Undercarboxylated Osteocalcin: Marker of Vitamin K Deficiency, or Booster of Insulin Signaling and Testosterone?

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Osteocalcin is a vitamin K2-dependent protein that our bones produce. The job of vitamin K is to activate this protein by adding carbon dioxide to it, which in scientific jargon we call “carboxylation.” Vitamin K2 researchers widely regard the ratio of undercarboxylated to carboxylated or total osteocalcin as a marker of inadequate vitamin K2 status. Evidence has accumulated over the last half decade, however, that undercarboxylated osteocalcin may stimulate the production of insulin and testosterone, while simultaneously enhancing insulin sensitivity, and by doing so, make us lean and fertile.

Is undercarboxylated osteocalcin a good thing or a bad thing? Could this represent a downside to getting enough vitamin K, particularly vitamin K_2, the form that most effectively reaches our bones? I’ll tackle these questions in this post as I critically review the literature on undercarboxylated osteocalcin’s role as an insulin- and testosterone-boosting hormone.

Widespread Deficiency of Vitamin K_2?

In my Spring, 2007 article, “On the Trail of the Elusive X-Factor: A Sixty-Two-Year-Old Mystery Finally Solved,” I followed the convention of the vitamin K research community by using the proportion of osteocalcin in its undercarboxylated form — which I then called “inactive,” a term that now seems inappropriate — as a marker of inadequate vitamin K status. More specifically, it indicates deficient vitamin K status of bone, and since vitamin K_2 reaches bone more effectively than K_1, it is in a certain sense more a marker of K_2 deficiency.

I supported this by pointing out that people with the highest proportion of osteocalcin in this form have a five-fold greater risk of fracture. Vitamin K_2 supplementation, moreover, improves the activation of osteocalcin, and in a series of Japanese trials it reduced fracture risk by 80 percent. These data offer strong support for using undercarboxylated osteocalcin as a marker of vitamin K deficiency in bone tissue.

In a 2010 blog post, I argued that “10-20 percent of serum osteocalcin in its inactive form indicates a state of deficiency” on the basis that within this range small improvements in the proportion of osteocalcin that is carboxylated are associated with large decreases in the risk of advanced prostate cancer. I further argued that there is “widespread deficiency” of vitamin K_2 in children, based on studies showing that the proportion of osteocalcin that is inactive is remarkably high in children, considerably higher than 10-20 percent, and increases during puberty, reaching in some children as high as 83 percent.

Our bone-building cells, osteoblasts, produce osteocalcin. As a result, we make more osteocalcin when we are building more bone. Childhood is a period of rapid bone growth, especially adolescence, during which bone mass approximately doubles (1). This would seem to offer a very simple and elegant explanation of why the proportion of undercarboxylated osteocalcin is so high during childhood and especially during puberty: when bones are growing, the production of osteocalcin, and thus the demand for vitamin K, is very high; if the intake of vitamin K, especially vitamin K_2, is low, then a large

proportion of this osteocalcin will be undercarboxylated. According to this paradigm, undercarboxylated osteocalcin reflects widespread deficiency of vitamin K_2 in growing children.

Undercarboxylated Osteocalcin: A Beneficial Insulin- and Testosterone-Boosting Hormone?

Beginning in 2007, however, a body of literature began to emerge suggesting that undercarboxylated osteocalcin plays an important physiological role as an insulin-stimulating, insulin-sensitizing, testosterone-boosting hormone — at least in mice, anyway. These findings, if they can be generalized to humans, have the potential to throw a major monkey wrench into the standard interpretation of undercarboxylated osteocalcin as a marker of vitamin K deficiency.

Undercarboxylated Osteocalcin, Insulin, and Energy Balance

In 2007, Lee and colleagues from the labs of Gerard Karsenty and Patricia Ducy at Columbia University published a study (2) showing that mice engineered to lack the osteocalcin gene were fat, had elevated blood glucose, burned energy at a lower rate, and were both deficient in and insensitive to insulin.

Incubating fat cells with osteoblasts caused them to produce adiponectin, an insulin-sensitizing hormone, and incubating pancreatic cells with osteoblasts caused them to produce insulin itself. Osteoblasts were only effective, however, if they produced osteocalcin; osteoblasts taken from the mice with a deletion in the gene had no effect. Actually, osteoblasts themselves weren't needed. Just incubating the cells with osteocalcin worked fine.

But here's the catch: treating the osteoblasts with warfarin, which reduces the carboxylation of osteocalcin by interfering with vitamin K metabolism, actually *increased* the effect. In fact, when the investigators compared purely carboxylated osteocalcin to purely uncarboxylated osteocalcin, only the uncarboxylated form was effective. Giving the live, osteocalcin-deficient mice uncarboxylated osteocalcin, moreover, improved their glucose tolerance and insulin secretion.

We should note here that the osteocalcin the investigators used wasn't just "**under**carboxylated" as it tends to occur in humans and live animals (meaning it has some carbon dioxide added to it, but less than it should), but totally "**un**carboxylated" because they genetically engineered bacteria to make it, and these bacteria were among the vast majority of microorganisms that lack the vitamin K-dependent enzyme responsible for carboxylation.

The same group published a second study early the following year (3) showing that these phenomena held true not just in genetically engineered mice but even in wild-type mice. Subcutaneous infusion of uncarboxylated osteocalcin protected mice against the damaging metabolic effects of both highly purified, industrial, high-fat rodent diets as well as damage to the hypothalamus, a key part of the brain that contributes to the regulation of energy balance.*

Undercarboxylated Osteocalcin, Testosterone, and Fertility

In 2011, the Karsenty and Ducy labs, along with several other collaborators, published a landmark paper expanding their findings from energy metabolism to male fertility (4). In male mice, experiments involving deletion of the osteocalcin gene or administration of uncarboxylated osteocalcin showed that undercarboxylated or uncarboxylated osteocalcin increases production of testosterone, the size and weight of testes, and both the frequency and size of sired litters.

Mice lacking osteocalcin also had an excess of luteinizing hormone (LH), a pituitary hormone responsible for increasing testosterone production. The excess of LH seems to be an attempt to compensate for the lack of testosterone, but it obviously isn't effective at restoring testosterone to normal.

In female mice, by contrast, the protein had no effect on fertility or on production of estrogen and progesterone. The paper makes no mention of female testosterone or male estrogen and progesterone.

The investigators also identified a protein that may act as a receptor for undercarboxylated osteocalcin, present in testes but not ovaries, which would explain why the effect seems to apply to male mice but not females.

The Critical Role of Bone Resorption

Additional studies from the Karsenty lab and various collaborators showed that genetically altering or pharmaceutically treating the mice to increase or decrease the rate of bone resorption controlled the release of undercarboxylated osteocalcin into circulation and its subsequent effects on energy balance and testosterone (5, 6).

Bone growth and bone resorption are both parts of normal, everyday, healthy bone metabolism. Bone resorption is the acidic dissolution and digestion of mineralized bone matrix. It plays important roles in regulating the levels of minerals in the blood, mainly calcium and phosphorus, and in allowing bone matrix to reorganize as needed to best fulfill the demands of the body and environment.

While the vitamin K-dependent addition of carbon dioxide allows osteocalcin to accumulate in the bone matrix, bone resorption creates an acidic environment that removes some of the carbon dioxide and allows release of undercarboxylated osteocalcin into the blood. Removal of carbon dioxide is known as "decarboxylation." According to the paradigm Karsenty and his collaborators have been presenting, this process allows the activation of osteocalcin to its hormone form.

These authors follow the exact opposite usage that I have over the past six or seven years and refer to undercarboxylated osteocalcin as the "active" form. For clarity, I may refer to this form as "hormonally active."

Sarah Booth and her colleagues at Tufts University have pointed out that when human osteoclasts are cultured on bovine bone, only a small amount of osteocalcin is released and enzymes subsequently digest most of it into fragments that are unlikely to act as hormones (7).

The Karsenty lab's data, however, is quite convincing that bone resorption releases functional, hormonally active osteocalcin in mice. As mentioned above, genetic or pharmaceutical interventions to increase or decrease bone resorption not only controlled the release of undercarboxylated osteocalcin, but also produced the expected effects on energy metabolism and testosterone. When the researchers mimicked the process outside of a live animal, moreover, they verified the hormonal activity of the osteocalcin that was released.

Roles for Insulin and Leptin

In the initial paper reporting that mice lacking the osteocalcin gene were fat and in metabolic disarray, the investigators also uncovered a role for the *Esp* gene: deleting it increased the amount of undercarboxylated osteocalcin circulating and had the exact opposite metabolic effects as deleting the osteocalcin gene. Subsequent experiments published by the same group (5) showed that the protein encoded by this gene neutralizes the insulin receptor once it has been activated. Although this gene isn't active in humans, we have a different enzyme known as PTP1B that fulfills the same function.

In the same paper (5), the researchers reported that, although insulin signaling in osteoblasts promotes bone growth and ultimately leads to stronger bones, it also promotes bone resorption. Bone growth involves the production of osteocalcin, its vitamin K-dependent carboxylation, and its accumulation in bone matrix; bone resorption involves its decarboxylation and release into circulation as a hormone. Insulin signaling in osteoblasts is therefore a key pathway that promotes the release of circulating hormonally active osteocalcin.

This group had also published a separate paper (8) showing that leptin, a hormone secreted by fat tissue, acts on the brain to increase signaling of the sympathetic nervous system to osteoblasts, which increases the activity of the *Esp* gene. This antagonizes insulin signaling in osteoblasts, decreases bone resorption, and thereby decreases the circulating amount of hormonally active osteocalcin.

This paper remarkably showed that, in mice, fat tissue, bone tissue, and the brain all communicate with each other to regulate energy metabolism and fertility.**

This evidence suggests that a higher insulin-to-leptin ratio may promote bone resorption and thereby promote the release of hormonally active osteocalcin. We should exercise caution when generalizing from these studies, however, since even if this hormonal axis works similarly in humans, simply measuring the concentrations of these hormones in the blood does not necessarily provide adequate information about their signaling activity at the cellular level where they are fulfilling their functions.

Of Mice, Men , and a Little Protein In Need of a Job

So far, all of the direct experimental evidence supporting the hormonal role of osteocalcin is in mice. The Karsenty lab and its collaborators argued that it would be unprecedented for this work to have no implications for humans, but also admitted the need for direct evidence (4):

. . . there is no example yet of a molecule being a hormone in the mouse that has abruptly lost this attribute in humans. This is, nevertheless, an aspect of osteocalcin that will need further investigation in the future.

Mouse Osteocalcin Could Hypothetically Be Unique

In a critical review referenced above (7), Sarah Booth and colleagues pointed out that the sequence of the mouse osteocalcin gene has less similarity to that of the human gene compared to many other species. The way the gene is organized on chromosomes differs and the way vitamin D regulates its expression also differs between mice and humans. Rats are actually closer to humans than mice in these respects. While these points hardly refute a hormonal role for osteocalcin in humans, they do support, in a very limited way, the possibility that the function of osteocalcin could vary between species, which further emphasizes the need to generate direct evidence for its hormonal role in humans.

If Osteocalcin *Isn't* a Hormone, What on Earth Does It Do?

On the other hand, if these newly discovered hormonal roles of osteocalcin hold across species, this would help disperse some of the fog of mystery that has enveloped for so many years the question of just what it is this protein actually does. As I pointed out back in 2007, mice that lack the osteocalcin gene have no problems mineralizing their bones, but the bone matrix is organized somewhat differently. I concluded that "this could mean that osteocalcin is important to the functional quality of bone and the ability to regulate its shape," but "could mean" is a critical phrase in that sentence.

It was the Karsenty lab that carried out these studies back in the 1990s, the same lab that has been promoting the paradigm that osteocalcin acts as an insulin- and testosterone-boosting hormone. One of their early studies (9) suggested that mice with no osteocalcin gene actually have *better* bone strength than normal mice. Their subsequent analysis (10) of these mutant mice indicated the bone matrix seemed less "mature," but the functional benefit of osteocalcin remained elusive.

To go beyond "could mean" when the only clearly demonstrated function of the protein was to reorganize bone in a way that decreases its strength would have been a stretch. Indeed, although osteocalcin must logically have *some* beneficial role in the body, the question of just what that role actually is was at that time extremely puzzling.

In retrospect, the figure in my 2007 article depicting the role of osteocalcin as "organization of minerals" over-interpreted the evidence available back in 2006 when I was researching the article. I was assuming that, if this was osteocalcin's only known function, it must be beneficial in some way even if its benefit was far from obvious.

When we consider that these mice have no obvious bone defects yet are fat, infertile, and metabolically damaged, it would seem that in the mouse the primary role of osteocalcin is to regulate energy metabolism and fertility rather than to do anything particular to bone.

And since in mice osteocalcin affects the production or activity of numerous other hormones that affect bone metabolism, such as insulin, adiponectin, and testosterone, there is no reason to assume that osteocalcin's modest yet quite puzzling effects on bone are directly a result of its accumulation in bone matrix. Indeed, the changes in the bones of osteocalcin-deficient mice could simply be a relatively minor side effect of the disturbances in these other hormones.

If undercarboxylated osteocalcin is not a hormone that regulates energy balance and fertility in humans, we are back to square one with little understanding of its function. These mouse studies, then, provide us with hope that we may be making progress towards solving the enigma.

Limited Support From Epidemiological Evidence

There is a considerable amount of epidemiological evidence associating total osteocalcin with energy metabolism in humans, but this sheds little light on the matter because the studies do not look at undercarboxylated osteocalcin specifically (for example, 11, 12). This could simply reflect an association between bone growth and overall health.

There is a growing body of favorable epidemiological evidence looking at undercarboxylated osteocalcin, but because of the complex interactions between the cells and hormones involved, these studies are difficult to interpret. Here are some examples:

- Among just under 300 men and postmenopausal women with type 2 diabetes, undercarboxylated and total osteocalcin were inversely related to fat mass and HbA1c, a marker of poor glucose metabolism (13). Puzzlingly, the *ratio* of undercarboxylated to total osteocalcin had the opposite association with fat mass in men but no association in women, and the associations between undercarboxylated osteocalcin, fat mass, and glucose metabolism lost statistical significance after adjustment for putative confounders in women, but not in men.
- Among just under 60 male subjects across a wide spectrum of body weights, morbidly obese men had lower undercarboxylated osteocalcin than normal-weight men, and a lower ratio of undercarboxylated to total osteocalcin (14). Among all the obese subjects, undercarboxylated osteocalcin inversely correlated with waist circumference and fasting glucose.
- Among just over 60 overweight men, the ratio between undercarboxylated and carboxylated osteocalcin, but not either individual form of the protein, correlated with free testosterone, but not with total testosterone or other sex hormone-related measures (15).
- Among just over 50 healthy boys ranging in age from 7 to 21, both undercarboxylated and total osteocalcin correlated with serum testosterone after adjusting for "bone age," an estimation of the maturity of a child's skeleton (16). These authors did not report correlations with the ratio between the two forms of osteocalcin.
- Among just under 70 men with severe type 2 diabetes, undercarboxylated osteocalcin did not correlate with testosterone until the authors statistically adjusted for markers of bone and glucose metabolism, gonadal hormones, age, and body mass index (17). After adjustment, undercarboxylated osteocalcin correlated positively with free testosterone and inversely with luteinizing hormone. The ratio of undercarboxylated to total osteocalcin was similarly correlated with testosterone, whereas total osteocalcin itself was not.
- Among just under 250 healthy postmenopausal women, by contrast, Cees Vermeer's Netherlands-based vitamin K research team found very different results: *carboxylated*osteocalcin was inversely related with body weight, body mass index, hip and waist circumference, and body fatness, whereas the ratio of undercarboxylated to carboxylated osteocalcin had smaller positive associations with these parameters, and our putative hormone, undercarboxylated osteocalcin, had no such associations (18).

These studies are difficult to interpret. The reasons are myriad:

- Undercarboxylated osteocalcin could reflect the insufficient carboxylation of the protein, or could reflect its decarboxylation during bone resorption.
- Insufficient carboxylation of the protein could, in turn, reflect a high rate of its production during bone growth, inadequate vitamin K status, or most likely some combination thereof.
- The ratio of undercarboxylated to total osteocalcin could reflect poor vitamin K status, but it could also reflect a greater rate of bone resorption compared to bone growth.
- It is unclear whether the absolute amount of undercarboxylated osteocalcin or its ratio to total osteocalcin would be the best measure of its hormonal activity because no one to my knowledge has determined whether the carboxylated form interferes with the hormonal activity of the undercarboxylated form.
- Since all of the downstream targets of undercarboxylated osteocalcin, such as insulin, adiponectin, and testosterone, affect bone metabolism, correlations between these factors are riddled with chicken-and-egg questions.
- To confuse matters further, some recent reports (14, 15) indicate that, in addition to osteoblasts, pre-adipocytes in fat tissue produce osteocalcin, including undercarboxylated osteocalcin. They produce more osteocalcin in response to testosterone, but less osteocalcin as the fat tissue proliferates and the pre-adipocytes turn into true fat cells. This adds another chicken-and-egg question to correlations between osteocalcin and testosterone. It also adds a further layer of confusion: lower undercarboxylated osteocalcin in obesity could reflect not only a fat-burning effect of the putative hormone, but also a lower production of it by adipose tissue in people with greater numbers of fat cells.

Overall, then, I would say the epidemiological evidence is, although somewhat conflicting in some respects, generally *consistent* with a fat-burning and testosterone-boosting effect of undercarboxylated osteocalcin in humans, but I would be reticent to claim the evidence is more than slightly *supportive.*

Human Genetic Evidence

The strongest and most direct evidence to date that undercarboxylated osteocalcin acts as a hormone in humans comes from human patients with genetic defects in the putative osteocalcin receptor (6). The Karsenty lab and their collaborators analyzed the genetics of just under 60 men with primary testicular failure presenting with low sperm count and high luteinizing hormone (LH), but without any increase in testosterone resulting from the high LH. Two of them (3.4%) had genetic defects in the putative osteocalcin receptor.

Although this genetic defect is present in 1.2% of African Americans and 0.02% of Europeans who submitted DNA to the NHLBI Grand Opportunity Exome Sequencing Project, none of the more than 900 healthy controls recruited by the Karsenty team had the defect. This provides strong preliminary evidence that the defect is associated with and perhaps causes testicular dysfunction that resembles the infertility seen in mice lacking the osteocalcin gene.

The patients with this defect resembled these mice in other ways as well. One had a large waist circumference and excess body fatness as well as glucose intolerance, while the other had a history of high blood glucose that he kept under control with daily exercise and strict caloric restriction.

I refer to this receptor as a “putative” osteocalcin receptor because in test tube experiments it binds to a variety of different compounds. The only compound for which there is thus far clear evidence of receptor activation in live animals is undercarboxylated osteocalcin. Thus, the resemblance of men with defects in the receptor to mice with defects in the osteocalcin gene suggests that undercarboxylated osteocalcin is hormonally active in humans, but the evidence is not conclusive.

Looking at the Totality of the Evidence

Adding up a bunch of inconclusive studies can never yield a conclusive result, but when we view the hints of the hormonal role of undercarboxylated osteocalcin in humans from epidemiological and genetic evidence in the context of the conclusive evidence for its hormonal role in mice and in the context of the lack of any other compelling explanation for the function of this protein in any species, we arrive at very strong hints that this protein is, in fact, a hormone in humans.

While the evidence is not yet conclusive, I would hedge my bets that future evidence, as it improves both in quantity and quality and pushes us towards a conclusion, will support rather than refute the hormonal role of undercarboxylated osteocalcin in humans and across many species.

Should We All Get Deficient in Vitamin K?

If we accept the probability that undercarboxylated osteocalcin has positive hormonal roles in humans, as I do, this naturally leads us to consider the implications for vitamin K intake. Since the function of vitamin K is, in part, to carboxylate osteocalcin, and since it decreases circulating amounts of undercarboxylated osteocalcin, could obtaining an abundance of vitamin K from foods or supplements be harmful?

On the one hand, the experiments I cited above showed that osteoblasts or their secretions could elicit hormonal responses more effectively when made vitamin K-deficient with warfarin.

On the other hand, the Karsenty team and its collaborators have consistently argued, with strong evidence, that bone resorption is the trigger for release of hormonally active osteocalcin into the bloodstream. If this paradigm is correct, one could argue that adequate vitamin K is needed to ensure that osteocalcin is fully carboxylated as it is produced, allowing it to accumulate in bone matrix, so that the presence of the undercarboxylated form in the bloodstream accurately reflects the degree of bone resorption.

Vitamin K, moreover, is involved in much more than osteocalcin metabolism. As I pointed out back in 2007, it not only supports strong bones and teeth, adequate growth, and the health of the kidneys, brain, and heart, but it appears to support energy metabolism and fertility as well, since it accumulates in the pancreas and testes and activates a protein of unknown function in sperm.

Rats on vitamin K-deficient diets develop poor glucose tolerance (19). There is some weak indication, conversely, that vitamin K_2 supplementation in humans with poor status improves glucose and insulin metabolism (20). Vitamin K_1 or K_2 supplementation in rats, moreover, lowers body fatness (21) and vitamin K_2 supplementation increases testosterone (22).

Clearly, the research on the hormonal role of undercarboxylated osteocalcin does not suggest in any way that the road toward leanness and virility is paved by vitamin K deficiency.

Undercarboxylated Osteocalcin: Why So High in Growing Children?

This brings us back to the original question: why are blood levels of undercarboxylated osteocalcin so high in growing children? Is it a marker of vitamin K deficiency, or part of a developmental program to boost anabolic hormones?

I believe a consideration of the developmental endocrine program launched during puberty (1) indicates that the original interpretation of this protein as a marker of vitamin K deficiency is, in this case, correct. During adolescence, bone growth predominates over bone resorption, making bone resorption a rather untenable explanation for the presence of undercarboxylated osteocalcin in blood. Sex hormones and growth hormone increase the activation of vitamin D to its hormone form, calcitriol, which increases the production of osteocalcin, alongside massive increases in bone growth. If the supply of vitamin K to bone tissue is inadequate to meet the demand to carboxylate all this extra osteocalcin, it will be released into the circulation in its undercarboxylated form.

The incidence of fracture increases in boys and girls between the ages of 10 and 14, and in 14-year-old boys it reaches the same magnitude as in 53-year-old women. The author of a recent review (1) suggested that fracture risk increases during adolescence because bone volume and soft tissue mass grow so rapidly during this period that the process of mineralization can't keep up:

Adolescence may be a period of life during which the bones are relatively "thin" in comparison with the mass of soft body tissue. The inability of the mineralization process to keep pace with the growth in length of the long bones may be an inevitable consequence of the magnitude of the sex steroid-driven growth spurt. Indeed, bone modelling at the epiphyses and metaphyses may be so active that skeletal volume is expanding at a faster rate than the mineralization process.

Inevitable? Probably not. If the large increases in undercarboxylated osteocalcin indicate an inadequate supply of vitamin K to bone, then they likely also indicate an inadequate supply of vitamin K to the cells of cartilage and blood vessels, which make matrix Gla protein, one of the most important proteins known to support bone mineralization (even if it may do so indirectly).

Cees Vermeer's group published an epidemiological study consistent with this concept (23). Among over 300 children between the ages of 8 and 14, the ratio of undercarboxylated to carboxylated osteocalcin was positively associated with testosterone in boys and estrogen in girls, but inversely associated with bone mineral content.

The association with sex hormones is inconsistent with the mouse studies on the hormonal role of osteocalcin: it produces testosterone in male mice but has no effect on estrogen in female mice. Yet it is perfectly consistent with the hormonal program launched during adolescence (1), wherein both testosterone and estrogen play roles in increasing bone growth and osteocalcin production. The inverse association between undercarboxylated osteocalcin and bone mineral content is consistent with a supply of vitamin K too scant to support the mineralization process.

Conclusion? Back to Bone Resorption…

Is vitamin K *completely* off the hook? Not necessarily. Certain genetics, an excessively high ratio of calcium to phosphorus in the diet, statins, osteoporosis drugs, and a variety of high-dose nutritional supplements, possibly including vitamin K, could interfere with the process of bone resorption. Such conditions could suppress the normal release of hormonally active osteocalcin, and adding vitamin K into the mix could conceivably aggravate the situation.

In a future post, I'll attempt to fill in the rest of this story by making sense of the hormonal and nutritional regulation of bone resorption, and its role in regulating the circulation of hormonally active osteocalcin.

I think the evidence is clear, however, that when all systems are otherwise working properly, adequate vitamin K supports proper glucose metabolism, energy balance, and fertility. I would feel very confident hedging my bets that more vitamin K for growing children would mean better bone development and a lower risk of fracture.

This is consistent with Weston Price's emphasis on the extraordinary skeletal and dental health and the beautiful, broad, well developed faces of individuals consuming their traditional ancestral diets, free of refined foods and rich in fat-soluble vitamins.

Read more about the author, Chris Masterjohn, PhD, here.

Notes

* Oddly enough, however, the experiments with fresh pancreatic islets and fat cells taken from the mice suggested that the positive effects of uncarboxylated osteocalcin on insulin only occurred at concentrations extremely low compared to those of undercarboxylated osteocalcin normally present in mice, while the effects on adiponectin and energy expenditure only occurred at normal to high concentrations. Similarly, in the later experiment concerning fertility, only small doses of uncarboxylated osteocalcin enhanced testosterone production. Larger doses abolished the effect.

I chose to relegate this to the "notes" section because some of the in vivo evidence from these studies seems to indicate that osteocalcin has hormonal effects on all these parameters across a wide range. For example, both increasing or decreasing the rate of bone resorption affects energy balance and

testosterone, apparently via undercarboxylated osteocalcin, showing that departures from “normal” in both directions are effective, and thus that “normal” is within the effective range. In general this is true for a variety of other loss-of-function and gain-of-function genetic experiments reported in these papers that alter the biochemical pathways discussed. Overall, though, I think these findings related to dose need more attention in future research. [Back to Main Text]

** Fat tissue produces another factor involved, adiponectin (24). While leptin levels increase with body fatness, adiponectin levels decrease. Although adiponectin’s signaling pathways are generally thought to be distinct from those of insulin, in this case it acts through the same signaling pathway as insulin in both osteoblasts and in the brain. Paradoxically, its actions in osteoblasts promote bone resorption while its actions in the brain decrease bone resorption. The net effect of deleting the adiponectin gene in mice is to produce higher bone mass in young mice and lower bone mass in older mice. It would thus seem that the short-term effect of adiponectin is to promote bone resorption while its long-term effect is to inhibit bone resorption, but ultimately the implications of these diametrically opposed roles are unclear. [Back to Main Text]

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About Christopher Masterjohn

Chris Masterjohn, PhD, is creator and main- tainer of Cholesterol-And-Health.Com, a web site dedicated to extolling the benefits of traditional, nutrient-dense, cholesterol-rich foods and to elucidating the many fascinating roles that cholesterol plays within the body. Chris is a frequent contributor to Wise Traditions, the quarterly journal of the Weston A. Price Foundation, and is a perennial speaker at the annual Wise Traditions conference. He has written five peer-reviewed publications, and has submitted two additional experimental papers for peer review, one of which has been accepted for publication. Chris has a PhD in Nutritional Sciences from the University of Connecticut and is currently working as a Postdoctoral Research Associate at the University of Illinois where he is studying interactions between vitamins A, D, and K. The contents of this blog represents his independent work and does not necessarily represent the positions of the University of Illinois.