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An Ounce of Prevention: Securing Bone Health in Adolescence

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One of the Founding Fathers of the United States, Benjamin Franklin, wrote, “An ounce of prevention is worth a pound of cure.” A similar case is made by Dr. Dorn et al. in their article “Longitudinal impact of substance use and depressive symptoms on bone accrual among girls 11–19 years” [1]. The findings of this study are remarkable for several reasons (Figure 1). In a cohort of 262 adolescent girls observed throughout their development, the authors assessed to what extent smoking and depressive and anxiety symptoms modified the trajectory of bone accrual. Both factors affected spine and femur bone mineral density (BMD). Their study raises the following question: In addition to choosing the right parents and ensuring a proper amount of dietary calcium and vitamin D, what else can be done to guarantee that the genetic potential is exploited to its fullest in terms of bone mass?

The amount of bone mass at any given time is the net result of two processes, bone formation and resorption. In the course of life, bone goes through an incessant process of remodeling, a process that accelerates and decelerates at critical biological times of life. In the years after menopause, bone resorption exceeds bone formation because of a precipitous fall in estrogen levels, resulting in a net loss of bone mass of approximately 2%–3%/year. This amount may seem trivial, but it is not. Alendronate, the first bisphosphonate to be approved for the treatment of vertebral fractures in postmenopausal women, increased BMD by 2% at the spine compared with placebo, as demonstrated in the FIT Trial, and yet that apparently small increase cut the number of vertebral fractures by 50% [2]. Keeping in mind that the relationship between BMD and fracture risk is nonlinear and that small changes in BMD can translate into bigger changes in fracture rate, it is easier to appreciate the importance of the fact that 50% of BMD is accrued during adolescence. The study by Dorn et al. used dual-energy x-ray absorptiometry (DXA) to determine BMD, which is an excellent surrogate measure for osteoporotic fractures, because it accounts for two thirds of the variability in fracture rate. It may be considered akin to or better than to low-density lipoprotein as a marker for cardiovascular disease risk. Nevertheless, no surrogate end point is perfect: BMD leaves one third of the variability in fractures unaccounted for. The intrinsic limitations of DXA measurements are compounded by the fact that the subjects were adolescents. It is known that in youth, bone mineral content and BMD measurements by DXA are affected by height. How to adjust bone mineral content or BMD for short or tall

stature remains controversial [3]. Innovative technological research should thus be directed at developing noninvasive methods to assess bone fragility in vivo.

One third of subjects were either overweight or obese, as indicated by the body mass index Z-scores. Body mass index is a proxy of adiposity, not a true measurement. It would thus have been preferable to report body composition as well. Measurements of adiposity by DXA are easier than measurements of BMD because the need (and associated time) to exactly position a subject is less pressing when determining body composition. The relationship between BMD and weight is complex. Weight represents a stimulus to the osteoblast based on the piezoelectric effect; a lack of it—for example in zero gravity during space flight or during prolonged bedrest—causes bone loss. However, the simple assumption that heavier people must have stronger bones is compounded by several factors. The effect of increased weight on the osteoblast is counterbalanced by the effects of the fat-derived hormone leptin. Based on elegant work by Karsenty and Ferron [4], there is evidence that leptin has an inhibitory effect on the osteoblast that is centrally mediated by the sympathetic nervous system. Whether these findings can be translated from mice to men, or more specifically to women, is still not known [4].

One third of the subjects were African-American girls. Conducting subgroup analyses based on race would have been interesting, because black girls have earlier menarche, and black women have higher BMD [5]. Other factors, such as lower prevalence of smoking and lower socioeconomic status, are more common in African-Americans and may influence BMD [6]. No information on the socioeconomic status was provided in the article; of note, food insecurity, which is related to socioeconomic status, has been associated with lower bone mass in adolescent boys but not in girls [7].

Approximately 15% of girls reported smoking daily, less than expected based on a reported prevalence of 28% for 12th-grade girls [8]. Smoking was assessed with a validated questionnaire, whose use, albeit necessary, is inevitably marred by under-reporting and recollection bias [9]. Nevertheless, as girls grew, smoking was associated with a deceleration in bone formation. This may be the result of nicotine's dual negative effect on bone formation and resorption. Of interest, smoking in girls is associated with depressive symptoms [10]. Molecular pathways have recently been discovered that may explain a link between anxiety, memory function, mood disorders, and bone metabolism: for example, via the Wnt signaling pathway [11,12].

Depressive and anxiety symptoms were assessed with the Children's Depression Inventory and the Spielberger State-Trait Anxiety Inventory, respectively, two widely used standardized questionnaires. The fact that in the article the scores were reported as T-scores, rather than raw scores, impedes comparison with other studies. Osteoporosis is a disease of older age, but its roots start during adolescence, a time of great changes and psychological turmoil. Some of this suffering is inevitable and may even be a beneficial part of growing up. Our society is equipped with an unprecedented pharmacological, including psychopharmacological, armamentarium of what may have become cosmetic psychopharmacology. Because of this tremendous potential to modulate emotions, we may blur or even obliterate the pragmatically thin—but in principle, thick—line between normal

and excessive, protracted suffering. An example is the ongoing debate between normal and complicated grief and the importance of not overdiagnosing or underdiagnosing it [13]. What may tip the balance in the case of depression and anxiety in children regarding when to intervene may be the notion that the “suffering of the soul” might leave permanent scars in the body. In this case the “scar” is not negligible: An increase of 1 standard deviation (10 points) in depressive symptoms sets back bone development by 1 year. Even if this is not specifically advocated by Dorn et al. [1] in their article, some may be tempted to use these results to make a stronger case for an intervention.

But which type of intervention? Our species has been effective, but not necessarily good, at modifying our environment rather than adapting to it. Perhaps an effort should be made in the opposite direction: The environment in which our children grow up may be molded to become not so demanding and stressful, so that the depressive and anxiety scores of adolescents may remain in a “happier” range. It is worth mentioning that some antidepressant medications, such as the selective serotonin reuptake inhibitors and the tricyclics increase fracture risk by as much as twofold [14]. Their effect is rapid, reaching a peak within 1 month for tricyclics and 8 months for selective serotonin reuptake inhibitors. Many adolescent girls need or will need treatment for overweight and obesity and associated complications such as diabetes. Again, pharmacological treatment may have unwanted effects on bone: hypoglycemic drugs such as thiazolidinediones, including rosiglitazone and pioglitazone, increase fracture risk in postmenopausal women, with an odds ratio of a 1.71 (range, 1.13–2.58) [15].

Whereas DXA provides an instantaneous picture of BMD, biochemical markers of bone turnover and bone resorption inform us about how much bone is created, similar to how much money is deposited in our bank account, versus how much money is withdrawn. Banking operations usually take place, or used to take place before online banking, during the day, whereas bone formation is most active during the night. More research is needed to better understand the mechanisms mediating bone accrual. As an example: Do sleep disturbances, whether resulting from depressive symptoms or simply from voluntary sleep deprivation, impair bone accrual? One factor known to arrest bone formation, as indicated by bone formation markers, is fasting; it would be important to know the effects of regular meal schedules, in addition, perhaps, to regular and restorative sleep hours, a practice known to have many added benefits. To make things more challenging, although the biological need for sleep of adolescents is at least 10 hours, the chronotype is switching toward eveningness by as much as 2 hours, because there are so many friends to keep up with on Facebook and other social media, Red Bull and other super-caFFEinated drinks provide the stamina when most needed at night, and ... high school classes start at 7:30.

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Figure 1.

The Circle of "Bone Evil": How genetic and environmental factors conjure to prevent attainment of full bone mass in adolescent girls. Some of the factors contributing to bone health (center) are depicted. Genetic and environmental factors, including proper nutrition, as well as the presence of a certain genetic setup, have a major interactive role. Smoking and drinking habits, in connection with depressive and anxiety symptoms, may impair the achievement of optimal bone mass. The importance of creating an environment conducive to handle and limit psychological stress is depicted, as is the importance of enforcing a healthy schedule with regular mealtime and sleep time is indicated. Finally, the potential role of the fat-derived hormone leptin in impairing bone mass is listed.