

What Are the Mechanisms and Effects of Age-Related Shortening of the Spine?

Joseph Weingarten

Joseph Weingarten will graduate June 2019 with a B.S. degree in Biology

Abstract

Osteoporosis and Degenerative Disc Disease can cause a loss of height in the spine. This paper focuses on the mechanisms that cause age-related loss of height and its effects. Possible relationships between receptor activator nuclear factor kappa-B ligand (RANKL) and estrogen with osteoporosis are discussed, as well as possible genetic causes. Exercise may prevent osteoporosis. Osteoporosis may cause a loss of height, vertebral fracture, a decrease in maximum lung capacity, and hip fracture. Degenerative disc disease may cause shortening of the spine. Disc height loss can result in a reduction in the range of motion and stiffness at the affected spinal segments. Degenerative disc disease may cause a small increase in vertebral height which can lead to complications in treatments.

Introduction

As early as the age of 30, people may begin to become shorter. Studies show that from the age of 40, people begin to lose about half an inch per decade. Some health risks associated with loss of height are spinal fracture, back pain, hip fracture (Hannan et al., 2012), and a decrease in lung capacity (Krege et al., 2015). Total health care costs in the United States of osteoporotic hip fractures is estimated at 18 billion dollars annually (Hannan et al., 2012).

There are three main reasons why people become shorter as they age, and they are all related to the spine. One reason is osteoporosis, a decrease in bone density. As the skeleton loses density, it compresses, making the body shorter. Osteoporosis is the most common bone disease, affecting 200 million people worldwide, and leading to over 9 million fractures annually (Yu & Wang, 2016). Giving the aging population, the predicted annual healthcare costs of an osteoporotic compression fracture in the USA alone is 25.3 billion dollars. Loss of water in the intervertebral discs due to aging also accounts for shortening of the spine. The discs become compressed, because of the weight placed on them by the upper body, resulting in a loss of height (Jarman et al., 2015). Another possible cause for shrinking is the abnormal bending of the spine. However, the body isn't really shortening, rather bending, and just giving the appearance of loss of height. Flattening of the arch of the foot may also give a person the appearance of a shorter stature; however, most of a person's height loss can be attributed to changes in the lumbar spine (Videman et al., 2014). This paper discusses the possible causes and effects of osteoporosis and degenerative disc disease, and how they result in a loss of height.

Methods

Data was found by using ProQuest and PubMed databases through Touro college's online library. Keywords used were loss of height, osteoporosis, and degenerative disc disease.

Physiology of Osteoporosis

Bone is 30% collagen fibers and 70% non-organic minerals such as calcium. Osteoblasts are cells that make bone. Osteoclasts break down the bone and resorb the minerals into the blood, but osteoblasts keep making new bone to counter the loss; this is known as bone remodeling. Osteoporosis is a condition where osteolysis overshadows osteogenesis (Yu & Wang, 2016). Osteoporosis can begin at the age of 30, but it is most

pronounced in older people, especially in postmenopausal women because estrogen suppresses the receptor activator of nuclear factor kappa-B ligand (RANKL), a molecule that promotes osteoclast differentiation and formation (Eghbali-Fatourehchi et al., 2003). Estrogen also increases the expression of osteoprotegerin (OPG), which functions as a decoy receptor for RANKL (Hofbauer et al., 1999). During menopause, when there is a decrease in estrogen, there is an increase in RANKL and decrease in OPG, resulting in increased osteoclast activity, and a net loss of bone.

Studies show that men also experience bone loss due to a decrease in estradiol concentrations (Falahati-Nini et al., 2000). However, in both men and women, a decrease in growth hormone secretion due to aging is also responsible for a decrease in bone formation (Drake et al., 2015).

Trabecular bone loss begins in the third decade of life while cortical loss typically begins in the sixth decade of life (Drake et al., 2015). Trabecular loss, which occurs before gonadal sex steroid deficiency, may be caused by secondary osteoporosis. Secondary osteoporosis is bone loss caused by factors other than aging or postmenopausal status. Glucocorticoid excess can cause decreased production of osteoblast precursors and increased apoptosis of mature osteoblasts. Primary hyperthyroidism causes cortical bone loss. Vitamin D deficiency causes demineralization of bone and is associated with lower bone density. Type I diabetes mellitus causes osteoporosis because of an inability to reach peak bone mass (Emkey & Epstein, 2014). There are many other causes of secondary osteoporosis, but this paper focuses on age-related causes.

Since both genders experience trabecular bone loss with aging, age-related factors other than sex steroid deficiency may be involved. Cytokines accumulate due to aging factors, including menopause, and make the bone marrow prone to inflammation (Yu & Wang, 2016). Inflammation activates transcription factor nuclear factor kB, which causes osteoclast differentiation and inhibits osteoblasts (Chang et al., 2009). Also, oxidative stress, characterized by the presence of too many reactive free radicals in the body, increases with age. Oxidative stress activates nuclear factor-kB which in turn causes bone loss (Khosla et al., 2011). It is unclear if osteoporosis causes further inflammation in the bone marrow which would then activate more nuclear factor-kB, exacerbating the osteoporosis (Yu & Wang, 2016).

Osteoporosis may indirectly cause further bone loss.

Osteoblasts and adipocytes both come from a mesenchymal stem cell. In osteoporosis, since osteoblasts production is inhibited, there are more adipocytes forming instead. Adipocytes secrete the hormone leptin which has been found in mice to promote adipogenesis and inhibit osteogenesis (Yue et al., 2016).

Osteoporosis is also caused by gene expression. Histone Demethylases KDM4B and KDM6B remove gene silencing histones from the osteogenic master regulator gene (Ye et al., 2012). Mice that had KDM6B knocked out had impaired osteogenesis (Zhang et al., 2015). Aged mice and female mice that had their ovaries removed had elevated levels of the osteogenic gene silencing histones, suggesting an epigenetic link between aging and low estrogen levels with impaired osteogenesis (Ye, et al., 2012).

Studies of astronauts have shown that they lose bone from bones that are normally weight bearing, such as the femur and tibia. Astronauts returning to Earth have extensive bone resorption, which shows that osteoclasts were breaking down the bone (Shigematsu et al., 1997). Normal bone density was not restored after reambulation (Vico et al., 2000). Prolonged bed rest is also associated with decreased bone density in weight bearing. Interestingly, a study of 24 bedridden women showed that high load resistive exercise had no significant impact on bone loss, although it did prevent muscle atrophy (Beller et al., 2011). These studies show that the force of gravity is necessary for maintaining normal rates in bone remodeling, and a lack of this force may result in osteoporosis.

Predisposing risks for osteoporosis occur during childhood and adolescence because maximizing peak bone mass is important for its prevention. However, exercise during maturation can mitigate the effects of osteoporosis. Weight-bearing exercises are found to be effective in generating bone anabolism (Santos et al., 2017). Exercise may be a form of prevention, but once osteoporosis develops, exercise may lead to osteoporotic fracture due to the stress put on the weak bones.

Osteoporotic Vertebral Fracture and Height Loss

The decrease in bone density caused by osteoporosis can cause vertebral fractures. Vertebral fractures can be measured using the spinal deformity index (SDI). Using the SDI, a mild compression fracture (20-25% compression) in a vertebra is given a value of one, moderate fractures (25-40% compression) are two units, a severe fracture (more than 40% compression) is given a value of 3 (fig. 1). The SDI is the sum of the units of each vertebra from T4 to L4. Height loss was calculated by subtracting the current height from the arm span. The arm span length was considered the person's peak height. In a study of women aged 70 years and older with osteoporosis and a history of at least one moderate or severe vertebral fracture, for each unit increase in SDI, height decreased by about 0.5 cm (Krege et al., 2015). Osteoporosis causes a loss of bone in the vertebrae, resulting originally in a decrease in density of the vertebrae.

The weight placed on the spine may then cause the vertebrae to compress, increasing the bone density of the vertebrae (the density may be elevated due to compression; however, there is a decrease in bone mass and height). Therefore, height loss is a marker for vertebral fractures.

	FRACTURE STATUS	FRACTURE GRADE
T4	none	0
T5	none	0
T6	mild	1
T7	moderate	2
T8	none	0
T9	none	0
T10	none	0
T11	mild	1
T12	none	0
L1	mild	1
L2	none	0
L3	none	0
L4	none	0
SDI = 1 + 2 + 1 + 1 = 5		

Fig. 1. Spinal deformity index is the sum of fracture grades for T4 to L4 vertebrae. In the example shown, the patient has three mild and one moderate vertebral fracture, for an SDI of 5. SDI, spinal deformity index. Modified from Krege et al., 2015

Osteoporosis and Lung Capacity

SDI is also negatively correlated with pulmonary function. For each unit increase in SDI, forced inspiratory vital capacity, which is the maximum volume of air inhaled, decreased by 1.62% and inspiratory time, the time it takes for the maximum volume of air to be inhaled, decreased by 2.39% (Krege, et al., 2015). There was no significant correlation between the flow rate, which is a measurement of the volume of air inhaled per an amount of time,

What Are the Mechanisms and Effects of Age-Related Shortening of the Spine?

and the SDI. This result indicates that vertebral fracture is linked with restrictive, not obstructive, lung disease. Restrictive lung disease occurs when the lungs aren't compliant, and they become stiff, limiting the lungs' expansion, and causing a volume decrease. An obstructive disease does not affect the lung volume; rather it causes a decrease in flow due to the resistance of the obstruction. Therefore, since people with vertebral fractures experience a decrease in lung capacity but not in flow rate, osteoporosis can be classified as a restrictive lung disease. The reduction in inspiratory time is caused by a decreased lung volume, so there isn't as much air going into the lungs, and therefore it requires less time for inhalation. Perhaps the decrease in inspiratory vital capacity is due to a loss of volume in the thoracic cavity because of compression of the spine. This decrease in volume may limit the compliance of the lungs. No evidence was found that would suggest an effect of height loss on the heart.

Other studies were performed using expiratory measurements. One study found that for each thoracic vertebral fracture forced vital capacity declined 9% (Leech et al., 1990). Others suggested that there is no relationship between vertebral fractures and pulmonary function. However, the analysis performed by Krege et al. is unique in its use of SDI to quantify the vertebral fracture. Another possible reason for different results found in the studies is because the other studies used expiratory measurements while Krege et al. used inspiratory measurements. Also, the measurement done by Leech et al. was only considering thoracic fractures while the study done by Krege et al. considered both thoracic and lumbar segments. A limitation to the Krege et al. study is that it combined both thoracic and lumbar segments rather than assessing them separately.

Osteoporotic Hip Fracture

Height loss is also associated with osteoporotic hip fracture, defined as incident fractures of the proximal femur occurring either after age 50 or in postmenopausal women. A study that followed 3081 adults over 50 years revealed a positive correlation between height loss and risk of hip fracture. For this study, hip fracture was defined as a first-time fracture occurring in the absence of overwhelming trauma. The study recorded height loss of male and female participants over 24 years. Most participants were middle-aged during these 24 years. The study also considered recent height loss, height loss occurring during the two years prior to the hip fracture, as a possible correlation to the risk of hip fracture. Most participants were elderly during the two years of their recent height loss.

The study used Cox proportional hazards regression (HR) to calculate hazard ratios and 95% confidence intervals for height loss and risk of hip fracture. For each inch of height loss occurring during the 24 years, the HR was 1.4 in men and 1.04 in women. These results show that height loss was significantly associated with hip fracture in men but not in women. Men with

long-term height loss of two inches or more had about twice the risk of fracture than men with less height loss. Recent height loss occurring two years prior to hip fracture increased the risk of hip fracture by 54% for men and 21% for women. Recent height loss was more of an indicator of fracture risk compared to long-term height loss most probably because recent height loss occurred during elderly ages while long-term height loss occurred during the participants' middle-aged years.

That study proved a relationship between height loss and hip fracture; however, height loss can be caused by many factors, postural changes, osteoporosis, disc degeneration, and kyphosis which may contribute to fracture risk. No information was given about posture for the participants, which is a limitation of the study. The exact cause is unknown, but height loss is an indicator of an increased risk of hip fracture. Another limitation of the study is that participants were all from one town and were primarily Caucasian (Hannan, et al., 2012).

Physiology of Degenerative Disc Disease

The intervertebral disc has a hard-outer portion called the annulus fibrosus and a gelatinous inner portion called the nucleus pulposus. The annulus fibrosus can further be divided into 2 portions. The outer zone is made of type 1 collagen fibers and the inner zone is comprised of type 2 collagen fibers. The nucleus pulposus is 85% water. The intervertebral discs act as a water cushion and distribute pressure uniformly over the endplates of the vertebrae. While a person is in an upright position, the weight placed on the intervertebral discs causes the discs to lose water. The water escapes to blood vessels in the bone marrow space in the endplate of the vertebrae. These blood vessels are also responsible for giving the intervertebral discs nutrition. When the pressure on the intervertebral discs decreases, like when a person lays down or in a zero-gravity environment, fluid reenters the intervertebral disc. The difference in height between a person in a vertical and horizontal position can be 1% of his height (Schuenke et al., 2011).

As people age, they may get what is known as degenerative disc disease. However, there are those who view degenerative disc disease different than normal disc ageing, maintaining that degenerative disc disease is "an accelerated ageing process including structural failure", while there are those who use the two terms synonymously (Galbusera et al., 2014). In this paper, degenerative disc disease refers to disc degeneration associated with normal ageing.

Over time, the annulus fibrosus weakens and loses elasticity. Also, proteoglycans, water retaining molecules, diminish within the degenerating discs. With the decrease in water, the discs lose their ability to resist compression and torque. The discs shrink because of the weight placed on them, and less water is present to counter this force (Jarman et al., 2015). This compression of the intervertebral discs results in a decrease in a

Joseph Weingarten

person's overall height. Studies show that a decrease in estrogen can cause disc degeneration (Lou & Chen, 2014).

Disc Height Loss

A study of 37 men and 33 women, with an average age of 48 showed that degenerative disc disease is positively correlated with disc height loss. The 70 participants were asymptomatic for back pain to exclude pathologic degeneration. Additionally, participants were not diagnosed with osteoporosis and didn't have any spinal fractures. T2-weighted MR images were used to determine if the patient had degenerative disc disease. T2-weighted MRI signals water content; therefore, an MR image showing a white disc indicated a healthy disc that contained water, while images of a dark disc indicated degenerative disc disease since the dark color in the image indicated that the disc lacked water. Another indicator of degenerative disc disease is an absence of the differentiation of the nucleus pulposus and the annulus fibrosis. The study used MR imaging of the lumbar spine to assess the height and shape of the intervertebral discs. The height of the disc was measured as the mean of the anterior and posterior disc height. Disc convexity was calculated as the ratio of the central disc height and the mean of the anterior and posterior height.

The study showed that disc degeneration resulted in a decrease in disc height. Also, the lower intervertebral discs were shorter than discs higher in the spine (for example, the disc between L2 and L3 was shorter than the disc between L1 and L2), most probably because the greater weight placed on the lower discs cause them to be more compressed. Degenerative effects on disc height were found to be more pronounced with increasing age. Weight, overall height, and gender did not correlate with disc height. Discs were found to be less convex in the presence of disc degeneration. Also, the lower level discs were less convex. One drawback of this study is that participants didn't have osteoporosis, so the effects of degenerative disc disease together with osteoporosis can't be determined (Pfirrmann et al., 2006).

Height Changes in Intervertebral Discs and Vertebrae

Another study was done using 232 monozygotic twin men. The fact that they are twins is not relevant to the findings of this study. Intervertebral disc and lumbar vertebrae heights were measured from MRIs and compared with the measurements of one group after five years and the remainder after 16 years. After five years, the vertebrae did not significantly increase in height. However, after 15 years, the vertebrae significantly increased by an average of 3.1% which was an average of 0.8 mm. The lower vertebrae increased in height more than the upper vertebrae did. The disc heights had a mean decrease of 3.45% or 0.4 mm after five years and an average decrease of 10% or 1.2 mm after 15 years. Disc

height loss was greater than the height increase of the vertebrae, resulting in a net loss of height. The axial disc areas significantly increased by 4.7% over 5 years and 14.2% over 15 years. Disc volume was calculated by multiplying the mean disc height by the axial disc area. Over 5 years, the disc volume did not significantly change, but after 15 years, the volume significantly increased by 2.3% in the discs between L2 and L4, and significantly increased by 3.7% in the discs between L4 and S1.

This study shows that disc shortening is associated with an increase in vertebral height. A 1 mm decrease in the height of either the superior or inferior discs was associated with an increase of .09 mm in vertebral height. The effects of the superior and inferior discs are additive. Age was not a confounder on the relationship between the discs and the vertebrae. Since the vertebrae increase as the discs decrease, the lumbar spine only minimally decreases. The reason for this vertebra-disc relationship may be because the increased tension between the vertebra and annulus fibrosus causes ossification to strengthen the connection between the disc and the vertebra. This reason would help explain why vertebral height increases occur more at the anterior and posterior sections of the endplates, because it attaches to the annulus. Another possible explanation for the relationship between disc height and vertebral height is that endplate lesions can expose the vertebrae to disc substances, which may lead to inflammation and bone growth on the endplate. Support to this hypothesis is that studies have found an association between disc degeneration and lesions of the bony endplate.

Over the 15-year study, the lumbar spine decreased by an average of 1.4% or 2.0 mm. The mean decrease in total height of participants was 3 mm. Most of the overall height loss experienced by participants of this study occurred in the lumbar spine (Videman et al., 2014).

Degenerative Disc Disease and Spinal Flexibility

Intervertebral disc height loss may result in a decrease in the range of motion and stiffness of the affected spinal segment. It is unclear however if disc height loss is the cause, or possibly due to damages of annular tissue or ligaments. One possible way to restore spinal flexibility is to inject a hydrogel to compensate for the loss of height of the discs (Balkovec et al., 2016).

A possible concern with simply using a hydrogel to add height to the discs is that sometimes the surrounding vertebra increases in size as was found in the Videman et al. study, so there may no longer be sufficient space for a larger disc in the spine.

Conclusion

Osteoporosis may cause a loss of height, vertebral fracture, a decrease in lung capacity, and hip fracture. Osteoporosis is caused by activation of RANKL and a reduction in osteoprotegerin. Histone demethylase KDM4B is also linked to osteoporosis. A

What Are the Mechanisms and Effects of Age-Related Shortening of the Spine?

decrease in Estrogen can cause osteoporosis. Weight-bearing exercise may reduce the progression of osteoporosis.

Degenerative disc disease may cause shortening of the spine. Discs lower in the spine experience a greater loss of height, presumably because the greater weight placed on them causes them to condense more. Disc height loss may result in a decrease in the range of motion and stiffness of the affected spinal segments.

Further studies should be done to determine the effects of the enlargement of the vertebral bodies in response to degenerative disc disease. Using a hydrogel to restore height in the intervertebral discs may not be a sufficient method of treatment since the intervertebral space may be partially occupied by newly formed vertebral bone. Also, further studies are needed to examine if degenerative disc disease can cause an increase in bone density of the lumbar spine. Bone density scans are taken of the lumbar spine to diagnose a patient with osteoporosis, but if degenerative disc disease is increasing the bone density, then the diagnosis may be incorrect. The bone density measurements would appear to be within normal limits even though the patient may have osteoporosis.

References

- Balkovec, C., Vernengo, A., & McGill, S. (2016). Disc height loss and restoration via injectable hydrogel influences adjacent segment mechanics in-vitro. *Clinical Biomechanics*, 36, 1-7. doi:10.1016/j.clinbiomech.2016.05.004
- Beller, G., Belavy, D., Sun, L., Armbrecht, G., Alexandre, C., & Felsenberg, D. (2011). Bed-rest Induced Changes In Bone Mineral Density In Women During 60 days Simulated Microgravity. *Bone*, 49(4), 858-866. doi:10.1016/j.bone.2011.06.021
- Chang, J., Wang, Z., Tang, E., Fan, Z., McCauley, L., Franceschi, R., et al. (2009). Inhibition of Osteoblast Functions by IKK/NF- κ B in Osteoporosis. *Natural Medicine*, 15(6), 682-689. doi:10.1038/nm.1954
- Drake, M., Clarke, B., & Lewiecki, M. (2015). The Pathophysiology and Treatment of Osteoporosis. *Clinical Therapeutics*, 37(8), 1837-1850. doi:10.1016/j.clinthera.2015.06.006
- Eghbali-Fatourehchi, G., Khosla, S., & Sanyal, A. (2003). Role of RANK ligand in mediating increased bone resorption in early postmenopausal women. *Journal of Clinical Investigation*, 111(8), 1221-1230. doi:10.1172/JCI17215
- Emkey, G., & Epstein, S. (2014). Secondary osteoporosis: Pathophysiology & Diagnosis. *Best Practice & Research Clinical Endocrinology & Metabolism*, 28(6), 911-935. doi:10.1016/j.beem.2014.07.002
- Falahati-Nini, A., Riggs, B., & Atkinson, E. (2000). Relative contributions of testosterone and estrogen in regulating bone resorption and formation in normal elderly men. *Journal of Clinical Investigation*, 106(12), 1553-1560. doi:10.1172/JCI10942
- Galbusera, F., van Rijsbergen, M., et al. (2014). Ageing and degenerative changes of the intervertebral disc and their impact on spinal flexibility. *European Spine Journal*, 23(3), 324-332. doi:10.1007/s00586-014-3203-4
- Hannan, M., Broe, K., Cupples, L., Dufour, A., Rockwell, M., & Kiel, D. (2012). Height Loss Predicts Subsequent Hip Fracture in Men and Women of the Framingham Study. *Journal of Bone and Mineral Research*, 27(1), 146-152. doi:10.1002/jbmr.557
- Hofbauer, L., Khosla, S., & Dunstan, C. (1999). Estrogen stimulates gene expression and protein production of osteoprotegerin in human osteoblastic cells. *Endocrinology*, 140(9), 257-263. doi:10.1210/endo.140.9.7131
- Jarman, J., Arpinar, V., Baruah, D., Klein, A., Maiman, D., & Muftuler, L. (2015). Intervertebral Disc Height Demonstrates the Threshold of Major Pathological Changes during Degeneration. *European Spine Journal*, 24(9), 1944-1950. doi:10.1007/s00586-014-3564-8
- Khosla, S., Melton, L., & Riggs, B. (2011). The Unitary Model for Estrogen Deficiency and the pathogenesis of Osteoporosis: Is a Revision Needed? *Journal of Bone and Mineral Research*, 26(3), 441-451. doi:10.1002/jbmr.262
- Krege, J., Kendler, D., Krohn, K., Genant, H., Alam, J., Berclaz, P.-Y., et al. (2015). Relationship Between Vertebral Fracture Burden, Height Loss, and Pulmonary Function in Postmenopausal Women With Osteoporosis. *Journal of Clinical Densitometry*, 18(4), 506-511. doi:10.1016/j.jocd.2015.02.004
- Leech, J., Dulberg, C., Kellie, S., et al. (1990). Relationship of lung function to severity of osteoporosis in women. *American Review of Respiratory Disease*, 141(1), 68-71. doi:10.1164/ajrccm/141.1.68
- Lou, C., & Chen, H.-L. (2014). Menopause is associated with lumbar disc degeneration: a review of 4230 intervertebral discs. *Climacteric: the journal of the International Menopause Society*, 17(6), 700-704. doi:10.3109/13697137.2014.933409
- Pfirrmann, C., Metzendorf, A., Elfering, A., Hodler, J., & Boos, N. (2006). Effect of Aging and Degeneration on Disc Volume and Shape: A Quantitative Study in Asymptomatic Volunteers. *Journal of Orthopedic Research*, 24(5), 1086-1094. doi:10.1002/jor.20113
- Santos, L., Elliot-Sale, K., & Sale, C. (2017). Exercise and Bone Health Across the Lifespan. *Biogerontology*, 18(6), 931-946. doi:10.1007/s10522-017-9732-6
- Schuenke, M., Schulte, E., & Schumacher, U. (2011). *General Anatomy and Musculoskeletal System*. Germany: THIEME.
- Shigematsu, T., Miyamoto, A., Mukai, C., et al. (1997). Changes in Bone and Calcium Metabolism with Space Flight. *Osteoporosis International*, 63-67. doi:10.1007/BF03194345
- Vico, L. C., Guignandon, A., Lafage-Proust, M.-H., Thomas, T. R., & Alexandre, C. (2000). Effects of Long-term Microgravity Exposure On Cancellous and Cortical Weight-bearing Bones of Cosmonauts. *The Lancet*, 355(9215), 1607-1611. doi:10.1016/S0140-6736(00)02217-0

Joseph Weingarten

- Videman, T., Battie, M., Gibbons, L., & Gill, K. (2014). Aging changes in lumbar discs and vertebrae and their interaction: a 15-year follow-up study. *The Spine Journal*, 14(3), 469-478. doi:10.1016/j.spinee.2013.11.018
- Ye, L., Fan, Z., Yu, B., Chang, J., Khalid, A., Zhou, X., et. al. (2012). Histone Demethylases KDM4B and KDM6B Promotes Osteogenic Differentiation Of Human MSCs. *Cell Stem Cell*, 11(1), 50-61. doi:10.1016/j.stem.2012.04.009
- Yu, B., & Wang, C.-Y. (2016). Osteoporosis: The Result of an Aged Bone Microenvironment. *Trends in Molecular Medicine*, 22(8), 641-644. doi:10.1016/j.molmed.2016.06.002
- Yue, R., Zhou, B., Shimada, I., Zhao, Z., & Morrison, S. (2016). Leptin receptor promotes adipogenesis and Reduces Osteogenesis by Regulating Mesenchymal Stromal Cells in Adult Bone Marrow. *Cell Stem Cell*, 18(6), 782-796. doi:10.1016/j.stem.2016.02.015
- Zhang, F., Xu, L., Xu, Q., Karsenty, G., & Chen, C. (2015). Histone demethylase JMJD3 is required for osteoblast differentiation in mice. *Scientific Reports*. doi:10.1038/srep13418.