INSIGHTS OF PEAK BONE MASS

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Keywords: *peak bone mass, vitamin D, calcium, anorexia nervosa, serotonin*

Abstract: *Peak Bone Mass (PBM) represents the maximum bone capital throughout the lifespan displaying a multi-factorial panel. Lifestyle elements include nutrients (as vitamin D intake), breastfeeding, physical exercise, weight control. Genetic factors underline connexins, Wnt signal transduction of skeletal development; adipose fat-bone crosstalk via leptin, serotonin; timing of puberty through kisspeptin, dopamine regulation. Hormones and associated disorders refer to endogenous/exogenous persistent hypercortisolemia, untreated hypogonadism (including anorexia nervosa and Turner syndrome), type 1 diabetes mellitus etc. Chronic health conditions in cancer/transplantation survivors during childhood with definitely impair the peak skeletal achievement. Depression and specific medication are recently found as risk factors for bone loss considering serotonin effect against bone formation, vitamin D deficiency and hypercorticism. Achieving optimal PBM is the best way to protect against future osteoporosis and subsequent fractures. Knowing the constellation of neuroendocrine, biological and biochemical pathways will help the current clinician to prevent and treat any potential skeleton damage.*

INTRODUCTION

Peak Bone Mass (PBM) represents the maximum bone capital achieved throughout the lifespan.(1,2) The correlated bone strength and further decline of bone mass will involve many disorders and the most common condition is primary osteoporosis which associates a dramatic medical, economic and social burden.(3,4) Thus, PBM and physiological bone loss will influence the skeleton properties especially in menopausal women or elderly like bone density and qualitative features (as microarchitecture, trabecular geometry etc).(5,6) All these combined with the risk of fall will eventually be connected with fragility fractures.(5,6)

PURPOSE

Our objective is to analyze PBM data from literature.

MATERIALS AND METHODS

This is a PBM review from a neuroskeletal and endocrine point of view. As tool of research we used PubMed.

RESULTS

PBM is connected with multiple factors.

1. Lifestyle factors influence 30-60% of PBM.(7) This represents the most important aspect from a practical point of view since their optimization improves PBM.(8) For instance, we mention the type and amount of nutrients, history of breastfeeding after birth, physical exercise (especially during puberty) and weight/ body mass index (BMI) control.(9) The major positive elements are related to vitamin D and calcium intake, food formulas based on fibers, fruits and vegetables.(10) The negative effects are related to caffeinated beverages, cola, drugs, smoking.(11) BMAS study has nicely showed that peak skeletal growth and mass is closely related to a diet program in adolescents.(12)
2. Genetic factors & elements of skeletal neuroendocrinology: PBM is extensively programmed by genes legacy.(13) The classical Bone Mineral Density (BMD) correlation within mother - daughter pairs is modulated by BMI as showed the KNHANES V cohort.(14) Connexins (especially gap junction protein connexin43), as well as Wnt pathway is actively involved in signal transduction of skeletal development and balance.(15) Novel genes SNPs (single nucleotide polymorphisms) were described related to peak bone mineral density in some populations, for instance: rs1298989 SNP of CATSPERB gene and rs3762397 SNP of NR5A2.(16) Adipose tissue regulates the bone status during lifespan based on *in vitro* and *in vivo* experiments and studies.(17) One of the mediators is adipokine leptin acting via opposite pathways: direct osteoblast stimulation and indirect central (hypothalamic) suppression of bone formation.(18) Timing of puberty and estrogen/testosterone balance as well as connected neurotransmitter modulation (including kisspeptin and dopamine) affects also the maturation of the skeleton and its peak of density and strength.(19,20) Vitamin D receptor polymorphism, although intensively studied, did not point out any consistent association with PBM based on most observations.(21,22)
3. Hormonal factors & associated disorders during childhood and puberty as hypogonadism, use of oral contraceptives, anomalies of cortisol levels, etc. are a complex and challenging panel.(23) Raine cohort showed that healthy male subjects aged of 20 years (but not females) associating higher values of circulating cortisol

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Article received on 26.02.2016 and accepted for publication on 27.05.2016
ACTA MEDICA TRANSILVANICA June 2016;21(2):82-85

(which is correlated with positive stress tests) involves a decreased total body bone mass content.(24) A 4-year longitudinal study on females aged of 18 years showed that BMD improvement was found for spine at half of subjects while at hip at third of them: lumbar BMD gain is positively correlated with menstrual cycle frequency and it is disturbed in patients with eating disorders.(25) Hip BMD decreases with weight loss when compare with stationary or increased weight.(25) In youth with type 1 diabetes mellitus impaired bone mass is correlated with increased s-RANKL and osteoprotegerin and potentially with the inhibiting role of sclerostin.(26) Anorexia nervosa is well established as risk factor acting via hypothalamic amenorrhea, low BMI, malnutrition, hypovitaminosis D, etc.(27,28) A growth-hormone resistance has been described with decreased levels of IGF-1 and high ghrelin and peptide Y.(29) Weight gain directly improves BMD but this is a slow process.(30) Fail to correct BMI will also impair the skeleton quality and the final height.(31) Untreated persistent hypogonadism of other causes (and delayed puberty) also impact BMD of youth and adults despite the evidence that not only sexual steroids count for the bone.(32) The prolonged exposure to thyroid hormones excess may disturb the skeleton mass despite a transitory advance of height and bone age.(33) Turner syndrome associates lack of estrogens and hypovitaminosis D which may contribute to BMD anomalies as well as inherited defects correlated with SHOX gene (also responsible for dwarfism).(34)

4. Chronic health conditions as cancer during childhood with definitely impair the peak skeletal achievement during adolescence, correlated with chemotherapy, glucocorticoid therapy, radiotherapy etc.(35) Depression and associating co-morbidities as well as specific medication (like Selective Serotonin Reuptake Inhibitors) are new entries for the osteoporosis list.(36,37) Modern days associate a decreased onset age of depression toward pubertal years and disturbances of peak skeleton achievement should be taken into account through serotonin effect against bone formation, persistent hypercortisolemia, vitamin D deficiency etc.(36,37)

DISCUSSIONS

Further studies are necessary to point out the exact role of each etiological component. Moreover, the tools we currently have to assess the peak bone mass are not routinely recommended for teenagers. The use of central Dual-Energy X-Ray Absorptiometry (DXA) is limited to age, height matched for reference population and to the extrapolation of Z-score.(38) Traditional methods as quantitative ultrasound have the advantage of non-irradiation.(39) A new device derived from lumbar DXA namely Trabecular Bone Score (TBS) is extensively spreading its use including the adolescent population and promising data are yet to be revealed.(40) However, this method still needs validation from different large populations all over the world while there are still numerous centers without TBS software on DXA machine.(41,42) Other tools which may obtain data of bone microarchitecture are useful only for studies and clinical experiments, for instance High Resolution-peripheral Quantitative Computed Tomography (HR-pQCT).(43) The endocrine and rheumatologic panel of investigations related to PBM is circumstantial in cases with potential causes of low PBM, respective risk of fractures. The calcium-phosphorus metabolism involves the assessment of total and ionic calculated serum calcium and phosphorus, 25-hydroxyvitamin D as best predictor of vitamin D deficiency, as well as intact parathyroid hormone in selected cases.(44,45) Glucose profile and glycaeted hemoglobin values are necessary in type 1 diabetes mellitus and Cushing's syndrome (CS).(46) Cases with suspected endogen persistent hypercortisolemia should be checked at least by performing baseline Adrenocorticotropic Hormone (ACTH) assay and Dexamethasone suppression test.(47,48) After the removal of CS cause long term follow-up of bone, metabolic and cardiovascular parameters is necessary.(49,50) The algorithm of actively seeking for PBM deterioration and secondary osteoporosis young population needs to be apply in cancer survivors, in patients receiving transplantation, in subjects with long term glucocorticoid therapy for different conditions, in those who were treated for a prolonged period of time with anti-depressants and/or anti-psychotics, anti-epileptics.(51,52,53)

CONCLUSIONS

Achieving optimal peak bone mass at a young age is the best way to protect against future osteoporosis and subsequent fractures. Knowing the constellation of neuroendocrine, endocrine and biochemical pathways will help the current clinician to prevent and treat any potential skeleton damage.

Acknowledgment:

This work is partially supported by "Carol Davila" Univeristy of Medicine and Pharmacy project 33878/11.11.2014/Young researchers.

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