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Review Article

Hossam Zero Holes (HZH) Unravel Osteoporosis Roots and the Coincidental Soft Tissue Calcification in the Elderly: Granted US Patent Review

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Abstract: The mineralization of the bone is the most important step in its strengthening & preventing its fracture. Calcium is by far the most important and most predominant mineral inside the bone. There is a wrong concept that blood calcium always has access to the bone. This is the basis of calcium supplementation in the elderly or patients with low bone mineral density (BMD). There is an increasing evidence that low BMD is almost always associated with soft tissue calcification. This is why the precipitating factors predisposing to low BMD may have a role in soft tissue calcification. For the calcium to be fixed in the bone, it needs collaboration from all its components namely, the functional collagen, the apatite chips, and the bone cells. The most fundamental point is the zero holes and the zero channels of the collagen bundles. Other factors that could modulate bone mineralization are outside the bone. These extra-osseous parameters act as adjuvants or co-factors that can modify the process of bone mineralization. By the same token, these co-factors may lead to soft tissue calcification. These adjuvant co-factors include hormonal status, visceral fat, hyperinsulinemia, and some minerals in the serum other than calcium itself. If these co-factors are not in an optimal condition for the bone, they would induce low BMD. Therefore, calcium supplementation is not always the right choice in cases of low BMD. This is because it may exaggerate the consequential soft tissue calcification. The US patent (US9801905) suggests that calcium can be supplemented in low BMD only if the bone is prepared to accept the calcium. The molecular mechanics of the zero holes and the orientation of the apatite chips help in the better understanding of the mechanism of bone mineralization & the associated soft tissue calcification

Keywords: Zero Holes, Virtual Gate, DEXA, BMD, Zero Channels, Apatite Chips

1. Introduction

The bone is formed of 3 main components; Apatite, collagen, and water. The method of studying the effect of calcium precipitation in the bone includes collaboration between all bone components plus other extra-skeletal factors that help in bone mineralization.

1.1. Calcium as a Building Block of the Bone

Calcium is the most important mineral in the bone. It acts as

its cement substance. The mechanism of mineralization of the bone is poorly understood. It means calcium is strongly fixed in the substance of the bone or teeth. Calcium forms about 20% of the bone mass. The bony calcium equals 99% of the whole calcium of the whole human body. The remaining 1% of the calcium is distributed in the blood, tissue fluids, muscles, brain, and most of the human tissues. All the biological function of calcium is done by the free 1% of the Calcium. However, it has many fundamental functions in all the tissues of the human body, Calcium must not be allowed to precipitate except in the bone & teeth. All the tissues other than the bone & teeth are called the soft tissues which include the muscle, tendons, ligaments, blood vessels, and cartilage, etc. If calcium precipitates in any of the above soft tissues, it is called soft tissue calcification with subsequent damage and fibrosis of the affected tissue [1]. A great example of the fundamental role of calcium is in muscle and heart. It can not contract without free calcium. On the other hand, if it is precipitated in the valves of the heart, it would cause dysfunction of the valves and fibrosis with subsequent incompetence or narrowing of that valve. Its precipitation in the blood vessels causes atherosclerosis of the affected blood vessels. There would be ischemia of the affected part of the body and compensatory hypertension may occur [2].

To sum up the above point, Calcium is needed to precipitate in the bone as a major building block to strengthen it but it is not allowed to precipitate in all other different tissues. Its precipitation in tissue other than the bone & teeth causes its damage. The mechanism of attachment or precipitation of calcium to the bone is poorly understood. An extensive study was done by the US patent (US9801905). It claimed the mechanism of Calcium precipitation of the bone. It also claimed how the calcium interacts with other bone components for the optimal integrity of bone health and function [3].

Table 1. *The factors that affect Bone Mineral Density (BMD) & subsequent soft tissue calcification.*

Factors affecting the Bone Mineralization (BMD)			
Intra-osseous factors (inside the bone)		**Extra-osseous factors (outside the bone)**	
The affecting factor	**comment**	**The affecting factor**	**The comment**
1. The collagen	1. The piezo-electricity 2. The collagen-Apatite chips orientation 3. Zero holes & zero channels 4. Glycation / deglycation	1. Hormonal Homeostasis (virtual gate)	1. Vitamin D 2. Calcitonin 3. Parathormon hormone (PTH)
2. Bone cells interaction	Osteocytes are the commonest cells & Down-regulation of insulin receptors	2. visceral fat	(NF-kB)-(RANK) pathway and their axis with osteoclasts
	Osteoblasts are the cells that secret the building blocks of the bone. They interact with collagen	3. Hyperinsulinemia	Down-regulation of the insulin receptors on the osteocytes (Mitochondrial-nuclear axis)
	Osteoclasts are bone-eating cells. They interact with (RANK) of the visceral fat	4. Serum minerals	1. magnesium 2. zinc 3. copper 4. iron

1.2. Calcium Is a Considerably Large-sized Atom

Calcium occupies the number 20 of the periodic table. This means that its size is considered relatively large enough to reflect the X-ray. This means that calcium is a radio-opaque material. This helps in 2 main functions; Diagnosis of bone fracture and measuring of bone mineral density (BMD). This is why the urinary stone that contains calcium appears in the X-ray while the others that may be formed from other substances like magnesium are not apparent. Again its main function in the bone is the cement building block. This is why it is the commonest mineral inside the bone which is about 20% of the bone mass [4].

1.3. The Difference Between Calcification & Mineralization

Calcium configuration inside the bone is poorly understood. It is called mineralization which is the method by which Calcium is strongly anchored to the substance of the bone. Calcification, on the other hand, is the precipitation of calcium into the soft tissues. i.e. any tissue other than the bone & teeth. They may be to a certain extent similar but they differ in their positions. In the bone & teeth, it is physiological and needed for the optimal function of these organs. In all other tissues, it is a pathological process and is one major cause of soft tissue damage [5].

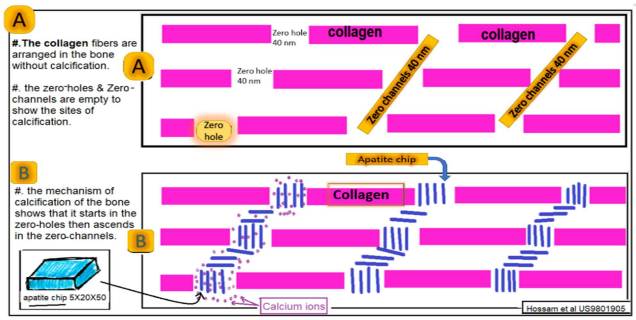

Figure 1. *Zero Hole is the starting point of bone mineralization.*

1.4. Bone Remodeling

The bone is under continuous remodeling. After the age of 40s, the normal person loses 10% of the bone mass every 10 years. This means that the bone of a normal person is under 2 opposing forces; the new bone formation & bone resorption. 3 types of cells are present inside the bone: osteocytes, osteoblasts, and osteoclasts. The osteocytes are the maestros that start and maintain the remodeling process. They give the order to the other cells either the osteoblasts or osteoclasts to work or to stop working. The osteoblasts secret vesicles that

have the building blocks of the bone. The osteoclasts cause bone resorption. It must be noted that the source of osteoclasts is not from the bone. They come from blood monocytes. The osteoblasts & osteoclasts are from the bone. The osteoblasts come from the stem cells they transformed into osteocytes when they become mature. The bone cells would be discussed in further detail in the cell section [6].

1.5. The Interpretation of DEXA (an Indicator of BMD)

DEXA is the method of measuring the bone scan and it is the abbreviation for (Daul Energy X-ray Absorptiometry). It measures the bone scan and compares it with a younger person. Therefore, it is always in minus. -1 or higher is considered normal. Between (-1 to -2.5), it is bone deficiency but it does not reach the degree of osteoporosis. This intermediate zone is called osteopenia. In case of -2.5 or less, osteoporosis occurs and the bone becomes liable to fracture with mild trauma. It is measured at 3 sites; distal radius, lumbar vertebrae, and proximal femur [7, 8].

2. The Collagen of the Bone

2.1. The Function of Collagen of the Bone

Collagen bundles constitute 28% of the bone mass. These bundles are arranged in a plywood appearance. It is known that collagen is a fibrous protein. It is formed of a triple helix which means each molecule is formed of 3 polypeptide chains. (2α1 & 1α2). It was thought that collagen has only one function which is its mechanical support. Recent studies by the US patent (US9801905) showed that collagen has a very fundamental role in bone remodeling via the stimulation of the osteoblasts to produce the osteoblastic vesicles necessary for new bone formation. This phenomenon is called piezoelectricity (PZE) [9].

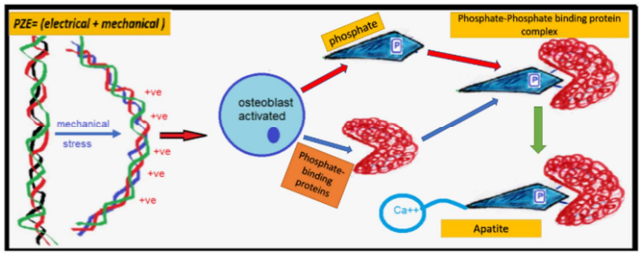

Figure 2. *Functional collagen explains the stimulation of osteoblasts to make new bone formation (piezoelectricity).*

2.2. The Piezoelectricity of the Collagen (PZE)

It means that collagen under mechanical stress conforms and shows a positive convex side & negative concave side. This created an electrical gradient difference (EGD) that can stimulate the nearby osteoblasts to secret the osteoblastic vesicles necessary for new bone formation. The explanation is each one thread of the triple helices of collagen is folded upon itself in an (α) manner. The cut-section of one thread of the collagen is formed of 3 sites (Gly, X, and Y) as in figure 3. The (Gly) is always the glycine while the (X) site is either (proline or hydroxy-proline). The (Y) site may be Lysine or to a lesser extent

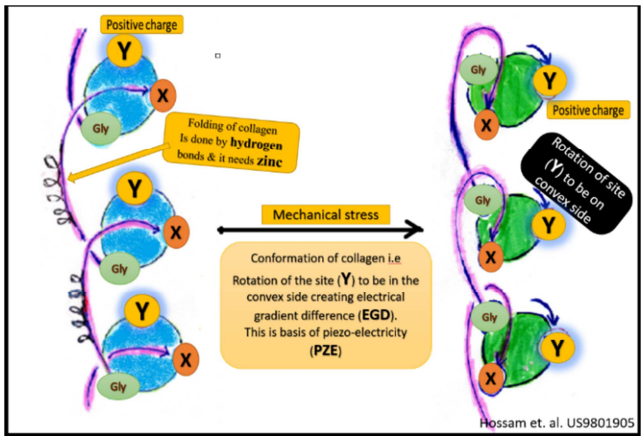

Figure 3. *The conformation of collagen under mechanical stress (PZE).*

Arginine, or very rare to be histidine. The study showed that all the amino acids at the site (Y) are positively charged. On the mechanical loading, the site (Y) is shifted towards the convex side (figure 3). Therefore, the convex side becomes positively charged while the concave side becomes relatively negative. The result is an electrical gradient difference (EGD) that can stimulate the osteoblasts to produce osteoblastic vesicles [27]. These vesicles contain either phosphate crystals (PO_4^-) or phosphate-binding proteins which are sialoprotein, osteocalcin, osteonectin, and/or osteopontin (figure 4). These 4 proteins have a great affinity for phosphate. This is the basis of the new theory of sacrificial bonds (hidden length) [9].

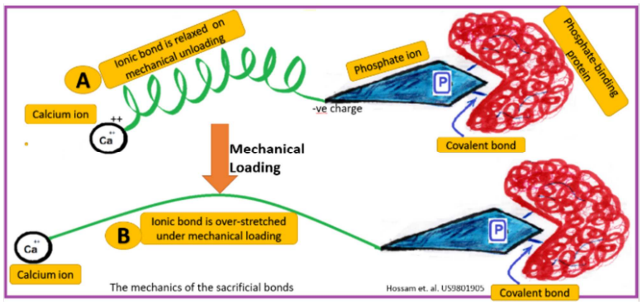

Figure 4. *The sacrificial bond mechanics (hidden length).*

These types of bonds have 2 main functions; dissipation of 75% of the externally applied mechanical stress, and return of the venous filtrate from the periphery of the osteocytes to the Haversian canal (H.C.). this circulation is called Hossam Osteonic Circulation (HOC) figure 5. Thus, it helps in protecting the bone against fracture by prevention the accumulation of externally applied mechanical stress. It also helps in enhancing bone vitality and integrity via improving osteonic circulation. The most fundamental point here is the complex of the phosphate-phosphate binding proteins that are seats for the precipitation of calcium atoms inside the bone. Thus, deficiency of this complex prevents the calcium from being strongly anchored inside the bone. In other words, the mineralization of the bone becomes less. This means low (BMD) which is the main subject of this review. The above explanation shows that functional collagen is the prime mover for bone mineralization [10].

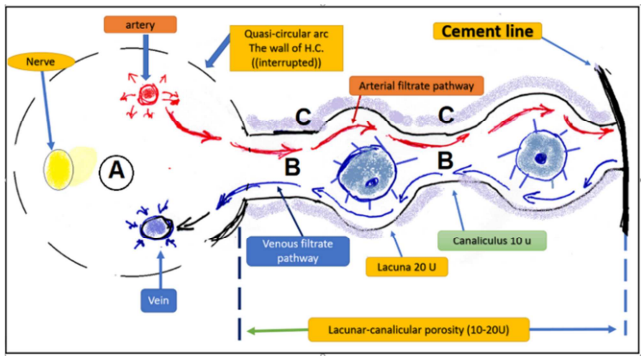

Figure 5. *The osteonic circulation for the nutrition of the bone cells.*

2.3. The Dysfunctional (Glycated) Collagen

The glucose attaches non-enzymatically to the collagen causes it to be dysfunctional or glycated. This can not conform under mechanical stress. Thus, it can not stimulate the osteoblasts to produce osteoblastic vesicles. Thus, the phosphate-phosphate binding proteins complex can not be manufactured or become of a very little amount. As said earlier, these complexes are the seats for the calcium to be precipitated inside the bone. Their deficiency means lack of Calcium precipitation with subsequent low bone mineral density (BMD) [11].

2.4. The Zero Holes & Zero Channels of the Collagen

The collagen is about 300 nm in length & 1.5 nm in diameter. The gap between 2 collagen bundles is about 40 nm. This gap is called zero holes. It ascends obliquely as figure 1 to be a zero channel. The starting site of calcification is the zero holes. Then, it ascends gradually as a zero channel. This is because this is the site of deposition of apatite chips. It must be stressed that the apatite chip size is (5X20X50 nm) while the zero hole is (40nm) at its widest area. This explains that the apatite chips must be oriented either obliquely or longitudinally in the site of the zero hole. Later, the apatite chips could be oriented horizontally in the zero channel. As the apatite chips act as the seats of calcium, this mechanism explains the mineralization of the collagen fibers [12].

3. Bone Cells & Mineralization

There are 3 types of bone cells which are; osteocytes, osteoblasts, and osteoclasts.

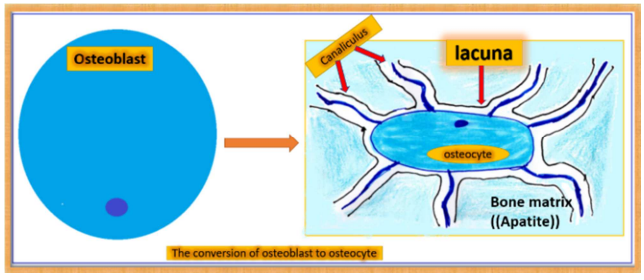

Figure 6. *The transformation of the osteoblasts to osteocytes.*

3.1. The Osteocytes

These are the commonest cells in the bone. They form more than 90% of the bone cells. They may live more than 4 decades. Their deficiency is associated with osteoporosis. They originate from the osteoblasts but undergo some changes to be converted to osteocytes. They lose 2/3 of their size and get many processes (80-120) per cell. The cells themselves are buried in lacunae and the processes are present in canaliculi. Therefore, the osteocytes are present in the lacunar-canalicular porosity (LCP) of the bone. All the cells are arranged in circles around the Haversian canals (H.C.). One of the distinctive features of osteocytes is that each cell has vascular and matrix sides. The vascular side has very fine processes. The matrix side has thicker processes to be tougher. The matrix side is also richer in cholesterol in its cell wall. The deficiency of cholesterol may disturb the function of these osteocytes. This point must be stressed in future studies [13].

Lastly, there is a strong relationship between the mitochondria & nucleus inside these cells called the mitochondrial-nuclear axis (figure 7). This is very important in the regulation of the number of insulin receptors on the membrane of osteocytes which explains the relation between hyperinsulinemia & osteoporosis. This is why osteoporosis is called DM IV [14].

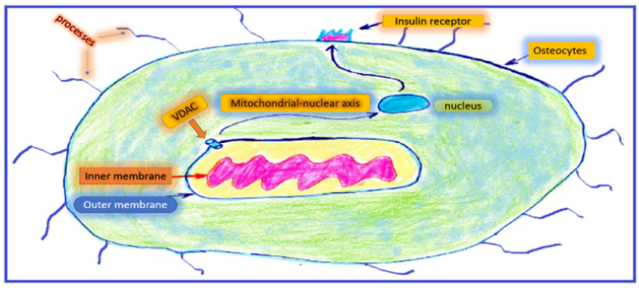

Figure 7. *The down-regulation of insulin receptors on osteocytes via hyperinsulinemia.*

3.2. The Osteoblasts and Mineralization

These cells originate from the stem cells of the bone marrow. Recent studies show that the stem cells are under the effects of 2 genes that compete with each other. These are (RUNX2) gene & zinc finger protein. Runx2 is in favor of the direction of the stem cells towards osteoblasts. While the zinc finger protein directs the stem cells towards fat cells. Vitamin D has a blocking effect of zinc finger protein. This may explain the obesity & osteoporosis that could occur in vitamin D deficiency (figure 8). Osteoblasts form about 5-6% of the bone cells. These cells do not last for a long time. After secretion of bone material around them, each one becomes trapped in a lacuna. Each cell loses 2/3 of its size and it gets many processes and becomes transformed into osteocytes. The most fundamental point of the osteoblasts is that they depend on the functional collagen in their vitality. This means if functional collagen conforms under mechanical stress, it could stimulate the osteoblasts to produce new bone substances. In other

words, the new bone formation is increased and bone mineral density (BMD) would be within the physiological limits. On another hand, if the collagen is dysfunctional i.e glycated, it can not conform under mechanical stress. The osteoblasts would not be stimulated and BMD is subsequently reduced [15].

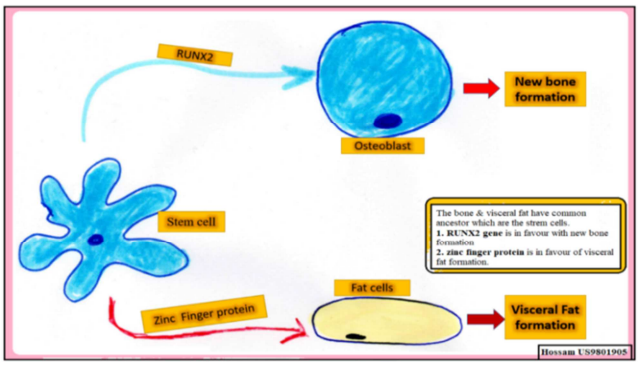

Figure 8. *The stem cells can be directed to osteoblasts or fat cells via (RUBX2) or zinc finger proteins.*

3.3. Osteoclasts and Mineralization

These cells are not originally from the bone. They are derived from blood monocytes. These are bone-eating cells. They form about 1% of bone cells. Recent studies show that these cells have a relation to the visceral fat via the (NF-kB)-(RANK) pathway (figure 9). This will be discussed later in detail [16].

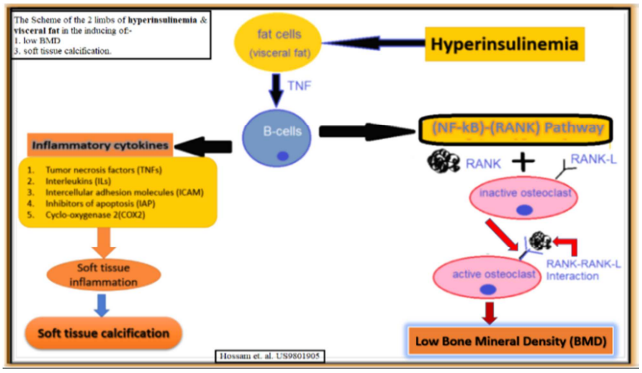

Figure 9. *The effect of hyperinsulinemia of producing low BMD & soft tissue calcification by its 2 limbs.*

4. The Extra-osseous Factors

These are all the factors that may affect bone mineralization & soft tissue calcification. These include:

1. Visceral fat
2. Hyperinsulinemia
3. Virtual gate (Vitamin D, PTH, Calcitonin)
4. some minerals can affect mineralization.

4.1. Visceral Fat

It has a catastrophic effect all over the body not only the bone. Visceral fat is the fat that is accumulated inside the viscera like the liver, pancrease, omentum, wall of the intestine, kidney, and even the pericardium. This fat is metabolically active and creates a large amount of inflammatory cytokine namely the tumor necrosis factors (TNFs). It is responsible for the inflammation in different distant tissues like the wall of blood vessels, the cartilage, tendons, valves of the heart, etc. In the case of the bone, it causes bone loss or low (BMD) via the activation of the (NF-kB)-(RANK) pathway (figure 9). The end-product of the RANK is the activation of the RANK-L on the osteoclasts. As these cells are bone-eating cells, the bone resorption is increased by the presence of excess visceral fat. As most of the visceral fat is present in the abdomen, measuring the circumference of the abdomen at the area of the umbilicus gives a rough indicator of the visceral fat. In men, the circumference should not exceed 90cm while in women it should not exceed 85 cm. Again, this is a rough indication because some patients still have visceral fat but because of shrinkage of their abdominal organs, the circumference is still within its normal level. The most accurate measure of visceral fat is via the CT scan. The other limb of the effect of (TNFs) on the transcription factors is the production of many inflammatory cytokines. The most important ones are interleukins (ILs), intercellular adhesion molecules (ICAM), inhibitors of apoptosis (IAP), and cyclo-oxygenase 2 (COX2). These Inflammatory cytokines induce a chronic subclinical inflammation of the soft tissues including blood vessels, tendons, ligaments, cartilage, any other soft tissue that could be affected. The net result of this low-grade chronic inflammation is soft tissue injury with subsequent tissue calcification. From the above, the visceral fat has 2 limbs, one on the bone to cause low BMD and the other limb is on the soft tissues to enhance their calcification [20, 26]. This is exactly, the subject matter of this paper that low (BMD) is associated with soft tissue calcification.

4.2. Hyperinsulinemia

Recently discovered that hyperinsulinemia has a direct effect on osteocytes to down-regulation of the insulin receptors on its membrane. This is done via the mitochondrial-nuclear axis (figure 7). This is also the axis of autophagy, apoptosis, and the regulation of insulin receptors. The down-regulation of insulin receptors of the osteocytes is a protective mechanism in its early stage to protect the affected cells from high blood glucose. Later, after a long time of down-regulation of insulin receptors on the affected cells, they may suffer from starvation and may show some degenerative changes.

The effect on the osteocytes is associated with low (BMD) while the same effect on the soft tissue is the calcification secondary to the tissue damage. It has to be stressed that damage of the bone has low (BMD) while damage of the soft tissue has more calcification [21, 26].

4.3. The Virtual Gate

This is not a true gate. It acts as a door on the bone that allows or rejects the calcium permission from entering the bone. This is controlled by 3 hormones: Vitamin D, Calcitonin,

and parathormone hormone.

4.3.1. Vitamin D

Vitamin D is a fat-soluble vitamin. It is very essential for bone health because it helps calcium absorption from the intestine and helps in the mineralization of the bone. The most critical point in vitamin D is that it is dose dependant. Its deficiency is associated with low (BMD) because calcium can not enter the bone except in presence of an optimal amount of vitamin D. If it is within the normal level, calcium can enter the bone and BMD would be normal. If it is toxic (higher than normal), the Calcium ion direction is reversed. This means that calcium goes from the bone to blood again leading to low (BMD). Vitamin D toxicity has many other side effects including hypercalciuria, hypercalcemia, renal stone, soft tissue calcification, and others. This condition is caused by self-medication of vitamin D supplementation in a large dose and for long times [17]. Vitamin D has a very critical function in its blocking effect of zinc finger protein. Thus, the stem cells would be directed towards osteoblasts rather than fat cells (figures 8, 10).

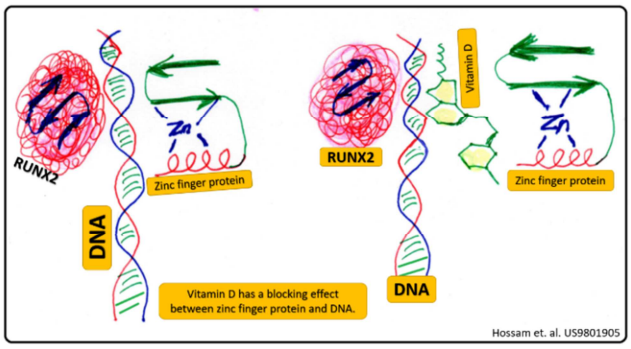

Figure 10. *Vitamin D has a blocking effect on zinc finger protein. RUNX2 would take the upper hand.*

4.3.2. Calcitonin Hormone

Calcitonin hormone is secreted from the thyroid gland. Its main function is allowing calcium to enter the bone. Therefore, it has a unidirectional action in allowing calcium to enter the bone. Its supplementation is not recommended as the natural calcitonin from the thyroid is blocked by the negative feedback mechanism [18].

4.3.3. **Parathormone** *Hormone (PTH)*

Parathormone Hormone (PTH) comes from the parathyroid. Its function is also the activation of osteoclasts. Thus, it causes the calcium to escape the bone. Excess (PTH) causes low BMD as in the case of adenoma of the parathyroid. Some medications appear in the market using the 1st 34 amino acids of the (PTH) to increase the BMD. It is called teriparatide [19].

4.4. Minerals Other than Calcium That Can Affect (BMD)

Calcium is the commonest mineral in the bone but it is not the only one that is essential for bone health. Other minerals are very essential to the bone. They are in the order of their importance magnesium, zinc, copper, and iron. There are other trace elements but their effect is negligible and out of the scope of this paper.

4.4.1. Magnesium and (BMD)

Magnesium (Mg^{12}) is the 2nd most important mineral in the bone after calcium. Its importance is that it stabilizes 2 phosphate crystals (figure 11). Therefore, it helps directly in the strengthening of the bone. Another indirect effect of magnesium on the bone, it increases vitamin D, and calcitonin hormones and reduces parathormone hormone (PTH). Lastly, magnesium enhances the production of collagen fibers from the fibroblasts & osteoblasts. As said earlier, collagen is the prime mover for new bone formation. Thus, Magnesium helps both directly and indirectly in enhancing (BMD). Its value is about 0.3% of bone mass. This means that calcium is 60 times more than magnesium but it is still the 2nd most important mineral in the bone [22].

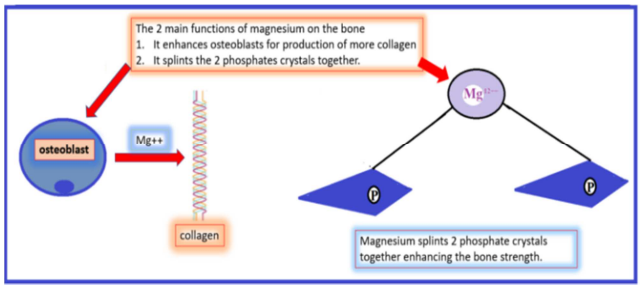

Figure 11. *The effect of Magnesium in the fixation of calcium into the bone i.e BMD.*

4.4.2. Zinc and (BMD)

Zinc (Zn^{30}) is very essential to bone. It is necessary for the proper folding of collagen. As said earlier, the osteoblasts that produce new bone substances can not work properly without normally folded collagen. The other very fundamental function of zinc is that it is necessary for the activation of the Alkaline Phosphatase enzyme (ALP) on the membrane of osteoblasts. This enzyme is necessary for the production of phosphate necessary for calcium precipitation in the bone. In other words, zinc is essential for Calcium to be precipitated in the bone i.e. BMD [23]. In figure 12, zinc is needed for activation of the 2 subunits of the alkaline phosphatase on the membrane of osteoblasts. Zinc is needed for hydrogen bonds that are necessary for the α-folding of the collagen.

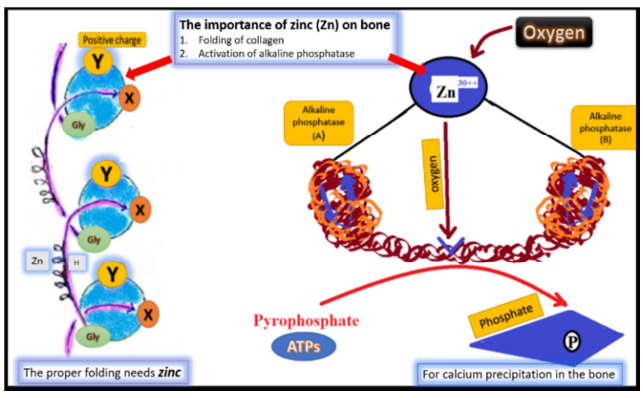

Figure 12. *The effect of zinc in the activation of alkaline phosphatase (ALP) & folding of the collagen.*

4.4.3. Copper and (BMD)

Copper has some benefits for bone mineral density via its activation of enzymes Lysyl Oxidase enzyme (LOX). This enzyme is needed for the cross-linking of the collagen at the site (Y). It is also needed for lysyl hydroxylase enzyme that is necessary for the conversion of proline to hydroxyproline at the site (X). Lastly, copper is very essential for vitamin C which is also needed in the conversion of proline to hydroxyproline for the collagen to be strong. This means copper is needed for the site (Y) in the cross-linking. In site (X), it is needed directly in the hydroxylation of proline and indirectly in the activation of vitamin C that is also needed for the (X) site [24].

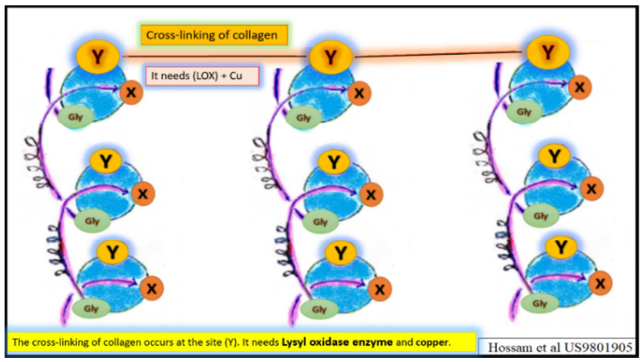

Figure 13. *The effect of copper in the cross-linking of the collagen at the site (Y).*

4.4.4. Iron and (BMD)

The importance of iron in bone is at the Lysyl oxidase enzyme as a co-factor. This is needed for the conversion of proline to hydroxyproline at the site (X) of the collagen. It is needed in very trace amount and has the least importance. This may explain the association between iron deficiency anemia and low BMD [25].

5. Discussion

Low bone mineral density (BMD) is a broad term including both osteopenia & osteoporosis. It acts as an indicator for a higher liability to bone fracture than normally mineralized bone. As discussed above, calcification of the bone is multifactorial. Not all the parameters are equally effective in enhancing the calcification. Some are inside the bone and some are outside the osseous tissues. Therefore, the control of this multifactorial disease is so difficult and sometimes not possible. Moreover, low bone mineral density is usually associated with soft tissue calcification.

The exact mechanism is poorly understood. US patent (US9801905) claimed the internal bone machinery theory. It postulated the Zero Hole of the collagen is the starting point of calcification of the bone which means (bone mineralization). It also claimed that the complicated process of bone mineralization starts at the zero holes and progresses obliquely in the zero channels. This process depends on the interaction between the functional collagen & osteoblasts. Subsequently, the production of osteoblastic vesicles occurs which are building blocks of the apatite chips deposited in the Zero Holes. These gradually ascend obliquely in the zero channels till the whole bone becomes calcified or mineralized.

This process is more or less similar to a gearbox of multiple cogwheels. The functional collagen is 1st wheel, and 2nd wheel is the activation of osteoblasts to produce the osteoblastic vesicles. The 3rd wheel is the precipitation of apatite chips in the zero holes then ascend in the zero channels. Therefore, it named this process (internal bone machinery). Damage of the 1st step of the machinery is associated with a complete breakdown of the machinery and the prevention of the process of mineralization.

To sum up the above step, the glycation of the collagen is associated with a reduction of bone mineral density (BMD). Therefore, the collagen of the bone, if functional, acts as the prime mover for new bone formation and the most important point is the zero holes of the collagen. In other words, the zero holes mechanics is the most important point in the mineralization of the bone. All other factors of mineralization like visceral fat, hyperinsulinemia, other minerals, hormonal status, and so on have some effect on modulating or reshaping the mineralization process. In other words, they are just adjuvants or co-factor that may enhance the mineralization process if they are at their optimal level. They also may have some inhibitory effect on the mineralization if they are not at their optimal level but they can not stop completely the mineralization. Therefore, The BMD depends on the mechanics of the zero holes & zero channels of the collagen.

Regarding soft tissue calcification, it occurs in tissue damage. It is well-known that the cell membrane of every cell in the body contains phosphates in its lipid membrane. Tissue damage causes disintegration of the lipid membrane and the phosphate particles escape in the tissue spaces in the area of the damage. As said earlier, phosphate crystals are the site where calcium ions can be precipitated in the tissue because it has a high affinity to phosphate. The best example of soft tissue calcification is that of arteries as a result of hypertension. The mechanism is that hypertension causes repeated trauma to the wall of blood vessels. This causes the damage of some cells of the media with the release of phosphate crystals from the damaged cells. The calcium ions are precipitated to these phosphate crystals causing calcification of the affected blood vessel.

The big question here is why the low BMD is associated with soft tissue calcification. The answer is present in the adjuvant parameters like visceral fat, hormonal status, hyperinsulinemia. These parameters *could modify* the process of bone mineralization. If these parameters are not in optimal condition for bone, they would make low BMD and at the same time, they would be a favorable medium for soft tissue calcification.

It may be concluded that these adjuvant parameters can oppositely affect the bone to that of the soft tissues. An example of that is visceral fat which has an inhibitory effect on the bone mineralization via (NF-kB)-(RANK) pathway. At the same time, It has a stimulatory effect on arterial calcification via the same mechanism via damage of the arterial wall via

(NF-kB) that causes the release of phosphate crystals from the dead cells as a result of subclinical chronic inflammation. The net result of this discussion, if the BMD is low in the elderly, it is expected that there would be associated soft tissue calcification by the same token.

6. Conclusion

The BMD is referred to as a bone mineral or inorganic component of the bone. It is called apatite which is formed mainly of calcium & phosphorous hydroxyapatite. The part that appears in the X-ray is the Calcium which is large enough to reflect the X-ray wave. This is why the bone is a radio-opaque structure. However, calcium is the main mineral of the bone and it is the cause of its opacity, its supplementation is not effective in improving BMD. Moreover, Calcium supplementation sometimes would be very hazardous as it precipitates in the soft tissues. this dangerous step is called soft tissue calcification which is usually associated with soft tissue damage. For the calcium to be anchored inside the bone, it needs certain pre-requisites which are multi-factorial. Some of these factors are inside the bone itself and some are outside the bone. The factors that are inside the bone are the functional collagen & the communication between the bone cells. Moreover, there there is a higher level of collaboration between the collagen and the different types of bone cells. Regarding the extra-osseous factors that control bone mineralization are hormonal homeostasis, the serum level of some minerals, visceral fat, and serum insulin levels. All these extra-osseous factors are considered adjuvant factors that may modify the process of mineralization of the bone. The adjuvant factor may not have the upper hand as that of the bone like the collagen and bone cells but they still have an important effect in bone mineralization. The most important effect of the extra-osseous factors is that their disturbance from normal is the starting point of soft tissue calcification. Their disturbance makes the bone more resistant to calcium to be anchored or at least hinders this process. The calcium has difficulty being anchored to the bone but it gets access to other soft tissue to be precipitated there. This is the explanation that low BMD is almost always associated with soft tissue calcification outside the bone. All this mechanism can be explained via a better understanding of the molecular mechanics of the zero holes of the collagen. This is the explanation of the mechanism of mineralization where the apatite chips are deposited and ascend obliquely in the zero channels. The clinical benefit of this paper is that low BMD may not be treated by calcium supplementation which may be not only of no clinical benefit but may be hazardous because it increases the soft tissue calcification. The process of mineralization is so complicated and needs to be treated at the root level and not just supplementation of calcium. The function of the collagen and other extra-osseous factors are overlooked in most of the papers before the (US9801905). This is why all the contributing factors of low BMD have to be addressed otherwise wrong treatment of the condition may be associated with more side effects like more soft tissue calcification.

7. The Recommendation for Future Studies

1. By deep studying the molecular mechanisms of the zero holes & zero channels, it is suggested that the bone resistance to calcium theory is the most acceptable one for enhancing the BMD and the prevention of soft tissue calcification. The medium of the bone needs to be more suitable to accept the calcium anchoring and fixation to the bone. By the same token, the calcium would not access the soft tissue and soft tissue calcification could be also prevented by controlling the extra-osseous adjuvant factors.
2. The Zero holes and zero channels act as the dark matter of the bone. This overlooked area is filled with many deep and hidden secrets of how the bone works. It is very recommended for further study to pay further attention to these areas more deeply. These areas act as undiscovered vistas. As said earlier, it does not control only the bone but also soft tissue calcification all over the human body. This is the suggestion in the US9801905 that hyperinsulinemia is DM IV.

References

[1] Robin M. Daly, 2010, Is Excess Calcium Harmful to Health? Nutrients. 2 (5): 505–522.

[2] Kun Zhu. 2012. Calcium and Bone. Clinic Biochem. 45 (12): 936-42.

[3] Rinaldo Florencio-Silva. 2015. Biology of Bone Tissue: Structure, Function, and Factors That Influence Bone Cells. Biomedical research international. 421746.

[4] Andrew J. Spiro. 2019. ARTIFACTS AFFECTING DUAL-ENERGY X-RAY ABSORPTIOMETRY MEASUREMENTS. AACE clinical case Reports. 5 (4): e263–e266.

[5] FriedaFeldman. 1986. Soft tissue mineralization: Roentgen analysis. Current problems in diagnostic radiology. Volume 15, Issue 3. Pages 166-240.

[6] Dimitrios J Hadjidakis, 2006. Bone Remodeling. Women's Health and Disease: Gynecologic, Endocrine, and Reproductive. Volume 1092, Issue 1. Pages 385-396.

[7] Stuart H Ralston. 2015. Diagnosis and Management of osteoporosis. Practitioner. 259 (1788): 15-9, 2.

[8] E. Legrand. 1999. Bone Mineral Density and Vertebral Fractures in Men. Osteoporosis International. 10, pages 265–270.

[9] Hossam Mohamed. 2017. Use of organic sulphur, antioxidants, and amino acids in conjunction with exercise and electromagnetic stimulation to treat osteoporosis. US patent. US9801905. https://patents.google.com/patent/US9801905B2/en.

[10] Hossam Mohamed. 2021. Hossam Osteonic Circulation (HOC) Deciphers the Root Causes of osteoporosis & Reveals the Hidden Secrets of the Physiological Lines of Its Treatment: US Patent Review. Frontiers. Volume 1, Issue 4, December 2021, Pages: 89-99.

[11] R G Paul. 1996. Glycation of collagen: the basis of its central role in the late complications of ageing and diabetes. The International Journal of Biochemistry & Cell Biology. Volume 28, Issue 12, Pages 1297-1310.

[12] Debonil Maity. 2019. Response of Collagen Matrices Under Pressure and Hydraulic Resistance in Hydrogels. Soft Matter. 15 (12): 2617–2626.

[13] Wenzhen Yin, 2019. Modulation of Bone and Marrow Niche by Cholesterol. Nutrients. 11 (6): 1394.

[14] Vikram V Shanbhogue. 2016. Association Between Insulin Resistance and Bone Structure in Nondiabetic Postmenopausal Women. Clinical Endocrinal Metabolism 101 (8): 3114-22.

[15] Naomi Dirckx. 2019. The role of osteoblasts in energy homeostasis. Nature Reviews Endocrinology volume 15, pages 651–665.

[16] William J. Boyle. 2003. Osteoclast differentiation and activation. Nature volume 423, pages 337–342.

[17] Daniel D. Bikle. 2012. Vitamin D and Bone. Current Osteoporosis Reports volume 10, pages 151–159.

[18] Chen-Yuan Hsiao, 2020. Calcitonin Induces Bone Formation by Increasing Expression of Wnt10b in Osteoclasts in Ovariectomy-Induced Osteoporotic Rats. Frontiers Endocrinology. Volume 11. Article 613.

[19] G Lombardi. 2011. The roles of parathyroid hormone in bone remodeling: prospects for novel therapeutics. J Endocrinol Invest vol 34 (7 Suppl): 18-22.

[20] Yahtyng Sheu. 2014. The Role of Bone Marrow and Visceral Fat on Bone Metabolism. Curr Osteoporos Rep. 9 (2): 67–75.

[21] Kaisa K Ivaska. 2015. The effects of acute hyperinsulinemia on bone metabolism. Endocrinal Connections. Vol 4 (3): 155–162.

[22] Sara Castiglioni. 2013. Magnesium and Osteoporosis: Current State of Knowledge and Future Research Directions. Nutrients. 5 (8): 3022–3033.

[23] J. Patrick O'Connor. 2020. Zinc as a Therapeutic Agent in Bone Regeneration. Materials (Basel). vol. 13 (10): 2211.

[24] Xinhua Qu. 2018. Serum copper levels are associated with bone mineral density and total fracture. J Orthopedic Translation. 14: 34–44.

[25] Laura Toxqui. 2015. Chronic Iron Deficiency as an Emerging Risk Factor for Osteoporosis: A Hypothesis. Nutrients. Vol 7 (4): 2324–2344.

[26] Hossam Mohamed. 2021. Visceral Fat-Glycation Interaction Deciphers the Hidden Roots of the Refractory Type of Osteoporosis: US Patent Review. Frontiers Volume 1, Issue 4, Pages: 100-111.

[27] Hossam Mohamed, 2017. Use of organic sulphur, antioxidants, and amino acids in conjunction with exercise and electromagnetic stimulation to treat osteoporosis. https://pubchem.ncbi.nlm.nih.gov/patent/US9801905.