How We Can *Kiss* Weak Bones Goodbye

By Fatima Miranda Chavez

Picture a bridge over a river that connects two sides of a city. When the bridge was first built, the bridge was strong and sturdy, able to support heavy loads and different weather conditions. However, as years and years pass by, that bridge is constantly run by traffic, exposed to different weather and other factors that day by day take its toll on the bridge and its structure.

The bridge will eventually show its scars of wear and signs of deterioration. There will be cracks in the concrete road, the rusting of its metal foundations, and the weakening of the deck; all of these characteristics compromise the bridge's overall integrity and further the bridge's risk of collapsing.

Just like the weakening of the bridge, in a bone loss disorder called osteoporosis, our bones begin to lose their structural integrity and strength as we age[1]. Different factors affect our bones and their susceptibility to fractures, such as gender, hormones, age, diet, and a variety of other environmental factors[2].

Osteoporosis increases fracture susceptibility, especially in the hip, spine, and wrist, and is responsible for hospitalization costs of $22 billion per year in the United States[3,4]. In addition to the economic burden, osteoporosis fractures lead to disabilities, physical limitations, and lower quality of life for those afflicted[5].

Women over 50 have a significantly higher risk of experiencing osteoporotic fractures compared to men over 50 worldwide[6]. This gender disparity is attributed to the hormonal changes brought on by menopause, specifically the decrease in estrogen levels[7].

Estrogen is a hormone that helps balance where energy is distributed in our body and where it will be used, as well as regulating our bone's stability[8]. Different types of estrogen are made in our bodies. The most common form is E2 (estradiol), which helps increase energy delivery and bone maintenance[9].

Bones are maintained by two types of cells—osteoclasts and osteoblasts (side note: the prefix "osteo" refers to bone). Osteo*clasts* are cells that tear down bone; think of them as osteo-cleaners. Osteo*blasts* are cells that build bone[10]; think of them as osteo-builders. Estrogen helps bone directly by managing osteoclasts in lowering their activity levels[7]; in other words, estrogen helps limit the tearing down of bone.

When older women go through menopause, their estrogen levels go down. This means that osteoclasts will be a lot more active due to the low levels of estrogen[,11]. We end up with too much bone being broken down while too little bone is being remade. Well, that sounds like a bone loss disorder to me! This is exactly what is happening in osteoporosis.

Does bone loss always occur because of low estrogen levels? Well, that is not always the case!

After women give birth, their E2 levels decline similar to women going through menopause. However, we see a huge amount of activity in osteoblasts in these new mothers, which is not seen in postmenopausal women.

So, the irregularity in new mothers is that, while they should be losing bone mass due to low levels of E2, they are not. Instead, they lose bone mass because of the requisite calcium loss that occurs when making milk for their newborn.

However, most women who breastfeed will eventually gain their bone mass back once they stop producing milk[15]. This is not true for postmenopausal women, even though they both share low levels of E2. Weird, right!?

Researchers are currently trying to understand the mechanism behind why new mothers experience high levels of activity from osteoblasts despite having low levels of E2. Understanding this mechanism could further increase therapeutic potential for combating bone loss disorders, such as osteoporosis, in women!

Aside from the effect of E2's direct work on bones, studies are showing that the relationship between the brain's central nervous system with estrogen plays a role in bone regulation. In 2019, Dr. Candice B. Herber and fellow researchers helped shed light on the brain-estrogen relationship when they found that some estrogen levels in the brain can prevent bone from being formed in women[16].

When the research team removed a specific protein (estrogen receptor alpha) in the brain of mice, through the magic of science, they saw these mice develop stronger bones compared to regular mice[16] (fig.1). The specific neurons targeted in the brain were *Kiss1* neurons that had these estrogen proteins. Well, I guess you can kiss them goodbye because we need these stronger bones!

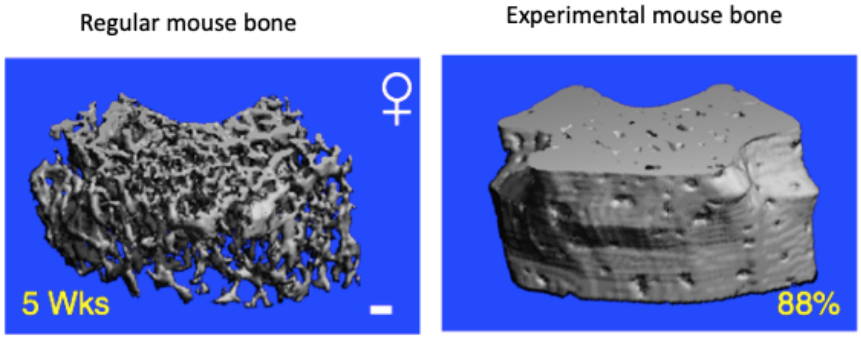

Figure 1. Three-dimensional (3D) images taken by Dr. Candice B. Herber and research group. Images come from scanning a regular mouse bone and their experimental mouse bone. The experimental mouse bone came from mice that had the estrogen protein removed (estrogen receptor alpha). The image represents the difference in bone density between the two mice[16].

But what is it about these *Kiss1* neurons that cause stronger bones to form when you remove these estrogen proteins?

Well, in 2023, Dr. Muriel E. Babey and their team discovered that *Kiss1* neurons release a specific hormone called Cellular Communication Network factor 3 (CCN3) when a mother is breastfeeding and experiencing naturally low estrogen levels. This hormone acted like a bone-building hormone that promoted the same strong bones in the mice Candice B. Herber used. Researchers noted that the hormone steps in when estrogen lowers in new mothers[17]!

In the UC Davis lab I will be working for this upcoming summer of 2024, we plan to further investigate the next piece of the puzzle that this hormone connects to. Understanding the communication path that is occurring could further our fight against osteoporosis and other bone loss disorders! Stay tuned for our next step!

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