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Hossam Osteonic Circulation (HOC) Deciphers the Root Causes of *osteoporosis* & Reveals the Hidden Secrets of the Physiological Lines of Its Treatment: US Patent Review

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Abstract: Osteoporosis is a catastrophic disease that affects the elderly population. There is continuous bone remodeling throughout the patient life. The bone has different biomechanical principles that may change in the elderly and may be the cause of osteoporosis. The bone is the only tissue that has no capillaries or lymphatic system. The arterial system of the Haverian canal (H.C.) has more than normal wide fenestrations. On the other hand, The vein of the Haversian canal (H.C) has very narrow pores with tight junctions that allow raising the pressure inside the H.C. Therefore, the arterial filtrate would be directed peripherally to the rest of the osteon via the lacunar canalicular pathway towards the *cement line* which is very dense collagen fiber and bone matrix. The bone cells are arranged in *circles* around and outside the Haversian Canal. This raises a question mark how the osteocytes can get their oxygen and nutrition in absence of a capillary system. The only acceptable theory is the presence of *a novel circulation* in each osteon and it is responsible for the nutrition and integrity of the bone cells. Disturbance of this circulation causes the bone cells to become sick or even to die with subsequent reduction of the bone mass and osteoporosis gradually issues. This paper discusses the mechanics of osteonic circulation by paying attention to all the key factors that may have a role in its performance. It is strongly believed that restoring this circulation is the fundamental element for the healing of osteoporosis.

Keywords: Osteonic Circulation, Sacrificial Bonds, Osteoporosis, Piezoelectricity, Glycation, Zero-hole, Zero-channel

1. Introduction

1.1. The Bone Is of a Relatively Low Blood Supply

It is well-known that bone is a tissue of a relatively low blood supply in comparison with other tissues of the human body. For example, the weight of human bone varies from *11 to 14 kg*. It is greatly variable according to many parameters namely, male or female, body weight, height, and other many factors [1]. The blood supply for the whole bone is about *10%* of the cardiac output [2]. On the other hand, the heart weight is about *280 gm* which means less than 1/3 kg but it receives *20%* of the cardiac output [3, 4]. The brain weight is about *1300 gm* and receives about *18%* of the cardiac output [5]. This concludes that the bone has a relatively less blood supply than most of the other organs of the human body. *This relative low vascularity of the bone is very essential for the bone to do its proper mechanical function*.

This is explained in detail in the granted US patent (US9801905) that shows the bone has a micro-flexibility that has a great effect in the prevention of bone fracture under externally applied mechanical stress. Moreover, the maintenance of the proper blood supply to the bone is a cornerstone to prevent osteoporosis. In other words, the disturbance of the blood supply of the bone is the starting point of osteoporosis. The most critical point is that the bone has no capillary system. This means that filtrate from the arterial system has to go via another system other than the capillaries to the venous side. Another important point is that the veins of the Haversian canal have narrow pores with tight

junctions that lead to raising of the tension inside the (H.C) and the filtrate rushes to the lacunar canalicular system. Subsequently, the filtrate can supply the cells with oxygen and nutrition in the outer zone of the osteon.

Table 1. *This shows that the bone has a relatively low blood supply.*

Comparison	Bone	heart	brain
Weight	11-14 Kgm/ body weight	280 gm	1300 gm
percentage Circulation	10% of the cardiac output	20% of cardiac output	18% of cardiac output
The arterial system	wide pores cause the filtrate to be under high pressure	Normal	normal
Venous system	Has narrow pores with tight junctions that allow the filtrate to out of H.C. towards LCP	normal	normal
Capillary system	Absent (replaced by a system of porosities.	present	present

1.2. Functional Collagen Plays a Key Role in Maintaining the New Bone Formation

The key factor to maintain the blood supply to the bone within the normal range is the functional collagen. This paper would explain the exact relation between bone vascularity and the functional collagen of the bone. At the end of this paper, it would be proved that the correction of osteoporosis depends on the recovery of the functional collagen [6, 7]. Therefore, osteoporosis is not corrected by increasing the bone mineral density (*BMD*) as it is thought. The recovery of the functional collagen is the most important element because it restores the normal blood supply of the *bone cells* with subsequent enhancement of their proper function as bone-forming cells [6]. The functional collagen of bone can do its function via controlling the osteoblasts, the osteonic circulation, and the sacrificial bonds. Moreover, each one of these components of the bone is interacting with one another as in *figure 1*. The osteonic circulation, the sacrificial bonds, and osteoblasts of the bone act as *cogwheels of the internal bone machinery*. The collagen loses its proper function in the elderly if it is glycated i.e non-enzymatic attachment of the glucose to the collagen. Then, the collagen becomes dysfunctional.

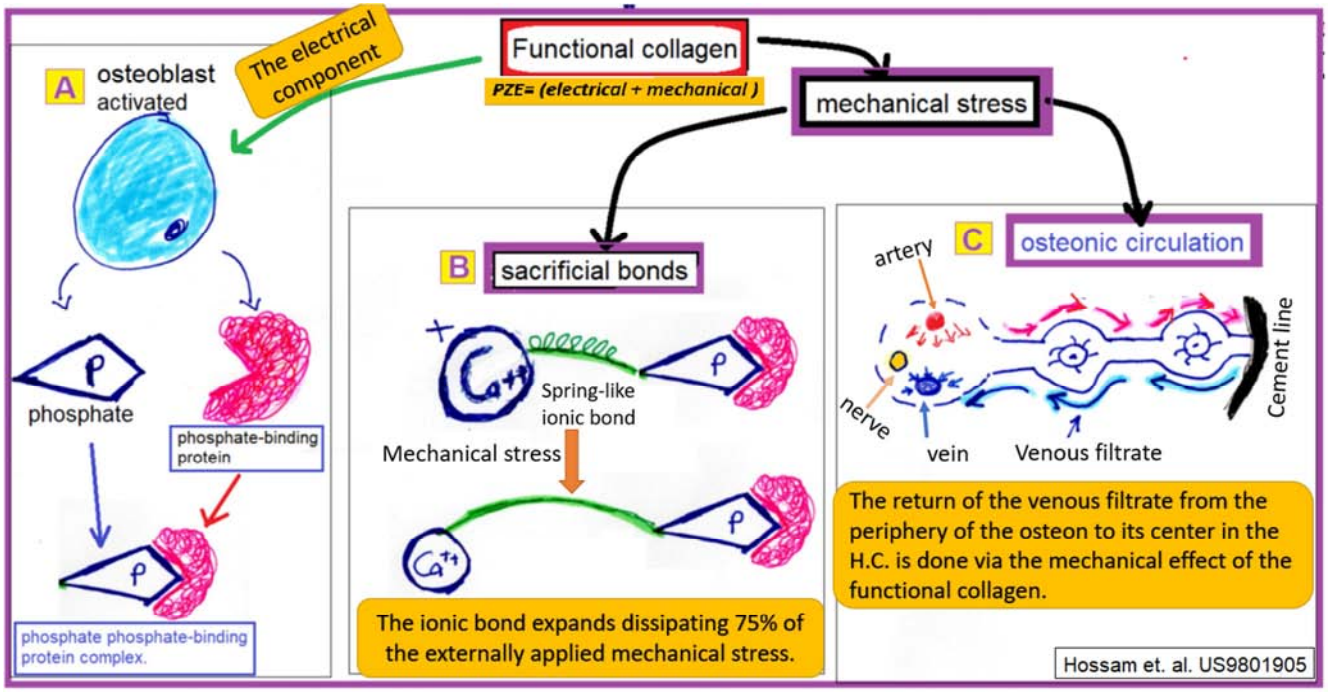

Figure 1. *The functional collagen controls all the components of internal bone machinery.*

1.3. The Already Present Concept of Osteoporosis

The mainstream concept considers osteoporosis just as an increase in bone resorption. Thus, all the efforts for the treatment of osteoporosis are exerted to reduce bone resorption. This explains why all medications in the market are directed to decrease bone resorption. Bisphosphonates medications are by far the commonest in the markets. Their mechanism of action is to reduce bone resorption via inhibiting the osteoclasts (bone-eating cells) or even killing them. Thus, the bone density would be markedly increased very much but becomes *dysfunctional*. Therefore, the bone is liable to fracture even if it is of a very high bone mineral density (*BMD*) e.g. Atypical Fracture [8]. It must be noted that this mechanism of treatment is very hazardous and is associated with many other complications like gastrointestinal upset, hepatorenal toxicity, esophageal irritation, and others that will be discussed later [20].

2. The Molecular Mechanics of the Bone

2.1. The 3 Main Components of the Bone

1. The *apatite* is the inorganic part of the bone and is formed mainly of calcium, phosphate, hydroxyl groups. It also contains other minor amounts of minerals such as magnesium and zinc. A very trace amount of copper, manganese, molybdenum, and iron are also present. It *forms 50% of the bone mass*. It supports 2/3 of the compressive force of the bone and 1/3 of the tensile force applied to the bone. The chemical composition is (Ca_{10}, $(PO_4)_6$, $(OH)_2$) [9].
2. *Collagen type I* forms most of the organic part of the bone. It forms about 28% of the bone mass. The osteonic circulation theory proves that the collagen has a very important function other than the supportive one which is the *piezo-electric* (PZE) property of the bone [6]. This means that the collagen can convert the mechanical stress into an *electrical gradient difference* (EGD) that can *initiate & maintain* bone remodeling. It must be stressed that the collagen must be functional to perform its piezoelectric property.

   NB: there are a very small amount of non-collagenous proteins namely: *sialoprotein, osteopontin, osteocalcin, osteonectin*. These proteins have a very important function in the formation of the *sacrificial bonds* of the bone which is called hidden length [10]. These bonds are responsible for 2 main functions: the dissipation of 75% of the externally applied mechanical stress. Thus, they have a great rule in the prevention of bone fracture under repeated mechanical loading. Also, the sacrificial bonds are the drive for the venous filtrate to go back from the periphery of the osteon to the Haversian canal to be excreted through the venous system [11].
3. The *water content* of the bone forms about *22%* of the bone weight. It is responsible for the nutrition of the bone cells via *the suggested osteonic circulation*. It has been divided into 3 parts of *porosities* as will be discussed later: vascular porosity (*VP*), lacunar canalicular porosity (*LCP*), and collagen apatite porosity *(CAP*) [12].

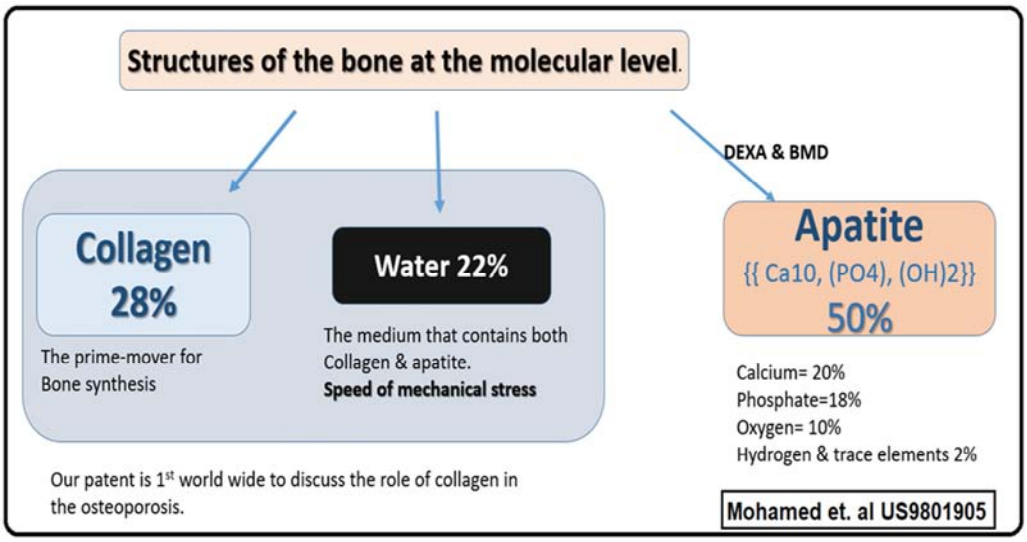

Figure 2. *The three main components of the bone.*

2.2. The Molecular Mechanics of the Osteon

The bone is formed of very small units that are arranged in circles. These circles are called osteons. Each circle acts as a separate unit that has its independent blood and nerve supply. Each one is surrounded by thick fibrous tissue called the cement line that separates each osteon from the others [13]. The size of osteon is about 200u. The central part of the osteon shows the Haversian canal (H.C.) that contains the artery, vein, and nerve [14]. As shown in figure 3.

The artery inside the Haversian canal {H.C} has special characteristics that make it different from other arteries of the human body. The artery has an endothelium with very wide side-fenestrations that make filtration to be under very high pressure. On the opposite side, the vein has very narrow fenestrations with tight junctions. The difference between the arterial and venous system creates a high tension inside the Haversian canal (H.C) which pushes the arterial filtrate out of (H.C) to the outer zone of the osteon towards the cement line passing through the *lacunar-canalicular porosity* (LCP). The return of the filtrate from the periphery of the osteon towards its center to the (H.C) again depends on the integrity of the collagen and the sacrificial bonds which has a spring-like effect.

It must be noted that the arterial filtrate is that expelled from the H.C towards the periphery of the osteon is rich in nutrition and oxygen. While the venous filtrate passes from the periphery of the osteon towards its center to the H.C. is rich in waste products & carbon dioxide. The drive for the venous filtrate is the integrity of the sacrificial bond which is also dependant on functional collagen as in figure 1.

Table 2. *The comparison between the arterial and venous filtrate of the osteonic circulation.*

comparison	Arterial filtrate	Venous filtrate
direction	From H.C to the periphery of the osteon	From the periphery to central towards the H.C.
composition	Rich in oxygen and nutrition	Rich in carbon dioxide and waste products
function	Supplying the bone cells with oxygen and nutrition.	Allows the cells to eliminate the waste products and carbon dioxide
The drive	High arterial filtration and narrow venous system	The integrity of the sacrificial bonds that act as spring-like to return the fluid to H.C
Sluggish circulation	Stop of the arterial system to lose oxygen and nutrition and cells become sicks and/or even die	The cells can not get rid of the waste products and the cells start to suffer and also become sick and/or even die

From the above table, sick or dead bone cells can not manufacture new bone. The new bone formation stops while the bone resorption continues. The net result is osteoporosis i.e gradual loss of the bone mass which becomes liable to fracture with mild trauma.

2.3. The Three Anatomical Zones of the Osteon

The osteon is the basic functional unit of the bone. It is 200 um in diameter. It is formed of a central channel known as Haversian Canal (H.C.). This is surrounded by growing circles of collagen and apatites chips. The orientation of the collagen and apatite chips is very important in the bone mechanical function (described later). The osteon has 3 zones of porosities.

1. *The central zone* (Haversian canal) is *50 um* in diameter. it has a very high pressure relative to the outer zone. The Filtration force is 10^8 as that of the outer zone which is lacunar canalicular porosity (LCP). The Haversian Canal is surrounded by an interrupted line called a *quasi-circular arc* [15].
2. *The 2nd zone* is called *lacunar-canalicular porosity (LCP)*. It extends from the quasi-circular arc to the cement line. This zone contains the bone cells which are present in lacunae and have processes in the canaliculi. Thus, its name just describes it as lacunar canalicular porosity *(LCP*) as in figure 3. Its diameter is from 10 to 20 nm. The pressure inside this zone is much lower than that of the Haversian canal [16].
3. The *collagen-apatite porosity (CAP)* is the area between the collagen and apatite chips. This zone is very narrow about *10 nm*. It also shows the fluids that are responsible for raising the pressure inside the osteon. It acts as a *valve-like* for the venous filtrate to return to Haversian Canal (H.C.). The collagen-apatite porosity (CAP) is essential for bone calcification. The orientation between the apatite and collagen is shown in figure 4. The space between the collagen molecule is *40 nm* where apatite chips could be assembled. The apatite chip size *is 5X20X 50* nm. This suggested that apatite chips must be *vertically* oriented in the zone between collagen bundles & horizontally oriented in the oblique channel between the collagen fibers. The space between the collagen fibers is called the *zero-hole* which is 40nm. This is the 1st site of calcification. The space of zero-hole ascends obliquely as the zero channel which is also 40nm. The apatite chips are deposited at the beginning in the zero-hole then it obliquely ascends in the zero channel. This explains the calcification occurs in the zero-hole followed by the zero-channels [figure 4].

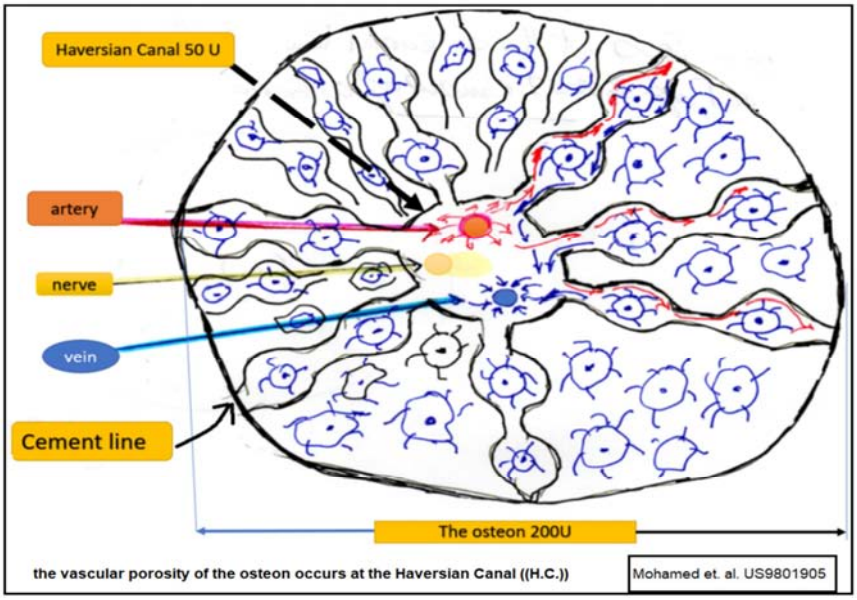

Figure 3. *The 3 anatomical zones of the osteons.*

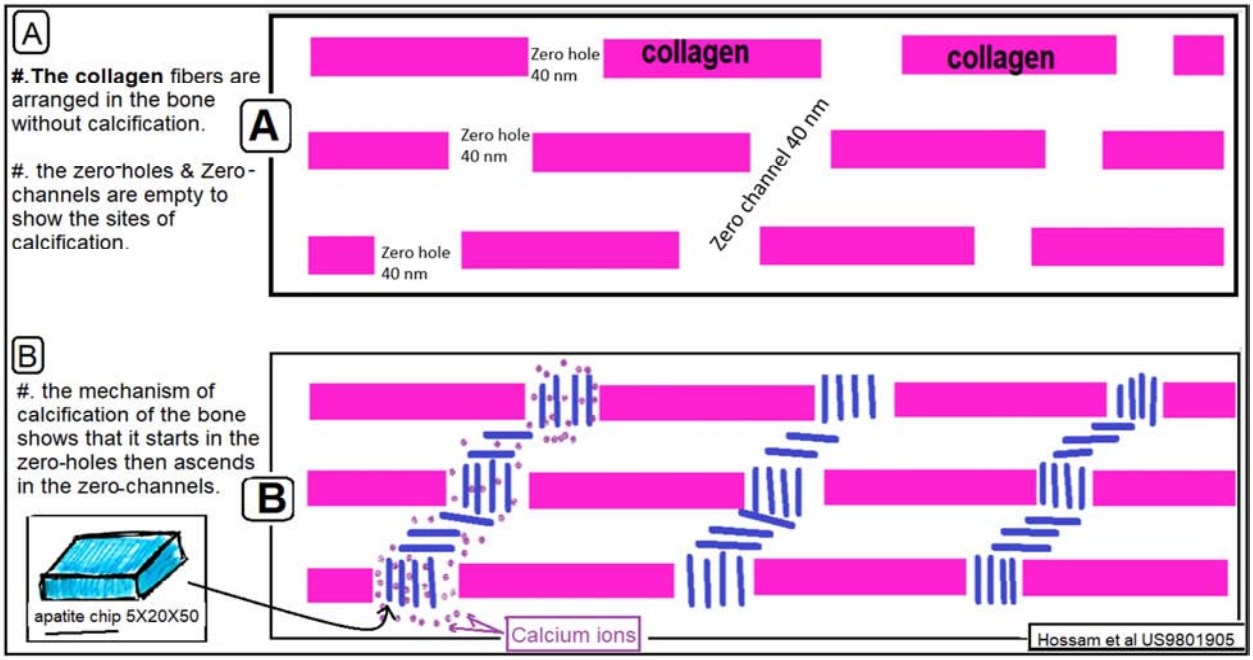

Figure 4. *The orientation of collagen and apatite shows collagen-apatite-porosity [CAP]. It shows also zero-hole 40nm & obliquely ascending the zero-channel which is also 40nm. This is very important in bone calcification which starts in the zero-hole. Then, it progresses obliquely to the zero-channel.*

Table 3. *The Comparison between the 3 types of porosities.*

Comparison	Vascular porosity (VP)	Lacunar canalicular porosity (LCP)	Collagen apatite porosity (CAP)
Site	In the center (H.C.)	In the remaining osteon between the quasi-circular arc and cement line in the LCP	In the calcified fibrous part of the osteon like the cement line and around the LCP
Pressure	Very high	lower	Intermittently high at the mechanical loading. Then, it drops on unloading
The drive	Arterial-venous difference	The difference between VP & LCP	The sacrificial bonds and the integrity of the functional collagen under mechanical loading
Importance	Creates the arterial filtrate	Supply of the bone cells with oxygen and nutrition.	The drive for return of venous filtrate and also the starting point of calcification at zero-hole & zero channel
Size	50 um	10-20 um	10 nm
components	Artery, vein, and nerve of the H.C.	The osteocytes in the lacunae and the processes in the canaliculi.	The apatite chips are arranged between the collagen in the zero-hole and ascend obliquely in the zero-channel

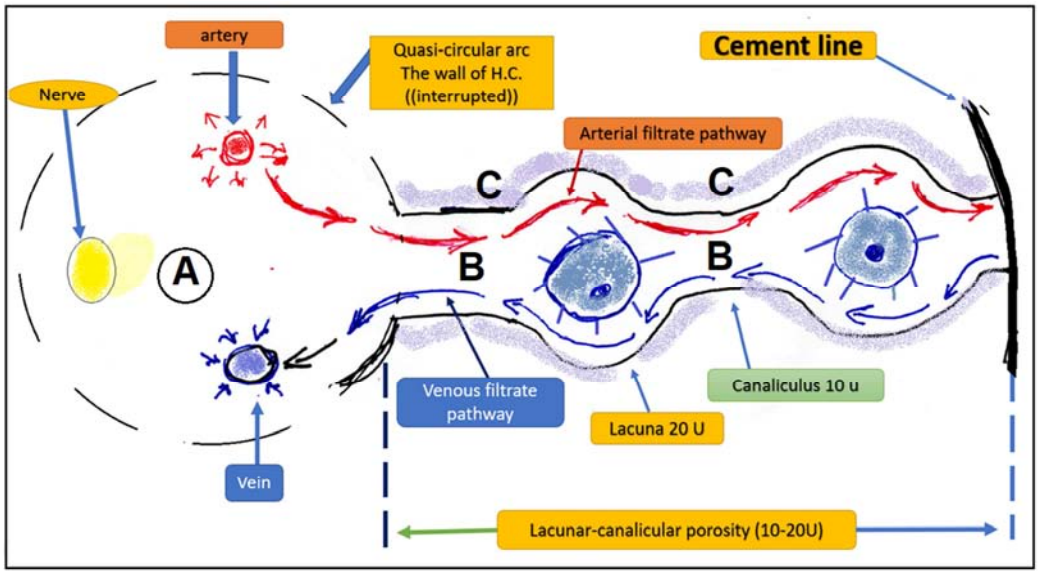

Figure 5. *The osteonic circulation shows the three zones; A). VP, B) LCP, C) CAP.*

3. Hossam Osteonic Circulation (HOC)

3.1. The Osteonic Circulation

As the cells are present only in the outer zone, they are relatively away from the blood supply in the Haversian canal. It is postulated that bone cells get their nutrition and oxygen from the filtrate from the arterial system and passes in the following steps:

1. The arterial system has wide pore fenestration that causes filtration in the central H.C.
2. The venous system has narrow pores and tight junctions that prevent the arterial filtrate from *easily* escaping to the venous side.
3. There is no capillary system in the H.C. This means there is no direct connection between the arterial and venous systems.
4. The created high pressure inside the (H.C.) enforces the filtrate to rush from the (H.C.) through the interrupted quasi-circular arc to the periphery of the osteon.
5. The escaped fluid is called arterial filtrate and is driven mainly by high arterial pressure & a narrow venous system. It is rich in *oxygen and nutrition* to supply the bone cells with oxygen and nutrition. It helps the cells to flourish and to build new bone.
6. After the filtrate reaches the periphery of the osteon near the cement line, it would lose *most* of oxygen and nutrition. The sacrificial bonds, if intact, push the fluid back to the Haversian canal under the intermittently applied mechanical stress.
7. On the course of the return of the filtrate, the bone cells pour their waste products and carbon dioxide into that fluid. This is why this fluid is called the *venous filtrate*.
8. The intermittent high pressure abruptly increases by the conformation of the functional collagen and the sacrificial bonds enforcing some of this fluid to escape through the semi-closed valve-like venous system. Thus, the circulation is completed.
9. The above circulation is repeated with every loading-unloading cycle. Its main provision is the presence of healthy and functional collagen that is responsible for the sacrificial bonds and activation of osteoblasts.

3.2. The Effect of Osteonic Circulation on Osteoporosis

The bone is considered a confined space. For the osteonic circulation to occur properly, it has to have 2 drives.

1. The 1st drive is the high pressure created in the Haversian canal from the pressure differences between arterial & venous systems. An arterial filtrate is created under very high pressure inside the H.C. but it can not escape from the venous system due to the presence of valve-like narrow holes and the tight junctions of the venous system.
2. The 2nd drive is the functional collagen that creates the sacrificial bonds that can contract and relax under the mechanical loading-unloading cycle. Therefore, the sacrificial bonds act as a spring-like to push the venous filtrate from the lacunar canalicular back to the venous side of the Haversian canal as in figure 6.

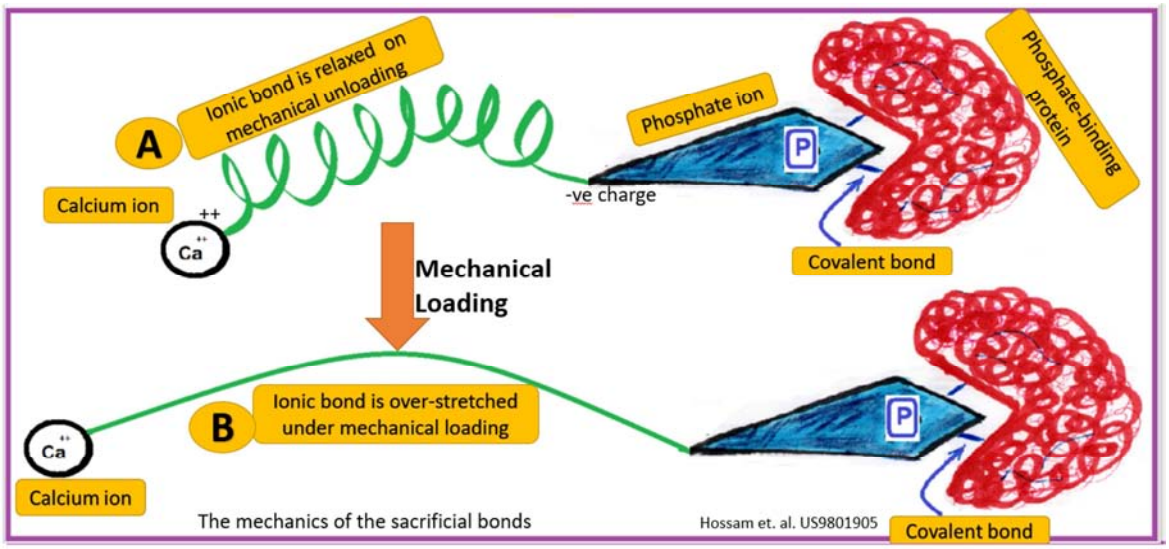

Figure 6. *The mechanics of the sacrificial bond as a shock absorbing mechanism of the bone. The phosphate ion has 2 sets of bonds on its either side; the ionic & the covalent bonds. The ionic is weaker & has a spring-like potential.*

Table 4. *The comparison between the bone and abalone shell regarding the sacrificial bonds.*

The comparison	The bone	The abalone shell
protein	Collagen and phosphate binding protein	The protein of the shell
Water content	22%	30%
The inorganic	Apatite (Ca_{10}), $(PO_4)_6$, $OH)_2$}}	Ca_{10},$(CO_3)_6$, $(OH)_2$
The sacrificial bonds	Is the ionic bond between the calcium and *phosphate* of the bone	Is the ionic bond between calcium and *carbonate*.

3.3. The Sacrificial Bonds

This is a novel theory that claims that the protein binding phosphate has a *covalent bond* with phosphate while the calcium makes *an ionic bond* with phosphate. This means that phosphate has 2 different types of bonds on its either side. As the covalent is stronger than the ionic, the ionic with calcium *yields* under mechanical stress. This sacrificial bond is responsible for the shock absorption of 75% of the externally applied mechanical stress to the bone. This theory is inspired by the abalone shell as in table 4. In an Abalone shell, the removal of the proteins causes the shell to become much weaker. On application of this theory to the bone, the bone becomes weak on the removal of its proteins. The protein component of the abalone shell increases its strength *3000 times.* This theory is called hidden length [18]. Another important function of the sacrificial bond is that it acts as a spring-like which drives the return of the venous filtrate from the periphery of the osteon to its center. i.e the Haversian Canal (H.C). The spring-like effect of the sacrificial bond is explained in figure [6].

4. Discussion

The osteonic circulation opens the gate for the treatment of osteoporosis at its *root level*. The lines of the treatment of osteoporosis via the roles of the osteonic circulation are done via natural supplements. This method of treatment usually has no side effects and is also more effective at the same time. All the other lines of the treatment, other than osteonic circulation, are done via pharmaceutical compounds that usually have many side effects and may be less effective as well. This is because all other alternative methods look at osteoporosis from only *one angle.* They consider osteoporosis as just an increase the bone resorption. *Thus, they tried their best to reduce bone resorption as can as possible*. The main mechanical drawback of all these methods is the newly formed bone is haphazardly oriented and fills the whole surface area of the bone. This is not physiological and may be associated with many side effects including the atypical fracture.

A comparison between the principles of osteonic circulation and all other methods for the treatment of osteoporosis.

4.1. The Basic Principles of the Osteonic Circulation

The bone is the only tissue that has *no capillary* or *lymphatic* system. Moreover, the arterial and venous systems are very near to each other in the Haversian Canal and the bone cells are arranged in circles outside the H.C. This creates a big question mark of how the bone cells could get their nutrition while they are relatively far away from the arterial system in absence of the capillary system in the same time.

1. The artery of the Haversian canal has very wide side pores for the filtration process. Thus, the filtrate would rush under very high pressure.
2. The vein of the H.C. has valve-like narrow pores with tight junctions which raises the tension inside the (H.C). Thus, the filtrate is forced to escape from H.C. through the Pores *of Quasi-circular arc* towards the periphery of the osteon.
3. The rushed arterial filtrate is rich in oxygen and nutrition and passes from central to peripheral. i.e. from the H.C. towards the cement line passing through the LCP.
4. The return of the venous filtrate carrying carbon dioxide and other waste products to the vein only if the collagen is functional. This loading-unloading cycle compresses the venous filtrate back from the periphery of the osteon to the H.C. as shown in figure 5.
5. It also has a very important protective function of the bone that the sacrificial bonds *dissipate* 75% of externally applied mechanical stress. Thus, the bone is protected from the accumulation of repeated mechanical loading that may lead to a stress fracture in cases of a deficiency of the sacrificial bonds.

4.2. The Explanation of Osteoporosis from the Osteonic Circulation Perspective

It must be postulated that there is a circulation at the osteonic level. The more the sluggish of this circulation, the more the *peripheral osteocytes* to suffer or even to die. As the osteocytes are responsible for the new bone formation, the death of these cells or part of them would lead to a decrease in the new bone formation with subsequent osteoporosis.

The drive of pushing the arterial filtrate out of the H.C. is via the vascular system of the H.C. especially the Vein which has valve-like narrow pores with tight junctions to prevent the escape of the arterial filtrate. On the other hand, The drive for the return of the venous filtrate from the periphery of the osteon back to the H.C. depends on the functional collagen and subsequently on the sacrificial bonds. If the collagen is *glycated* i.e. dysfunctional, the fluid may not return from the osteon to the H.C. This means *congestion* of the osteon especially in the periphery. The osteocytes become deprived of oxygen and nutrition and they become sick to death. The new bone formation is reduced and osteoporosis occurs.

From all of the above, the *deglycation* of collagen may greatly help osteoporosis via correction of the root causes of the osteoporosis. The deglycation means the recovery of the collagen from being dysfunctional to being functional again. Therefore, the functional collagen allows the stagnant venous filtrate to return to the H.C. The osteocytes recover and start to rebuild the bone again and the osteoporosis is gradually improved.

4.3. Correction of Osteoporosis According to Osteonic Circulation Perspective

For the treatment of osteoporosis at the root causes, The

recovery of the dysfunctional collagen is the basic step. i.e as said earlier, the glycated collagen can not do its proper function as the drive for the sacrificial bonds. Thus, the venous filtrate accumulates and arterial filtrate can not enter the outer zone of the osteon and the peripherally located osteocytes become sick or even die. Thus, restoring the osteonic circulation leads to the recovery of osteocytes. As the osteocytes are responsible for the maintenance of bone, their recovery means new bone formation. Subsequently, osteoporosis gradually improves physiologically.

Examples of the suggested lines of treatment are the combination *of two or more* of the following substances. This regimen may include certain supplements, antioxidants, vitamins, and/or amino acids which include:

1. Alpha-lipoic acid:- it is universal anti-oxidants. Its main function is the blocking of the ((*NF-kB*)) which is the main inflammatory product of the body. In figure 7, (RANK) is produced indirectly from the visceral fat. This is called the (NF-kB)-(RANK) pathway. Alpha-lipoic can block the production of RANK which is the main stimulator of osteoclasts. This is why alpha-lipoic can suppress osteoclasts (bone-eating cells) via a natural method and without side effects [21].
2. Taurine: its main function is the stimulation of new bone formation via enhancing the osteoblasts to secret their vesicles. This mechanism is called the taurine-bone pathway. The other important function is its blockage of ((MCU)) *mitochondrial calcium uniport* that is responsible for the aging of mitochondria which are the powerhouses of the cells. Damage or aging of the mitochondrial of the osteoblasts prevents them from the manufacture of the building blocks of the bone namely the collagen I & apatite chips. Thus, Taurine has a very novel function in enhancing bone mineral density (BMD) in a natural pathway without side effects. [22].
3. MSM:- is the source of organic sulfur which as said earlier its deficiency is the starting point of osteoporosis. Its most important point is its ability to stimulate ((*RUNX2*)) which can convert stem cells to osteoblasts. This could be done via a very complicated mechanism via stimulation of bone morphogenic protein on the osteoblasts (*BMP-2*) Thus, it can enhance new bone formation [23].
4. Lysine: is an essential amino acid that is necessary for the *cross-linking* of collagen. The most important point, from this study, is that lysine is positively charged and occupies the site ((Y)) of the collagen. Thus, it very essential for the collagen to become functional and to work properly. It is well-known that the site ((Y)) is occupied by the Lysine and to lesser extent Arginine, and to the least extent Histidine. These are the only 3 amino acids that are positively charged. The conformation of collagen under mechanical stress causes the site (Y) to shift to the convex side of the collagen. This is the explanation of the creation of the electrically gradient difference (EGD) of the collagen under externally applied mechanical stress. In other words, Lysine enhances piezoelectricity (PZE) that is the drive for osteoblasts, osteonic circulation, and sacrificial bonds. *Piezoelectricity* is the maestro that controls all cogwheel components of the internal bone machinery [24].
5. K2: is a supplemental vitamin. Its main function is gamma-carboxylation of *Matrix Gla protein* (*MGP*). The result of carboxylation is that protein becomes highly negatively charged. It would have a great affinity to calcium at 5 sites of the protein. The active sites of *MGP* are {*2, 37, 41, 48, 52*}. These are the sites that have a high affinity to calcium. These simply transfer the calcium from the soft tissue including the blood vessels, tendons, ligaments, cartilage, heart muscles, valves, etc to the bone. Therefore, the bone is calcified and becomes stronger while the above-affected soft tissues become less calcified, stiff, or inflamed. Thus, K2 is considered an excellent co-factor in the treatment of osteoporosis [25].
6. Citrulline: is an amino acid that does not enter the protein codon. However, it has many important functions in the human body. It acts as the most important source of nitrogen needed for the manufacture of nitric oxide (*NO*). It is needed for vasodilation of the side openings of the Haversian artery. This means enhancing the arterial filtrate with subsequent osteonic circulation. As said earlier, the osteonic circulation is formed of 3 main parts; the 1st two parts (V. P.) & (LCP) depend on the arterial filtrate. Thus, citrulline has a key role in driving two out of the three components of the osteonic circulation. This explains the improvement of the bone mineral density (BMD) in patients receiving citrulline [26].

4.4. The Commonest Other Lines of the Treatment of Osteoporosis

As said earlier all other lines of treatment of osteoporosis, other than osteonic circulation, have the following common drawback criteria:

1. They do not deal with the *root causes* of osteoporosis.
2. They *do not* consider the *osteonic circulation* principles.
3. They may have many side effects.
4. They are almost always pharmaceutical medications.
5. The efficacy of the treatment is doubtful because even increasing the bone mineral density (BMD) can not prevent the fracture. i.e. Atypical fracture.
6. They need a very long time for the osteoporosis to be fully improved 2-5 years according to the severity of the osteoporosis and patient specificity.
7. They have only one parameter for the osteoporosis measurement which is (BMD) which forms only 50% of the bone mass. Therefore, it fails to *predict* the fracture. This means a bone with high (BMD) may fracture while a bone with low (BMD) may not. That is to say, it is not an accurate parameter to measure the degree of the severity of osteoporosis. This leads to the appearance of new parameters like *bone marker turnover* (BMT) [27].

8. The most common lines of treatment of osteoporosis include.

4.4.1. Bisphosphonates

They are by far the commonest medications used worldwide for the treatment of osteoporosis. their mechanism of action is that they deceive the osteoclasts. As they are very similar to the phosphates of the bone, the osteoclasts take them instead of the phosphate ions of the bone. The bisphosphonates accumulate inside these cells and are not digested. The redox chain reaction inside these cells would stop. The affected osteoclasts become sick or even die. Therefore, their mechanism of action is either to kill or at least to cause the osteoclasts to become extremely sick. Thus, they can not perform their role in normal bone resorption. The bone becomes dysfunctional due to the accumulation of faulty bone which makes it liable to be fractured even though its bone mineral density is high. They have many side effects as in table 5.

4.4.2. Denosmab (Monoclonal Anti-bodies)

These act as decoy antibodies that attack reactive activators nuclear factor ((*RANK*)) proteins. As said earlier, the ((RANK)) is the main stimulator of osteoclasts. Thus, the osteoclasts are deprived of their main activators. The osteoclasts become inactive and bone resorption is greatly reduced. This method has the same side effects as that of the bisphosphonates and sometimes it is more dangerous.

4.4.3. Teriparatide: (Derivative of Parathormone Hormone)

The parathormone hormone is of a protein origin. Recent studies show that taking only the 1st 34 aminoacids is associated with enhanced bone mineral density. This technique is very expensive as it deals with genetic engineering. The long-term efficacy is not proved because it is very recent and mass studies are not done yet.

4.4.4. Calcitonin

It is a hormone from the thyroid gland that causes more bone calcification. Its main drawback is that after its supplementation for 3 months or so, the normally secreted calcitonin is suppressed via the negative feedback mechanism. The treatment of osteoporosis needs a very long time. The usual course of treatment of osteoporosis usually takes more than one year. The commonest cases heal from 2 years to 5 years. These variations depend on many factors including the severity of the osteoporosis, the degree of response of each patient which shows individual specificity. Thus, the treatment with calcitonin for only 3 months is a very short period for the treatment of osteoporosis. Therefore, it can not be recommended because, after 3 months, the patient develops shut down of his normal calcitonin while the course of his treatment is still in his early stages.

4.5. Summary of the Discussion

This discussion shows that osteonic circulation theory is a new modality in the medical treatment of osteoporosis that has many advantages:

1. Targeting osteoporosis at its root causes.
2. No or very minimal side effects
3. More physiological as the bone regain its micro-flexibility which is the main protective against stress fracture. The new bone is formed only at the lines of the mechanical stress.
4. This theory is the 1st to pay attention to the osteocytes in the *periphery of the osteon* near the cement lines. This is the starting location of osteoporosis. this area shows congestion of the osteon with low oxygen and nutrition. The recovery also needs to start from this area.

All other methods of treatment of osteoporosis depend on just the killing or damaging of osteoclasts. Thus, the bone resorption is reduced to its minimum. Subsequently, bone mineral density (BMD) is enhanced. This occurs at expense of the *quality* of the bone that even it has high BMD, it is still more liable to fracture than before the medical treatment e.g. Atypical fracture.

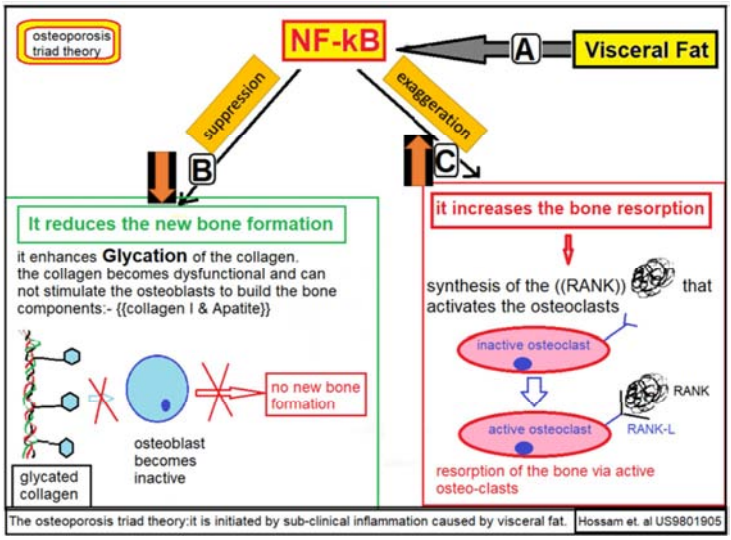

Figure 7. *The root causes of osteoporosis occur at 3 levels: general subclinical inflammation, reduced new bone formation, and/or increased bone resorption.*

Table 5. *Comparison between the lines of treatment of osteoporosis between the root causes of the osteonic circulation and the already present lines of treatment.*

Comparison of lines of treatment of osteoporosis	Osteonic circulation lines of treatment of osteoporosis.	The already present lines of treatment of osteoporosis.
Pathological basis	Osteoporosis is caused at 3 levels:- Generalized sub-clinical inflammation caused by visceral fat. Decreased new bone formation Increased bone resorption	They consider osteoporosis as only *increased bone resorption*. Thus, all the lines of treatment try their best to reduce bone resorption.
Lines of treatment	Usually natural supplements	Only pharmaceutical
The side effects	Usually absent as the treatment is of natural supplements	Usually, there would be side effects which sometimes may be life-threatening e.g Atypical fracture.
Examples of the line of the treatment of osteoporosis	Usually a combination of *2 or more* of the following supplements. 1. Alpha-lipoic acid 2. Taurine 3. MSM 4. Lysine 5. citrulline	1. bisphosphonates (the main line of treatment) 2. Prolia (monoclonal antibodies) 3. calcitonin 4. teriparatide (PTH derivatives)
The already bone	Usually, physiological as the newly formed bone is concentrated on the lines of the mechanical stress only.	The bone is usually pathologically liable to bone fracture. e.g. Atypical facture. Atypical fracture (most serious)
The side effects	Usually absent	Fibrosis of the mandible Esophageal irritation Gastrointestinal upset Hepatorenal toxicity
The cost of treatment	Usually cheaper	Much more expensive

5. Conclusion

Osteoporosis is a catastrophic disease that may cost the world more than $70 Bn per year [17]. The root causes of osteoporosis are the most essential steps in the treatment of osteoporosis. The already present lines of treatment namely the bisphosphonates which failed to prevent the fracture. Moreover, the DEXA scan also failed to predict the fracture according to bone mineral density (BMD). Both the lines of the treatments and the line of diagnosis needed *to be updated, modified, or even changed* with new ideas. A newly granted US patent (US9801905) shows for the 1st time that there is a hidden *micro-circulation* at the osteonic level that is responsible for the integrity of the osteocytes. The role of the collagen type I fibers of the bone in osteoporosis is *overlooked* in all other prior art studies. According to this new theory, collagen is blamed to be the starting point in osteoporosis. The functional collagen can improve the micro-flexibility of the bone. Thus, it prevents chronic congestion especially at the *periphery of the osteon*. The bone acts as a *confined space* which means no arterial filtrate enters the osteon except after the venous filtrate leaves it. This leads to more nutrition of the bone cells (osteocytes) that are responsible for the maintenance of the bone. Subsequently, the process of new bone formation is enhanced again and the osteoporosis is gradually corrected at its root level both safely and more physiological.

6. The Recommendation for Future Studies

1. *The piezo-electricity of the bone.* It includes micro-flexibility and functional collagen which are known as the biomechanical triad.
2. *The 3 main types of bone porosities;* vascular porosity (VP), lacunar canalicular porosity (LCP), and collagen apatite porosity (CAP).
3. *The sacrificial bonds* include the ionic bond between calcium & phosphate which can yield under mechanical stress.
4. This new theory opens the gate for future studies to look at the bone from these new views to know in fine detail (*How the bone exactly works*).
5. The arterial system in the *Haversian canal (H.C)* has the highest filtration rate because of its wide fenestration. The filtration power is 10^8 to that of lacunar canalicular porosity.
6. The venous system has valve-like narrow pores with tight junctions that are responsible for raising the tension inside the whole osteon. Thus, the filtrate would be directed from the (H.C) to the lacunar canalicular system.
7. The orientation of the *apatite chips* is *vertical* in the zero holes and horizontal in the zero channels and this is responsible for the starting point of the calcification to be in the zero holes. Then, it proceeds obliquely to the zero channels.
8. The *periphery of the osteon* has to be further studied because it is the starting point of osteoporosis. The new theory of osteonic circulation has the explanation that it is the area away from oxygen and nutrition. Other factors may be discovered in the future.

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