitectural texture will have **a Higher TBS** value **than** an **osteoporotic patient**

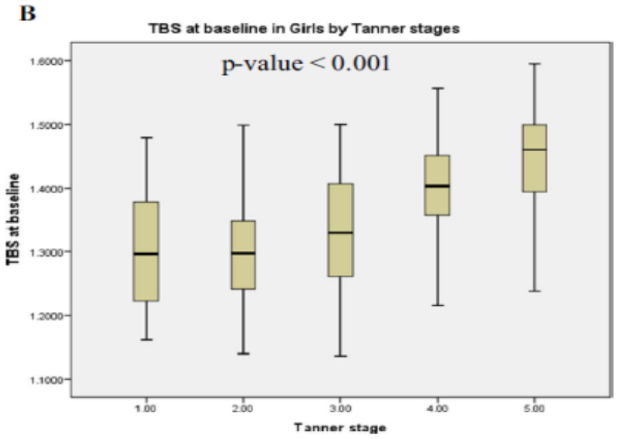


Pothuaud et al. Bone 2008;42:775-87. Hans et al. JCD 2011. Winzenrieth et al. JCD. 2012









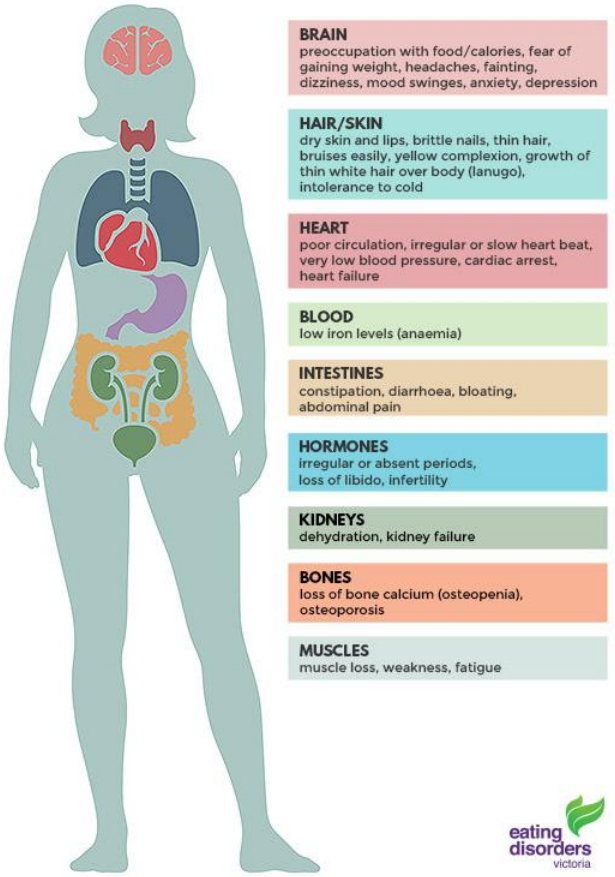
Shawwa et al, Osteoporos Int (2016) 27:703–710

5. Anorexia nervosa

Anorexia nervosa (AN) is an eating disorder characterized by low body weight/body mass index (BMI) secondary to a fear of weight gain and distorted body image.

AN is associated with numerous medical complications that are directly attributable to weight loss and malnutrition and affect the major organ systems

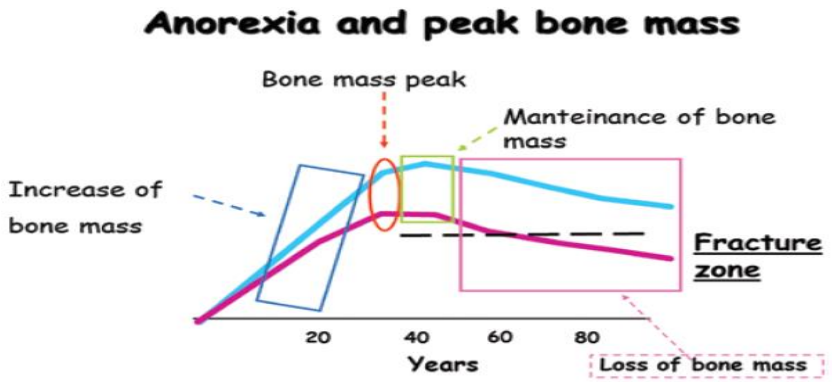
hypotension, bradycardia hypothermia, amenorrhea, qt prolongation, Gastroparesis and endocrine abnormalities affecting the bone .



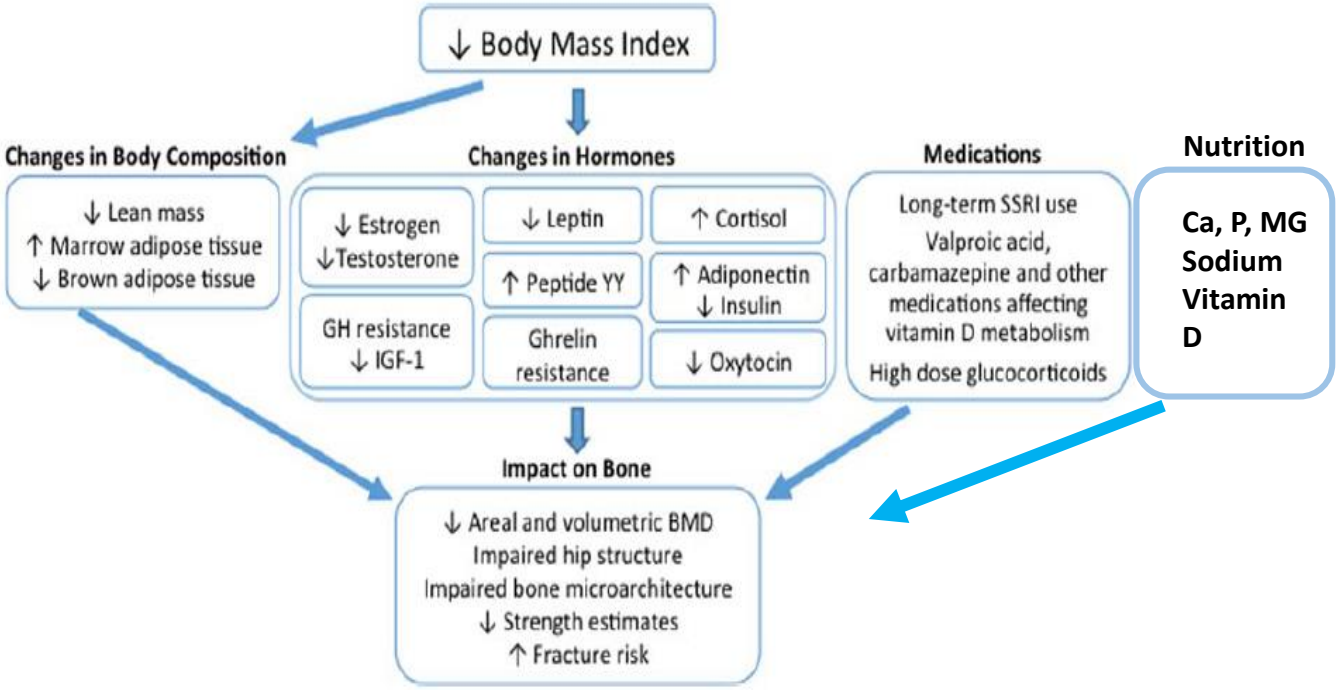
6. The Impact of AN on bone

- The peak age of onset of AN is during adolescence, the period during which 40–60% of peak bone mass is normally accrued.
- Failure to achieve peak bone mass during adolescence secondary to a disease like AN can have life-long implications for bone health.

Greco at el,
Horm Mol Biol Clin Invest 2016; 28(3): 121–132



7. Pathogenesis of impaired bone metabolism in AN



Misra at el, Int J Eat Disord 2016; 49:276–292
Zuckerman-Levin N, Hochberg Z at el, Obesity Reviews (2014) 15, 215–223

8.Anorexia nervosa and BMD

- Multiple studies have demonstrated reductions in BMD in AN, both in adolescents and in adults.
- Abnormal bone density and increased risk for fractures has been reported in 85% of adult women with active AN.
- Furthermore, studies have demonstrated that patients with a past history of AN have a 2 to threefold increased risk of bone fracture.
- Both cortical and trabecular bone sites are affected but there is preferential loss of trabecular bone which is more metabolically active.

8. Anorexia nervosa and BMD (cont.)

- Adults with AN lose bone mass, increased bone resorption markers whereas adolescents with AN show lower levels of bone formation markers compared with healthy control. This finding is suggestive of a reduced state of bone turnover in adolescents.
- Studies evaluating adults who have recovered from adolescent-onset AN, demonstrate persistent deficits in BMD up to 20 years after full recovery from the eating disorder and a 2 to threefold increased risk of bone fracture.

Misra at el, Int J Eat Disord 2016; 49:276–292

4. Treatment

- **Weight gain** Weight restoration is central to all treatment of AN. Weight gain to >90% of expected body weight is associated with resumption of menses, stabilization of hormones and an increase in BMD.
- **Calcium and vitamin D supplementation** - Calcium and vitamin D supplementation **alone** are not considered to be sufficient to increase bone density in AN, but should be optimized in all patients.
- **Estrogen replacement** - Oral contraceptives are not effective in increasing bone density measures in adolescents or adults with AN likely because of the IGF-1 lowering effects of ethinyl estradiol in oral contraceptives through hepatic first pass. In contrast, transdermal 17 b estradiol administration has been demonstrated to significantly increase spine and hip bone density in adolescents with AN.

4. Treatment (cont.)

- **RhIGF-1** given twice daily as SC injections, with an oral estrogen–progesterone combination pill has been shown to increase spine and hip bone density in adult women with AN over 9 months (compared to a group that received neither).
- **Testosterone / DHEA treatment** – not effective.
- **Bisphosphonates** have been shown to increase bone density in adult women with AN; controversial benefit in adolescent girls. These drugs are not recommended for women of reproductive age at this time due to their long half-life, and potential AE on the fetus.
- **Teriparatide (PTH)** One small study in older women with AN demonstrated that TPT use (20mg daily SC) led to significant increases in spine bone density. The 'black box' warning for TPT in the context of an increased risk of osteosarcoma limits the use of this agent as a treatment option for adolescents.

5. Literature review

- To date, evidence suggests that the safest and most effective strategy to improve bone health in adolescents with AN is normalization of weight with restoration of menses.
- However, this process is slow, and improvements do not become detectable until *more then 1 year* follow-up.
- There are not enough longitudinal studies that can demonstrate the long term process of bone recovery.
- TBS measuring isn't well established.

6. Our study

- **Objective:** To explore the association between longitudinal changes in bone density and the severity of the disease in adolescence girls with AN.
- **Method:**

1. A retrospective longitudinal study including 50 girls aged 10-19 with AN who had more then one BMD measurements available will be included in the study.

2. Demographic and clinical data, including age, anthropometric measurements, laboratory data, drugs in use and comorbidities, will be obtained from the patients' medical charts.

3. Statistical analysis.

7.My part

Data gathering
Into Excel charts

Statistical analysis

Research on the topic

Last Name	First Name	Patient ID	Birth Date	DATE_DIAG	age_diag	date_menarche	date_amenorea ha	TANNER1	MENAST1	admission1	discharge1	Hospital-duration (m)	DXA1 Date	Age_dxa1	dis_duration 1
BEN--CNAAN	YAEL	301148649	29/10/1987	01/12/2002	15.10	29/05/1999	01/03/2003	3	2	16/09/2003	11/03/2004	5.82	12/08/2004	16.80	1.70

Height at Exam1	HT-SDS1	Weight at Exam1	WT-SDS1	BMI1	BMI-SDS1	L1-L4 BMD1	L1-L4 BMC1	L1 Area1	L2 Area1	L3 Area1	L4 Area1	L1-L4 Z-Score1	BMAD1	bmad1 z score	TBS1	TBLH _BMD1
166.0	0.5	54.0	0.1-	19.6	0.4-	0.91	49.41	11.54	12	14.37	16.38	2.1-	0.2451644	2.82294-	1.336	0.951

p1	ca1	ALP1	VIT D1	1FT3	1TF4	1TSH	1ESTROGE N	LH1	FSH1	CORTISOL1	PROLACTI N1	co-morbidity1	co-morbidity1
3.6	10.3	71		1	21.3	3.06	20	0	1.3				