NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

Good to the Bone:

Biological Implications of a Potential Anti-Aging Drug

by

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Part I – Maria's Pain

Spring had arrived. Apple season would begin shortly, Maria thought to herself. She looked forward to this time of the year. Being out in the sunshine after the long winter they had in Vermont was much anticipated. The best part was that the grandkids, Jack and Elsa, would be spending the summer with her.

Maria had started on some spring cleaning in preparation for their arrival. Progress was slow as she continued to experience a dull pain in her wrist and knees. Maria had felt this pain all winter, but she had ignored it. It seemed to get progressively worse each year. She had mentioned it to her best friend Betty, who had recommended that she see a specialist. Maybe it was arthritis; her mother had had it, after all. Where did she leave that card again? She would have to admit to Betty that she never followed up on her recommendation. Maria could just imagine the argument that would follow. Ibuprofen, that would help; it always did, for a while anyway.

Questions

1. What are joints? How are they classified?

2. What are the names of the joints that bother Maria? What bones articulate with each other?

3. How would you classify these joints? Diagram one of these joints and explain how it differs from the other types of joints.

4. What range of motion would these joints have? Describe the movement.

5. What is arthritis? What treatments are currently available for arthritis?

6. What else might cause Maria's pain?

Part II – The Fall

Maria awoke to the postal service truck as it made its way down the gravel path to her mailbox. She remained lying on the sofa. The morning activities on the farm had taken their toll. After breakfast, she had intended to do a bit more reading on arthritis from the pamphlet Betty had left her, but she had drifted off to sleep.

Just one more thing to do, thought Maria. She was almost ready for Jack and Elsa's arrival, but she still wanted to clean out the linen closet. So many things got stashed there all winter. Getting up from the sofa, she found the ladder, climbed up to the top of the closet, and began taking things down from the upper shelf. As she ascended the ladder again, she felt her right knee give way and suddenly fell. The sound of bone breaking was unmistakable. The pain in her right thigh was excruciating. She knew it was going to be bad.

Luckily, Betty was slated to come over and help her with some last-minute chores before the grandkids arrived. Before Betty arrived, Maria must have passed out. Based on Betty's anxious face and the two paramedics who peered down at her, Maria knew her injuries were serious.

Questions

1. What is the most likely bone that was broken? Given the bone you selected, what regions of the bone were broken?

2. What tissues were most likely affected from this fall? List them in order from superficial to deep.

Part III – A Potential Cure for Brittle Bones?

"Three fractures on femur… ." The rest of the conversation was lost as the two nurses left Maria's room.

Grandma had had brittle bones. Had this condition as well as arthritis been passed on to her? Betty was right; she should have gone back and seen Dr. Maxwell when the pain started getting worse. He knew the family and had treated pretty much everyone. Now that she was in the hospital, she had no other option. Dr. Maxwell would soon be stopping by her room.

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Dr. Maxwell: Hi Maria, Betty. Not the best way to be meeting. How are things on the farm?

Maria: As well as can be expected. Please be straight with me. How bad is it? How fast can I be back on my feet?

Dr. Maxwell: Let's start with the bad news. You have a complete fracture of the femur near the hip and two hairline fractures along the length of the bone. That bone is completely broken near the hip, but not completely lower down. These are all serious fractures. This isn't typical given the height you fell from. Maybe a hairline fracture for someone your age, but not really for someone with good bones.

Maria: So what do three fractures mean? I don't have good bones, brittle like Grandma?

Dr. Maxwell: It seems so. I'm waiting on the lab results to confirm the diagnosis. Three fractures based on the height you fell from is a good indication something is wrong with the bones. Hmm, let's see, the last time you were here was five years ago; a lot can happen in that time. How are your joints?

Maria: This winter they acted up over and over again. You did mention my family history that included both osteoporosis and arthritis. No cure is what you said, and you recommended a diet high in calcium and exercise. Which I followed. So why is this happening?

Dr. Maxwell: I know, but sometimes these things alone are not enough. It may slow down the process for some, while having no effect for others.

Maria: So, what's the plan to get me out of here? What do I need to do?

Dr. Maxwell: We have stabilized the bones with a cast, as you can see. This will prevent the bones from shifting and allow the healing to begin. The initial process will take a month ...

Maria: One month! I can't afford to be off my feet for so long!

Betty: Calm down. We will help you, and Tim certainly will. After all the help you gave his wife this past winter with the triplets.

Dr. Maxwell: … and an additional three to six months after the cast is removed to be completely healed. You need to rest and let this process happen. If not allowed to heal properly …

Maria: Any way to prevent this from happening again, other than not falling?

Dr. Maxwell: Well, probably, but I can't guarantee it will work. There is a drug already on the market that is going into clinical trials with the potential to work on several diseases including osteoporosis and arthritis. Data so far is promising and may assist you in the future. Have you heard about metformin?

Maria & Betty: No.

Dr. Maxwell: Let me explain. Your bone marrow, which is in the center of your bone, houses various populations of cells called stem cells. These cells maintain and keep the body working through their ability to self-renew and replace dying, damaged, or lost cells. These special cells can become any cell in your body—for example, bone, cartilage or fat tissue—as needed, given the right conditions. In your case you may have bone cells that are being lost and not being replaced by your stem cells, and so the bones are not what they used to be. Now, several studies have shown that this drug metformin may be able to improve bone health. There may be a chance that you can be a candidate for this study, but the screening process will be rigorous.

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Questions

1. What is the difference between brittle bone (osteogenesis imperfecta) versus osteoporosis? What are the current treatments?

2. Dr. Maxwell was waiting to get some lab results back. What specific test/s would Dr. Maxwell have performed to assess Maria's bone?

3. What do you think is wrong with Maria?

4. What questions would you ask regarding metformin?

Part IV – Supporting Clinical Data

Metformin, a leading drug to treat diabetic patients, has been shown to improve bone homeostasis. The studies Dr. Maxwell is referring to involved the use of cell cultures (*in vitro*), mouse models (*in vivo*), and clinical trials. Please review the following two articles.

- McCarthy, A.D., A.M. Cortizo, and C. Sedlinsky. 2016. Metformin revisited: does this regulator of AMP-activated protein kinase secondarily affect bone metabolism and prevent diabetic osteopathy? *World Journal of Diabetes* 7(6): 122–33. <https://doi.org/10.4239/wjd.v7.i6.122>.
- Marycz, K., K.A. Tomaszewski, K. Kornicka, B.M. Henry, S. Wroński, J. Tarasiuk, and M. Maredziak. 2016. Metformin decreases reactive oxygen species, enhances osteogenic properties of adipose-derived multipotent mesenchymal stem cells *in vitro*, and increases bone density *in vivo*. *Oxidative Medicine and Cellular Longevity* 2016(9785890). <https://doi.org/10.1155/2016/9785890>.

Data supporting improvement in bone metabolism and turnover with the use of metformin is summarized in the figures below. Figure 1 is based on two figures that appear in the first article, McCarthy *et al.* (2016); Figure 2 is from the second article, Marycz *et al.* (2016).

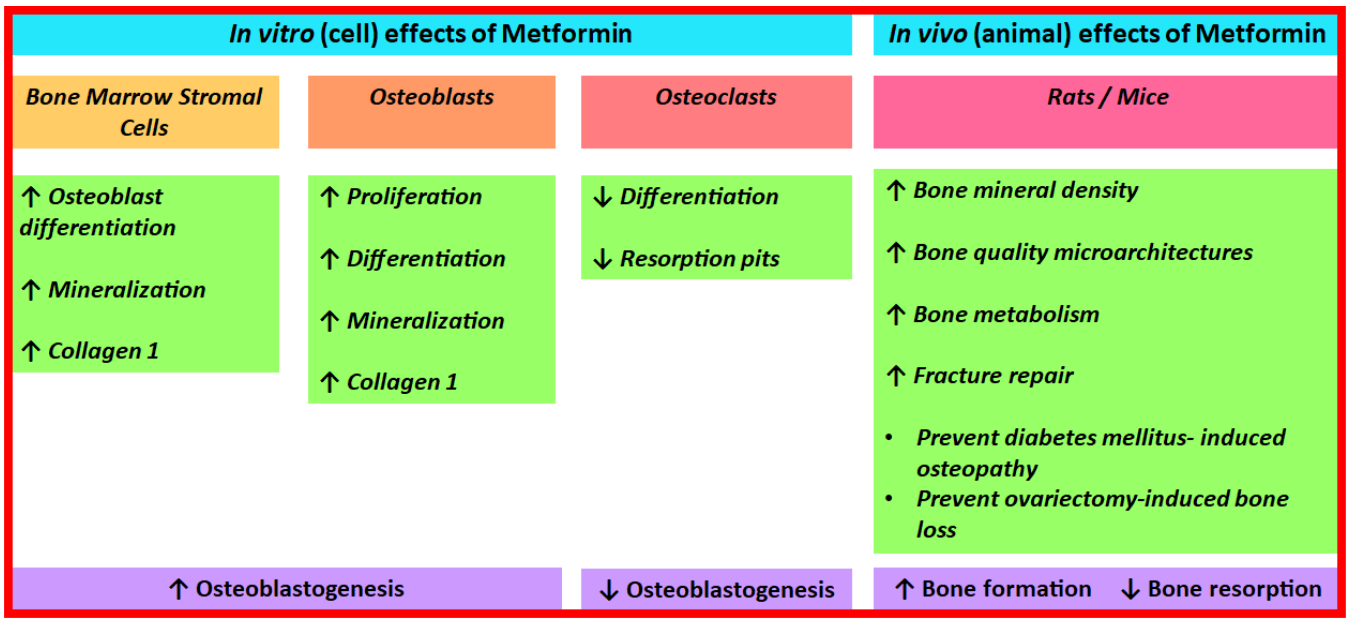

Figure 1. Effects of metformin on bone-derived cells and its action on bone metabolism in animals.

In vitro studies: The results from several *in vitro* studies show that metformin modulated the phenotypic balance of bone marrow stromal cells towards osteoblastogenesis. In addition, metformin increases *in vitro* the bone forming capacity of osteoblasts, while decreasing the recruitment and bone-resorbing activity of osteoclasts.

In vivo studies: Orally administered metformin increases the quality of bone tissue (improving its micro-architecture and mineral density) and facilitates the repair of bone lesions. In addition, metformin may prevent experimental diabetic osteopathy as well as ovariectomy-induced bone loss.

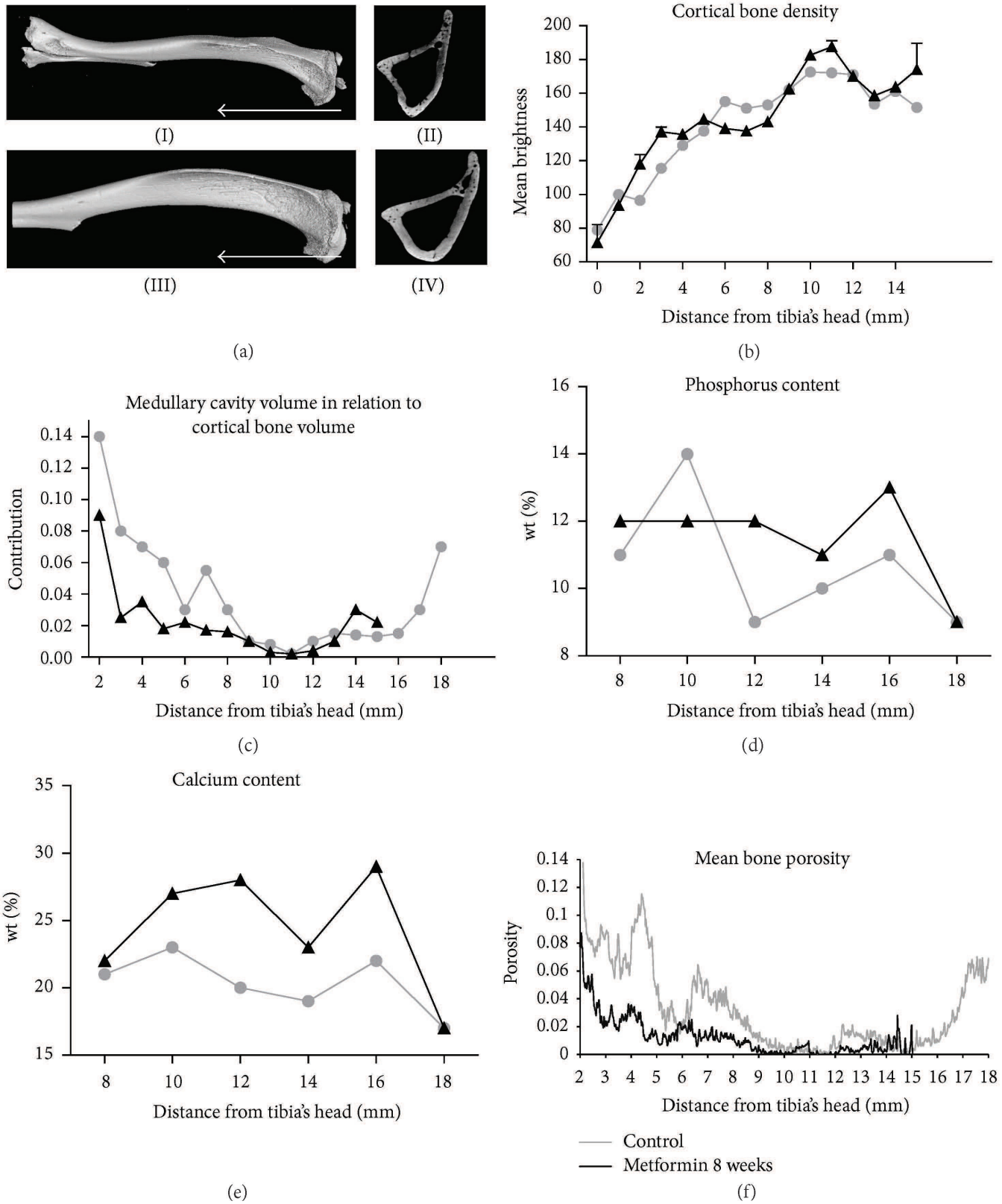

Figure 2. Nano-CT and SEM-EDX analysis. (a) Nano-CT images of tibia bones and their transverse sections from control (I, II) and Met 8 (III, IV) mouse. White arrows indicate direction of performed scanning. Quantification of cortical bone density (b) and medullary cavity volume (c) in mice tibias by Nano-CT. SEM-EDX assessment of calcium (d) and phosphorus (e) content in tibia from control and Met 8 group. Mean bone porosity assessed by Nano-CT in the studied groups (f). Results expressed as mean, $n = 5$. *Credit:* Marycz *et al.* (2016), CC BY 4.0.

Questions

1. What role do osteoblasts and osteoclast perform in bone homeostasis? Study the activities of metformin in Figure 1. How does metformin contribute to bone deposition and repair? What is happening at the cellular level?

2. What would you do to assist the bone repair process in Maria's case? Explain what would happen during this process.

3. What is the role of calcium and phosphate in bones? In Figure 2 (d and e), how does the calcium and phosphorus content differ between the control and metformin treated animals?

4. Examine Figure 2 (a, b, c and f) and compare the data between the control and metformin treated animal; which had more bone deposition? Provide a brief summary of your evidence that supports your answer.

5. Explain why the results shown in Figure 2 are of significance to Maria.

6. The case so far has not looked at cartilage, only bone. However cartilage is part of functioning bones. What would be your prediction of metformin effect on cartilage? Can you propose an experiment to test the effect of metformin on cartilage? What would be the controls for these experiments?