Frontiers
2021; 1(4): 100-111
http://www.sciencepublishinggroup.com/j/frontiers
doi: 10.11648/j.frontiers.20210104.17

Review Article

Visceral Fat-Glycation Interaction Deciphers the Hidden Roots of the Refractory Type of Osteoporosis: US Patent Review

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To cite this article:

Hossam Mohamed, Houda Almansour, Dalal Alsaadoun, Mariam Almansour. Visceral Fat-Glycation Interaction Deciphers the Hidden Roots of the Refractory Type of Osteoporosis: US Patent Review. *Frontiers*. Vol. 1, No. 4, 2021, pp. 100-111. doi: 10.11648/j.frontiers.20210104.17

Received: November 14, 2021; **Accepted**: December 3, 2021; **Published**: December 9, 2021

Abstract: Osteoporosis is a chronic disease of the bone in the elderly causing its liability to fracture on a mild trauma. The metabolic type of osteoporosis is the commonest. Its relation with hyperinsulinemia and/or diabetes Mellitus II (DM II) is poorly understood. The most hazardous effect of either hyperinsulinemia or DM II is the glycation process. The US patent (US9801905) discovered a very important link between the glycation process and the down-regulation of the insulin receptors on the osteocytes. Moreover, it was very clear that hyperinsulinemia even without diabetic manifestations sometimes has a more dangerous effect than DM II. The possible explanation is that hyperinsulinemia may raise glucose concentration inside the tissues despite its blood level might be still within its normal range. This would come at the expense of high insulin levels that maintain blood sugar within its normal ranges. On the other hand, DM II has high blood sugar but the sugar inside the tissue may be much less in most cases. Therefore, the glycation process is more likely to occur with silent hyperinsulinemia than in DM II. Furthermore, the incidence of hyperinsulinemia is much more common than DM II. Roughly, hyperinsulinemia is at least 3 times more common than DM II. Lastly, the glycation process causes down-regulation of the insulin receptors on the cell membrane of the osteocytes leading to starvation of these cells. Subsequently, the new bone formation would be greatly reduced predisposing for osteoporosis. By this paper, the very fine link between hyperinsulinemia and osteoporosis could be updated. The new lines of treatment could also be updated according to the patented data (US9801905).

Keywords: Osteoporosis, Piezoelectricity, Glycation, Hyper-insulinemia, NF-kB, RANK-L

1. Introduction

1.1. The Molecular Structure of the Bone

The bone is generally formed of 3 main components at the molecular level:

The Apatite (Calcium & phosphorous hydroxyapatite). It forms about 50% of the bone mass. Its function is to support 2/3 of compressive mechanical stress & 1/3 of tensile mechanical stress. Its chemical composition is (Ca_{10}, $(PO_4)_6$, $(OH)_2$) which shows that its calcium is highest, followed by phosphates, then the least amount is hydroxyl groups.

The collagen fibers form 28% of bone mass. The collagen is a fibrous protein and is responsible for 2/3 of the tensile stress & 1/3 of the compressive stress. Each of the collagen molecules is formed of 3 threads of polypeptide chains. Their mechanism of folding is of alpha-folding type. Therefore, they are called triple helix [1]. It was believed that the main function of collagen has just a supportive function. It is confirmed now that collagen has a new

fundamental function that is much more important than its mechanical support. This is its piezo-electric property. This simply means that collagen under mechanical stress acts as a transformer of the mechanical stress into an electrical gradient difference (EGD) [2].

Water content is about 22% of the bone mass. Its function is very important as a shock-absorbing mechanism for the gradually applied mechanical stress. This explains that the bone could tolerate more mechanical stress if it is gradually applied without failure. On the other hand, the same amount of mechanical stress could break the bone if it is abruptly applied. The explanation is the gradually applied stress gives a chance for water to partially escape and allows the bone to tolerate more mechanical stress without failure. It also acts as a medium for the transport of oxygen & nutrition to the bone cells. It also helps in the transport of waste products out of the cells to the venous system. This circulation is defined as Hossam osteonic circulation (HOC) [3, 4].

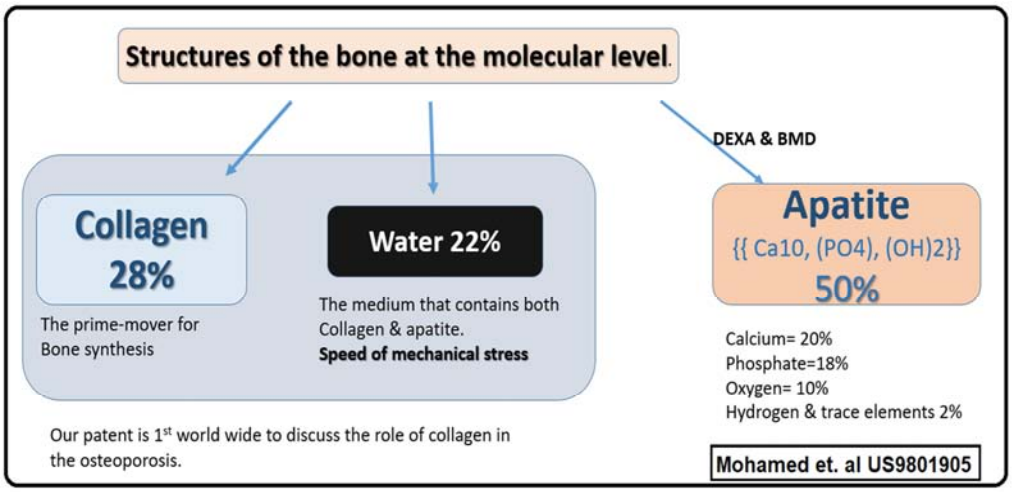

Figure 1. *The molecular components of the bone.*

1.2. Bone Mineral Density (BMD)

Osteoporosis is defined as a decrease in bone mass per unit volume. The hazard of osteoporosis is a fracture of the bone with mild trauma. The causes of the reduction the bone mass have been extensively studied with many trials to stop them but the results were always not satisfactory. The theory of bone remodeling has been confirmed. It means that the bone throughout the life of the human is under 2 opposing forces; the new bone formation & bone resorption. In a normal healthy person, the bone is under an equilibrium between the above 2 forces. Thus, there would be no osteoporosis. After the age of 40s, it is expected that the normal person loses about 10% of bone mass each decade. This is why bone mineral density (BMD) is measured by a minus. i.e the normal person bone scan is -1. From -1 to -2.5, it is considered osteopenia which means reduced bone mass but it is still not reaching the degree of osteoporosis. Osteoporosis starts to occur at -2.5 or less and this is associated with a high risk of bone fracture on a mild trauma [5].

It can not be stressed enough that (BMD) is just an indicator of the risk of bone fracture. Moreover, the (BMD) has some drawbacks because it measures only the apatite component of the bone which is about only 50% of the bone mass. This means that the other 50% of the bone mass is overlooked by the bone scan. Therefore, it fails to predict the future fracture [6]. It must be noted that the physiological loss of 10% of bone mass is not associated with osteoporosis. Osteoporosis is a pathological process with a marked loss of bone mass of more than the 10% that is lost with every decade [7].

1.3. Hyperinsulinemia Can Induce Osteoporosis Via 3 Mechanisms

A granted US patent (US9801905) has studied extensively the causes of osteoporosis. It confirmed that the glycation of the collagen fibers is the starting point of osteoporosis. Therefore, collagen acts as the prime-mover for new bone formation. Glycation is defined as the non-enzymatic attachment of glucose to the collagen that causes it to be dysfunctional. Therefore, it can not do its proper function as the starting point of the new bone formation. The electrical gradient difference (EGD) created by the conformation of collagen under the effect of mechanical stress is responsible for the stimulation of the osteoblasts (bone-forming cells) [3, 4].

Table 1. *The comparison between different types of bone density.*

comparison	normal bone	Osteopenia	Osteoporosis
T. score	**-1 or higher**	**-1 to -2.5**	**-2.5 or less**
The risk of fracture	is not likely to be fractured with normal trauma.	It is liable to be fractured with considerable trauma.	it is very liable to be fractured even with very mild trauma
The necessity of the treatment	No treatment is needed	It needs a prophylactic treatment	it needs an Urgent treatment

It also discovered the exact relation between functional collagen & the number of insulin receptors on the membrane of osteocytes. The glycation of the collagen occurs in hyperinsulinemia and to a lesser extent in DM II. It leads to down-regulation of the number of insulin receptors on the membrane of osteocytes [3]. The other important relation between hyperinsulinemia & osteoporosis is visceral fat. This type of fat is present inside the liver, intestine, kidney, pancrease, and even around the heart. This fat is metabolically active and is the main source of (NF-kB). Subsequently, there would be a production of Receptor activating nuclear factor-kB (RANK) which is the main stimulator of osteoclasts. Therefore, bone resorption would be increased with a predisposition to osteoporosis [8].

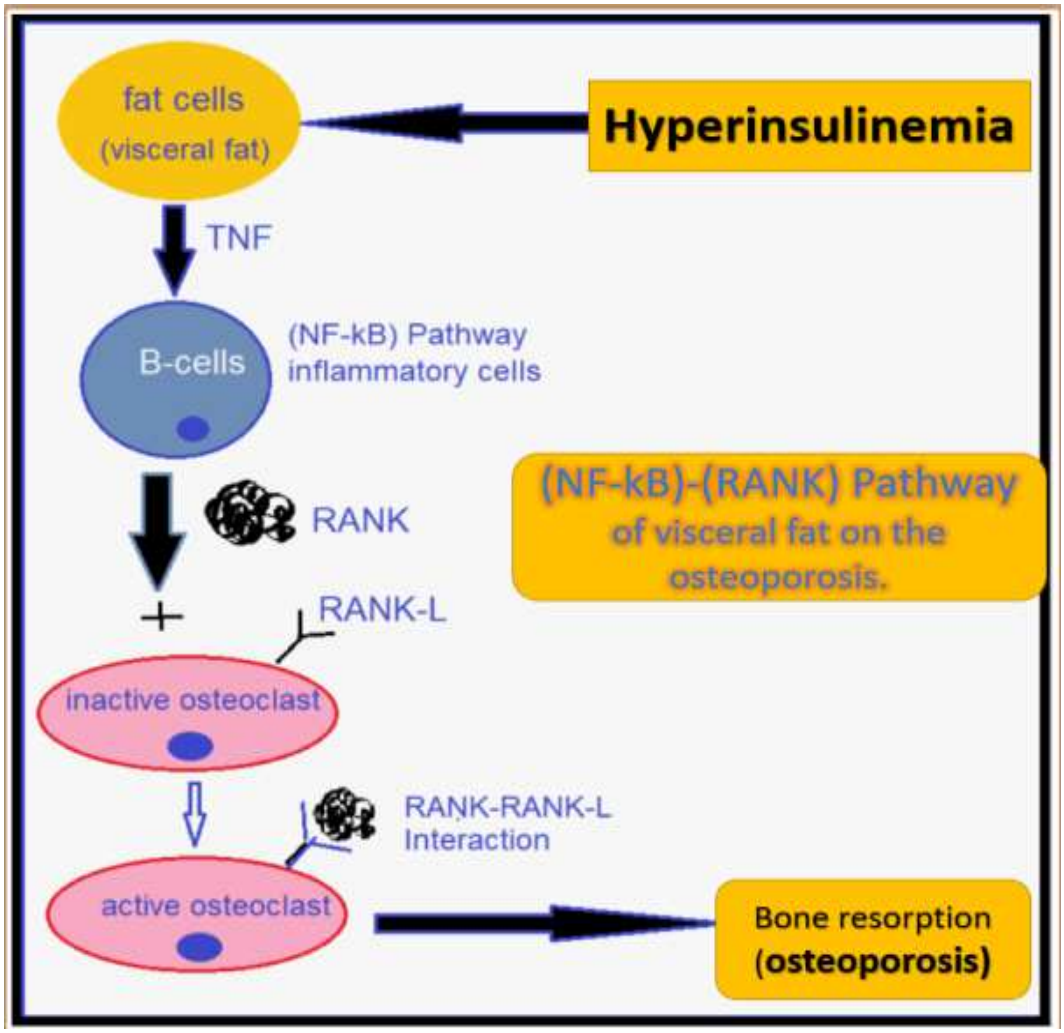

Figure 2. *The effect of hyperinsulinemia on the bone via (NF-kB)-(RANK) pathway.*

2. Hyperinsulinemia Is Associated with Osteoporosis More Than DM II

2.1. Hyperinsulinemia is NOT a Prediabetic Condition

It was strongly believed that hyperinsulinemia is a prediabetic condition. If there is compensation by the high insulin levels, DM II may not appear for the whole life. This is why hyperinsulinemia is much more common than DM II. It can be manifested by obesity, especially the central one due to the accumulation of visceral fat in the abdominal organs. This is because the liver can not handle much fat to store and has to export the excess fat to surrounding tissues i.e the pancrease, omentum, intestine, kidneys, and even the pericardium. This is collectively called the visceral fat that is metabolically active that can damage the distant tissues via secreting inflammatory proteins. Another US patent is granted about the side effects of visceral fat on the whole human body (US9.433.798) [9].

The relation between Hyperinsulinemia & DM II is not always clear-cut. It may occur before, with, or even after DM II. Sometimes, it occurs without DM II at all. Therefore, it is not considered a pre-diabetic condition. It is usually easier to be corrected by fasting, exercise, and cutting off carbohydrates. Not all the systems of the body are affected equally because the effect depends on the degree of glycation which differs from one system to another. The Glycation

depends on the blood supply of the organ and the amount of collagen inside that organ. Some systems may suffer from starvation because their cells are resistant to insulin. There are no accurate statistics for hyperinsulinemia like that of DM II. This is because many patients do not even know that they have hyperinsulinemia. It is the root cause for all metabolic syndrome (X) which includes DM, obesity, Alzheimer's, osteoarthritis, coronary artery diseases, and even osteoporosis which is the subject of this paper. The percentage of DM II in the US is about 11% which is about 31 million while hyperinsulinemia is about 36% of the population which is about 85 million [10].

Table 2. *The comparison between type 2 Diabetes Mellitus & hyperinsulinemia.*

The comparison	DM II	Hyperinsulinemia (not always prior to DM)
percentage	11% about 31 million	36% about 85 million
Fasting blood sugar	Higher than normal	Usually, high normal but sometimes may be fully normal
Insulin level	High but failed to correct blood sugar	High but can correct blood sugar
Effect on the body systems	Usually has a generalized effect all over the body system as blood sugar is high	May affect special system more than the other e.g. DM III is Alzheimer DM IV is the osteoporosis (rare to be systemic)
Glycation	Usually, less severe because the glucose is present mainly in the blood not in the tissues.	Usually, more severe as the glucose is higher inside the tissue not in the blood because high insulin admits glucose to the tissues
Insulin resistance	It is present but difficult to be corrected.	It is present but usually can be corrected by regimen, fasting, and exercise
Lines of treatment	Diabetic medications are the main line of treatment. Regimen and exercise are helpful	Cutting off carbohydrates Fasting Regular exercise
precaution	Diet must be adjusted with the medications to avoid fatal hypoglycemia.	Anti-diabetic medications may be dangerous and must be used with caution as insulin resistance is not equal all over the systems of the body. i.e one system may be affected more than the other. Some systems are not affected at all like adipose tissue.
System affection	Generalized and no system escapes from insulin resistance	Usually, one or more systems are affected by insulin resistance. It is rare to affect all body systems except after it is converted to DM II.

2.2. Diabetes Mellitus II (DM II)

It is one of the most prevalent metabolic diseases in the elderly. It is also the root of all other metabolic diseases which are called (X) syndrome. The pathogenesis of DM II is that the blood glucose becomes uncompensated and be higher than its normal level. This means that the pancrease can not control the high blood sugar which becomes higher than its normal levels. Osteoporosis is more common with hyperinsulinemia than with DM II. The explanation is that the prevalence of hyperinsulinemia is about 3 times more common than that of Diabetes. Hyperinsulinemia may damage the interstitial tissue more than that in the case of diabetes. The possible explanation according to the above patent (US9801905)) is sugar's concentration inside the tissues in case of hyperinsulinemia is sometimes much higher than that in DM II. This is by the effect of high insulin levels that is continuously pushing the glucose inside the tissue. This creates more possibility of glycation process than in the case of DM II [11].

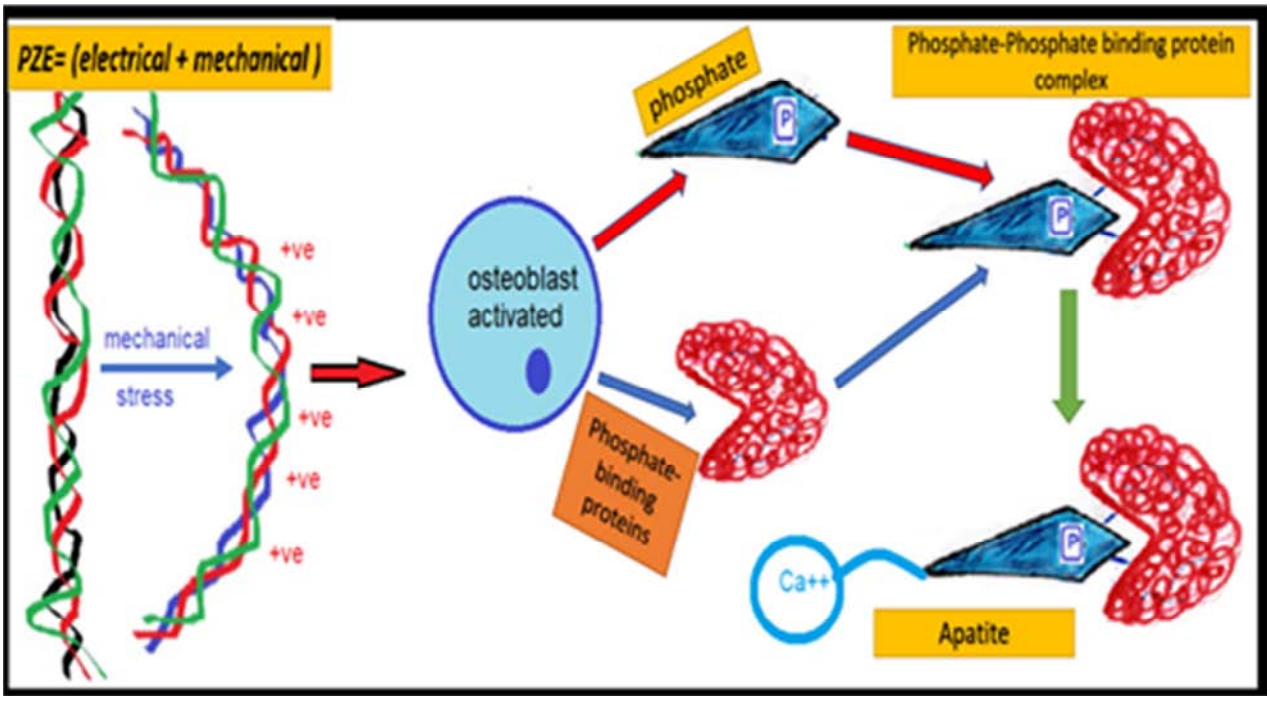

Figure 3. *Functional collagen can stimulate the osteoblasts to build a new raw material of the bone.*

3. The Effect of Hyperinsulinemia on the Glycation of the Bone Collagen

3.1. The Collagen Mechanics at the Molecular Level

The collagen forms 28% of the bone mass. It is formed of a triple helix which means 3 polypeptide chains folded upon each other in a helical form. There are 3 threads of the collagen that are folded in an alpha (α) manner (2 α 1 & 1α 2). The functional collagen has a very important property called piezo-electricity (PZE). This property causes the functional collagen to conform under mechanical stress and transforms some of the mechanical stress into an electrical one. This simply means that collagen, if functional, acts as a transformer that converts mechanical stress into an electrical one that can initiate bone remodeling [12].

3.2. The Piezo-electricity of the Collagen (Conformation)

The collagen molecule bends and shows a convex positive side and a concave negative side. the negative side facing the area of mechanical stress. Thus, it stimulates the osteoblasts for the production of osteoblastic vesicles of phosphates and phosphate-binding proteins. The area on the positive side is usually away from the mechanical stress, thus, it stimulates the osteoclasts to resorb the bone in this area. Thus the bone becomes biphasic; an area with concentrated bone mass at the line of the mechanical stress and an area with a decrease in the bone mass away from the mechanical stress. Thus, bone remodeling is done under mechanical stress through the conformation of functional collagen [13, 14].

3.3. The Glycation of the Collagen (Dysfunctional Collagen)

The glucose attaches non-enzymatically to collagen causing it to become dysfunctional. The collagen can not conform anymore under mechanical stress. This means that osteoblasts would not be stimulated. Thus, the new bone formation would not occur. As said earlier, the bone remodeling theory has 2 opposing forces that work against each other. These are the new bone formation and bone resorption. The new bone formation has stopped from working or at least slowed down by the glycation process. At the same time, the bone resorption continues and does not change, the bone mass gradually becomes less and less. To that end, the bone becomes osteoporotic [15].

4. The Effect of Hyperinsulinemia on Insulin Receptors

4.1. The Down-Regulation of Insulin Receptors of the Osteocytes

Recent studies show that insulin receptors of the osteocytes membrane have a great beneficial effect on new bone formation. On hyperinsulinemia, there would be gradual down-regulation of the number of insulin receptors on the membrane of the osteocytes. The mechanism of down-regulation of the number of the insulin receptors acts as a compensatory protective mechanism for the osteocytes to avoid their damage in the early stages. Later, it causes the affected cells to show some degenerative changes. The degree of the damage that affects osteocytes in the early stages, the damage is reversible but later it becomes irreversible. The affected areas of the bone have sick or dead osteocytes that show less or no new bone formation. This predisposes to osteoporosis via a decreased new bone formation [16, 17, 18].

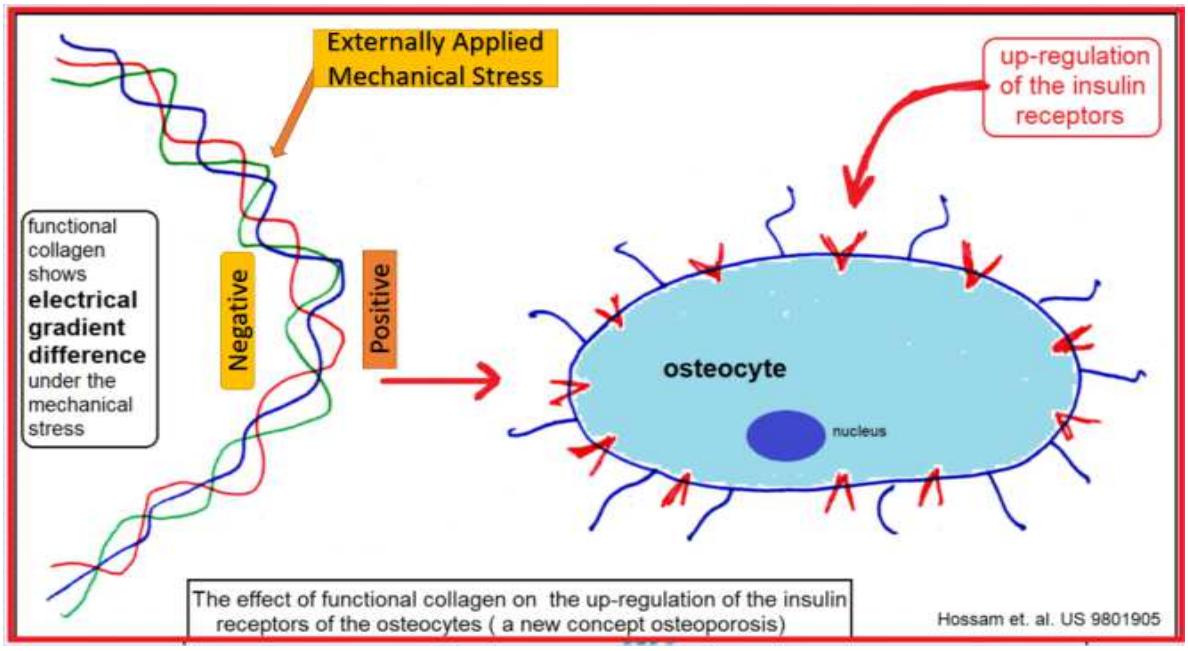

Figure 4. *Functional collagen conforms under mechanical stress & shows an electrical gradient difference that stimulates the osteocytes to up-regulate the insulin receptors.*

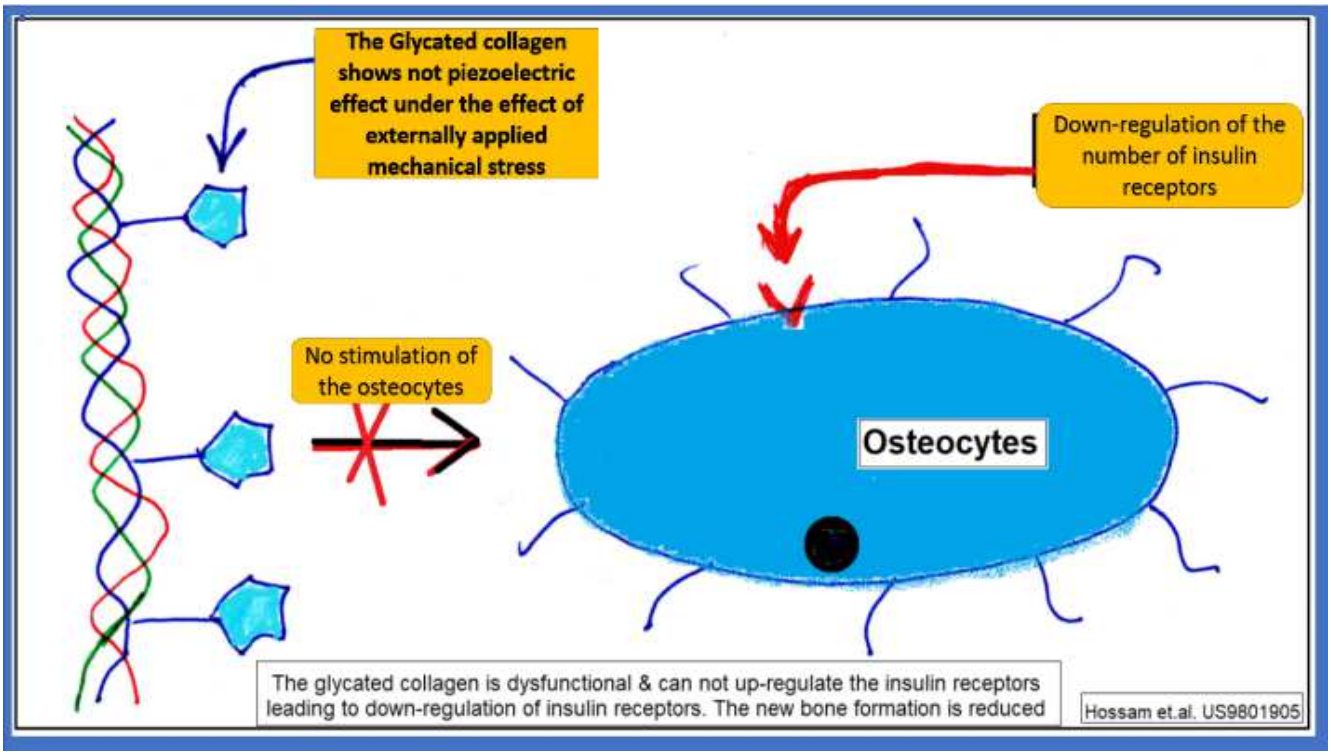

Figure 5. *The Glycated collagen can not conform under mechanical stress. The insulin receptors on the osteocytes are down-regulated.*

4.2. The Osteocytes of the Periphery of the Osteon Suffer More

The bone is formed of osteons which act as the functional unit of the bone. They are rounded structures of about 200 um. Each osteon has a central channel of 50 um which is called the Haversian canal (H.C) of about 50um. It is formed of the artery, vein, and nerve. The osteocytes are arranged around the H.C. in a nest-like structure called ((lacuna)). It has about (80 to 120) processes that are present in canaliculi. The cells are arranged around H.C. peripherally to the end of the osteon which is called the cement line. The osteocytes in the periphery of the osteons suffer more than the central ones because they are away from oxygen and nutrition according to the 3 types of porosities [19].

4.3. The Porosities (VP, LCP, CAP)

There are 3 types of porosities in the osteon. This is called Hossam Osteonic circulation (HOC). This means that there is a circulation of fluid that carries oxygen & nutrition from the (H.C) to the periphery of the osteon towards the cement line. The fluid returns from the periphery of the osteon to the (H.C) again carrying carbon dioxide and waste products. The circulation passes in 3 zones: the central called vascular porosity (VP), the lacunar-canalicular porosity (LCP), collagen apatite porosity (CAP). Recent studies show that the nutrition of the osteocytes depends on 2 synchronized circulation. The blood circulation is only present inside the Haversian canal (H.C.). The water circulation or filtrate outside the (H.C.). Also, there are 2 types of filtrate: an arterial filtrate and a venous filtrate. The arterial one goes from central to the peripheral towards the cement line and it passes through the LCP. The venous filtrate passes in an opposite direction from the peripheral to the central i.e back from the periphery of the osteon to the H.C. This filtrate goes through in collagen apatite porosity (CAP). As the bone is a confined space, the new arterial filtrate can not enter the osteon except after the venous filtrate escapes. This is the meaning of the synchronization between the blood and filtrate circulations [20, 21].

4.4. The Recovery of Osteocytes

The up-regulation of the number of insulin receptors on the surface of osteocytes could return to normal. This is done after the reduction of hyperinsulinemia by cutting off carbohydrates, exercising, and fasting for a long time. It does not need anti-diabetic medications because the blood glucose level is still compensated. The earlier the treatment of the condition, the better the results before the irreversible damage could occur in the affected area like scaring, fibrosis, by the chronic inflammatory process. It must be noted that the osteocytes around the Haversian canal (H.C) recover earlier than the osteocytes in the periphery osteon. This is because the cells near the H.C. have more nutrition and oxygen supply than the osteocytes in the periphery near or beside the cement line [20, 21].

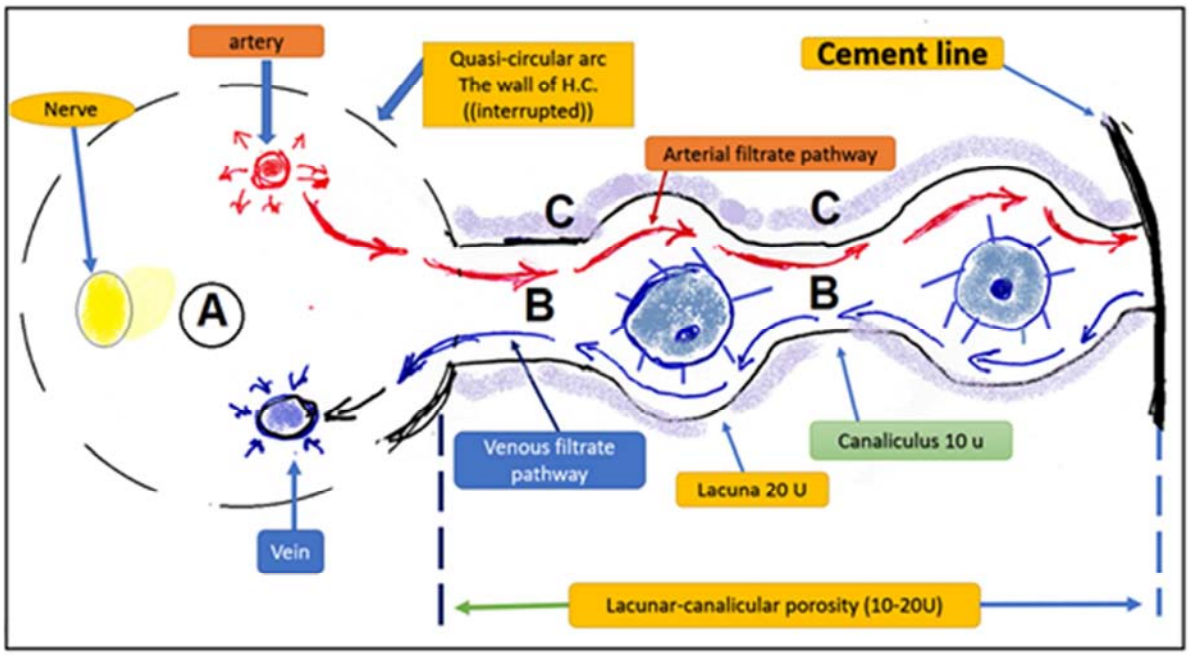

Figure 6. *The osteonic circulation shows that the cells of the periphery of the osteon suffer more than that in the center near the H.C.*

5. The Effect of Hyperinsulinemia on (NF-kB) (RANK) Pathway for Osteoclastic Activation

5.1. Hyperinsulinemia Is Associated with More Visceral Fat Formation

This is because fat cells have no resistance to insulin and can store much amount of sugar in the form of fat. As said earlier, visceral fat is metabolically active and emits (NF-kB) which is the main inflammatory product of the body. Subsequently, (NF-kB) enhances the production of (RANK) protein which activates the osteoclasts and causes osteoporosis [22].

5.2. The RANK-RANK-L Interaction for Osteoclastic Activation

The RANK (receptor activator of nuclear factor KB) is produced by the immune cells as a result of activation of (NF-kB) from visceral fat. The RANK interacts with surface protein on the membrane of the osteoclasts called (RANK-L) leading to their activation. The osteoclasts (bone-eating cells) can eat the bone and lead to bone resorption i.e osteoporosis [22].

6. Discussion

6.1. Osteoporosis Vicious Circle of Hyperinsulinemia

This means that all the components of the bone that could be affected by hyperinsulinemia are interacting and intercommunicating with each other. In other words, the glycation of collagen causes more reduction of insulin receptors on the osteocytes and more production of (RANK) that stimulates the osteoclastic activation. Therefore, hyperinsulinemia acts as the root cause of the metabolic type of idiopathic osteoporosis which is the commonest type (figures 7 & 8).

It is believed that osteoporosis, in general, is divided into 2 main parts: primary & secondary osteoporosis.

6.1.1. The Secondary Osteoporosis

This type of osteoporosis is secondary to another disease process. This type of osteoporosis is usually localized to the affected part of the body that suffers from that disease process. The treatment of this type is by the correction of the primary cause. The commonest example is splinting of the limb due to trauma would lead to osteoporosis of the bone of that limb. This type is rare and out of the scope of this paper.

6.1.2. The Primary Osteoporosis

It is also called the idiopathic type. There is no primary cause of this type. This is the subject of this paper. It is called either primary or idiopathic osteoporosis. It is believed that it is of unknown etiology. This paper which is backed by the US patents (US9801905) & (US 9433798) claimed that it is not an idiopathic type anymore. The primary cause is already known which is hyperinsulinemia. Therefore, it must not be called idiopathic anymore. Moreover, it could be called type IV diabetes mellitus (DM IV). This is because hyperinsulinemia is the hidden cause of idiopathic osteoporosis. Therefore, the lines of the treatment must be directed to all the 3 limbs of hyperinsulinemia. As said earlier, glycation of the collagen caused by hyperinsulinemia is the starting point of idiopathic osteoporosis and it is considered the peripheral limb of hyperinsulinemia. Visceral fat is considered the central limb of hyperinsulinemia. It works indirectly by enhancing the (NF-kB)-(RANK-RANK-L) pathway for the activation of the osteoclasts. The third limb of hyperinsulinemia is its down-regulation of the insulin receptors on the osteocytes. It must be noted that these 3 limbs are interconnected with each other.

6.2. The Severity of the Hyperinsulinemia Is Time-dependent

This means that in the early stages of hyperinsulinemia, the recovery is expected to be much easier and faster than long-standing hyperinsulinemia. The explanation is that in the case of long-standing hyperinsulinemia, the tissue damage may become irreversible or very hard to become reversible. The glycation of collagen over a long time causes the surrounding tissues to become damaged, ischemic, and shows fibrosis. Therefore, its full recovery would be very difficult.

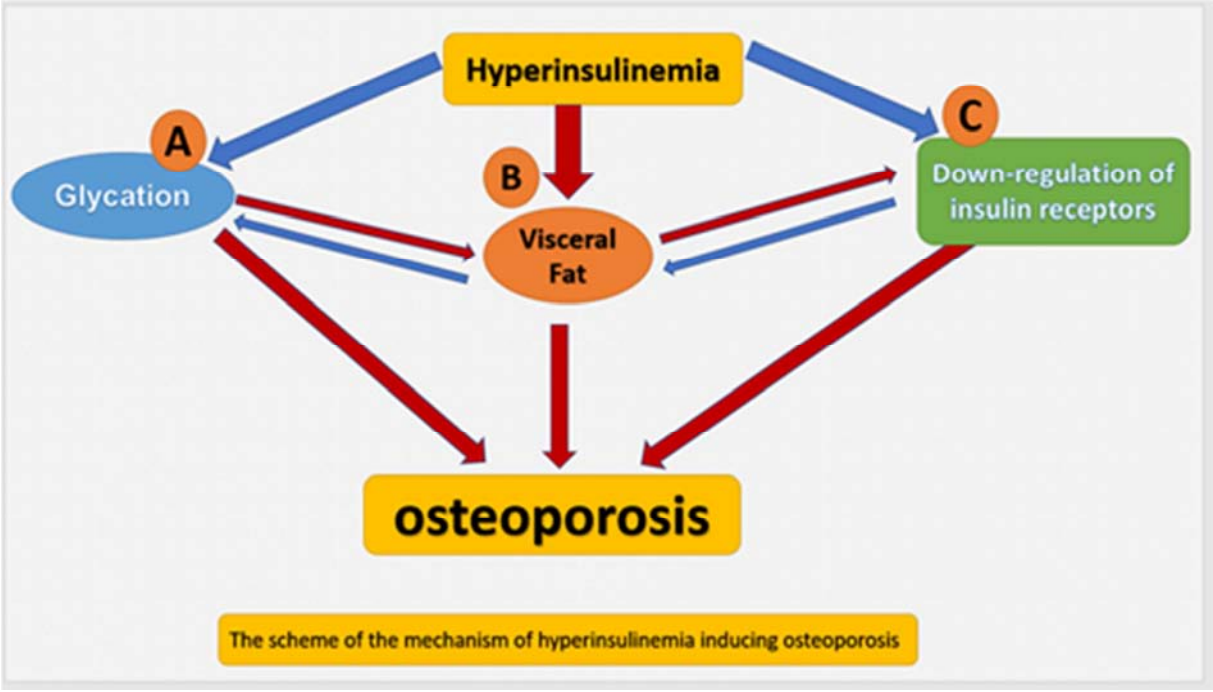

Figure 7. *The schematic relation between hyperinsulinemia & osteoporosis. The 3 limbs of hyperinsulinemia are inter-connected & inter-communicating with each other.*

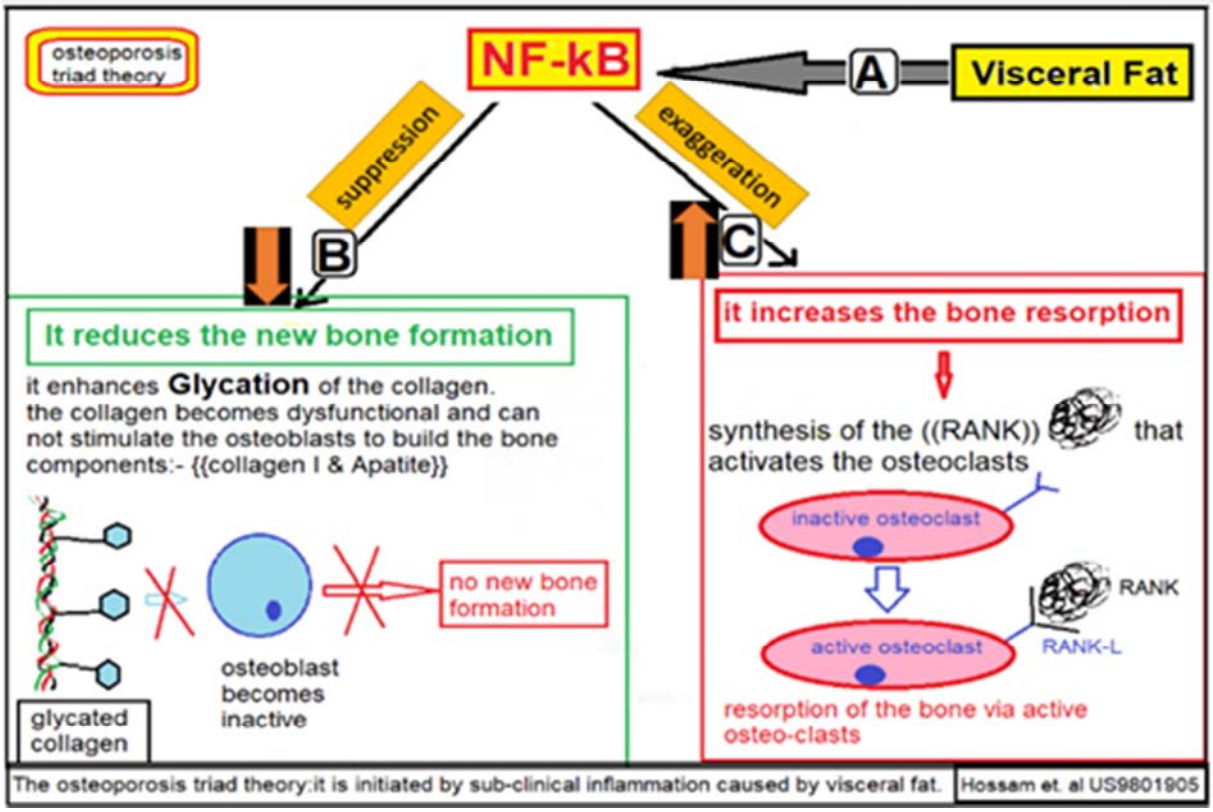

Figure 8. *The 3 Limbs of hyperinsulinemia are cooperating to reduce the new bone formation & increase bone resorption. The osteoporosis is end-result.*

Visceral fat is the main source of (NF-KB) which is the main inflammatory protein in the human body. It enhances the production of (RANK) which is the main activator of osteoclasts. The visceral fat is inaccessible to surgery. It is the fat that is present inside the viscera like the liver, omentum, wall of the intestine, pancrease, Kidney, and pericardium. This type of fat can only be reduced by cutting off carbohydrates, prolonged fasting, and exercise. It is illogical and not practical to remove surgically this type of fat. Moreover, it may be very difficult for most obese patients who always crave sugar and carbohydrate foods to fast.

The insulin receptors on the osteocytes are down-regulated by high blood sugar levels. This means that even the blood sugar is still high-normal because of the high insulin level, the osteocytes start to suffer from starvation. The osteocytes in the periphery of the osteon suffer more than the cells around the Haversian canal (H.C). This is because each osteocyte has 2 surfaces: a vascular surface that has narrow processes, and a matrix surface that has broader processes as in figure 9. The cells near H.C. are very near to oxygen supply and can withstand the unfavorable conditions more than the osteocytes in the periphery of the osteons [16, 17].

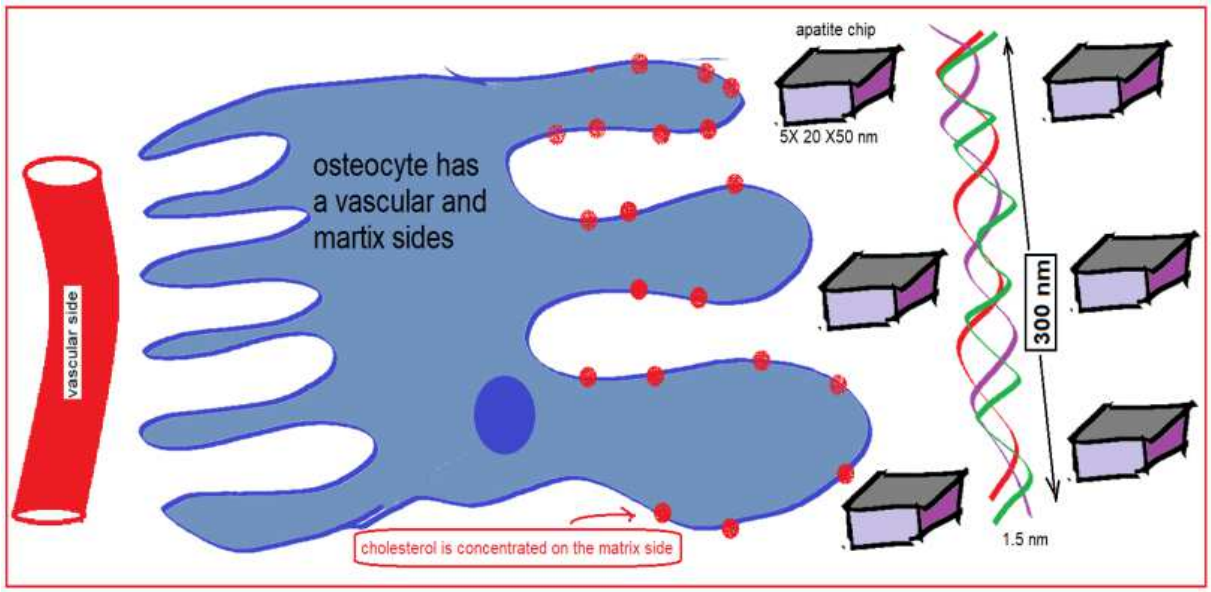

Figure 9. *Each osteocyte has vascular and matrix sides.*

6.3. The Mitochondrial Role in Insulin-Receptor Regulation

The mitochondria are a powerhouse of the cells. It is believed that they come from a bacterial origin e.g. alpha-fetobacteria. They have 2 membranes. The outer from the host and inner is of bacterial origin and is very impermeable [23].

6.3.1. The Inner Membrane of Mitochondria

This membrane is very impermeable and is responsible for energy production. All the enzymes of energy production are present on this membrane. There are 4 important proteins on this inner membrane. The 1st is the mitochondrial calcium uniport (MCU). This port is responsible for the blockage of calcium entrance to the mitochondria which subsequently causes the damage of the mitochondria as in figure 10. This port is blocked by Taurine amino acid. This is why the recovery of the mitochondria needs this supplement [24].

The 2nd port is carnitine which is very essential in fat metabolism. As explained earlier, visceral fat has a critical role in the induction of osteoporosis. Thus, an open carnitine shuttle for fat utilization as a source of energy production helps in the reduction of visceral fat. It is suggested in the patent (US9801905) to use lysine amino acid to enhance carnitine formation [25].

The 3rd protein is the pyruvate dehydrogenase enzyme. This is responsible for glucose metabolism. This protein is activated by alpha-lipoic acid. This helps in lowering blood glucose which is responsible for the glycation of collagen. Thus, alpha-lipoic can indirectly help in the treatment of osteoporosis [26].

The 4th protein is cytochrome oxidase which is essential for energy production. This can be activated by citrulline amino acid. Its main function is the production of nitric oxide (NO). This affects the activation of the mitochondria and allows more energy production. It also has a vasodilator effect that improves heart function and improves the circulation in general. It was explained earlier that citrulline opens the side channels of the artery of the Haversian Canal leading to enhancing osteonic circulation & bone health. Therefore, the patent includes citrulline [27].

6.3.2. The Outer Membrane of the Mitochondria

The outer membrane of the mitochondria has only one important protein which is called Voltage-Dependent Anion Channels (VDAC). These are very important in the communication between the mitochondria and the nucleus. They have fundamental functions in the cells like Apoptosis,

Autophagy, and more importantly the transcription of the protein on the surface of the cell membrane. This means that the opening of VDAC allows the insulin receptors on the osteocytes to become sensitive again [28].

6.3.3. The Mitochondrial Nuclear Axis

Hyperglycemia with subsequent hyperinsulinemia causes a rush of excess glucose inside the cells. The affected cells shift for energy production to be on the glycolysis pathway which is an incomplete burning of glucose rather than oxidative phosphorylation. The glycolysis is associated with more lactic acids and other metabolites which hinder the communication between the mitochondria and the nucleus. The communication is done via the VDACs. The order for the nucleus may be either to commit suicide (apoptosis), autophagy, or synthesis of the surface proteins like that of insulin-receptors. If the (VDACs) are not properly working, the transcription of the insulin receptors is down-regulated. As said earlier, this would be a protective mechanism to reduce the entrance of glucose to the cells. Later, the affected cells suffer from starvation and may die or show degenerative changes.

The correction can be done via cutting carbohydrates, fasting, exercise to reduce blood sugar as can as possible. This is followed by a subsequent reduction of insulin level and the insulin receptors would become sensitive again. The affected cells return to working properly again in the new bone formation.

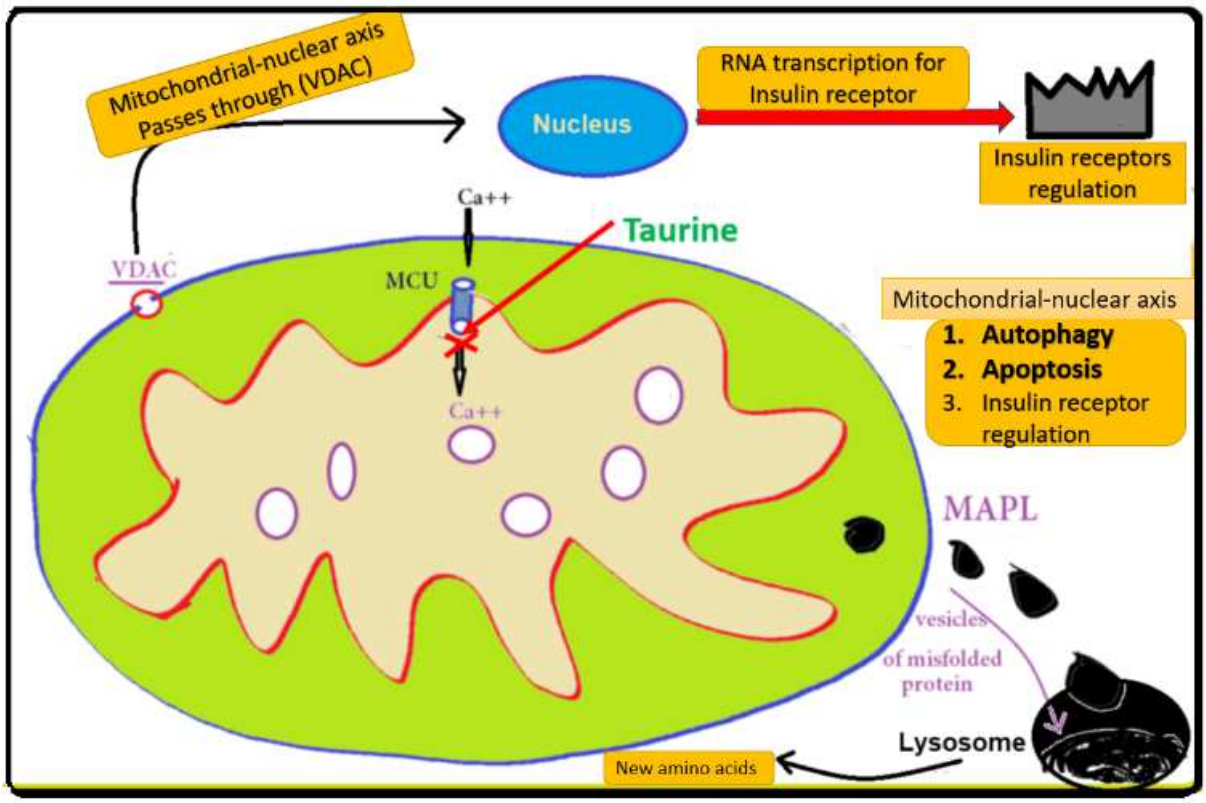

Figure 10. *The mitochondrial-Nuclear Axis controls Apoptosis, Autophagy, and insulin receptor regulation.*

6.4. The Line Treatment of Idiopathic Osteoporosis

6.4.1. Bisphosphonates

All the lines of treatment of idiopathic osteoporosis give no satisfactory results. The commonest medications are the bisphosphonates group. These types of medications depend on the deceiving of osteoclasts. They are similar to the structure to the phosphate component of the bone apatite $\{(Ca_{10}, (PO_4)_6, (OH)_2\}$ of the bone. Thus, osteoclasts eat them as phosphate of the bone. The bisphosphonates differ in that they have 2 phosphate groups and the osteoclast cells would die or become very sick. As explained earlier, the bone remodeling theory is formed of 2 opposing forces; bone formation & bone resorption. The loss or the reduction of the bone resorption component is associated with apparent an increase in bone formation. The new bone formation is not increased. There would be an obvious enhancement of the bone mass. This is because the bone formation is not opposed to the process of bone resorption. The bottom line is higher bone mineral density (BMD) but at the expense of the bone becomes not physiological and more liable to fracture. e.g. Atypical fracture. This is a life-threatening fracture [29].

Bisphosphonates have many other complications including fibrosis of the lower jaw, irritation of the esophagus, gastrointestinal upset, hepatorenal toxicity, and others [30].

6.4.2. Denosmab (Monoclonal Antibodies)

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 has more aggressive side effects.

6.4.3. 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.

6.4.4. 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.

6.5. The Lines of Treatment According to Hyperinsulinemia Theory

The lines of the treatment must depend on the reversal of the above pathological processes. As said earlier, hyperinsulinemia has 3 limbs. For the treatment to be successful, it must be directed to each limb separately. Therefore, the treatment must be applied to visceral fat, glycation, and the mitochondrial pathways that control the insulin receptors. For visceral fat, the main line of treatment is fasting and cutting off carbohydrates. There is no medication or supplement in this limb. For the glycation of collagen, the supplements that help in the deglycation process lead to the recovery of collagen can give excellent results. The upregulation of insulin receptors can be done via the stimulation of the dysfunctional mitochondria. The recovery of the mitochondria allows them to communicate again with the nucleus. The nucleus can make the transcription of the insulin receptors again and the cells become insulin sensitive again.

7. Conclusion

The commonest type of osteoporosis is the idiopathic type. This means the type of osteoporosis with no primary cause or unknown cause. In US patent (US9801905), osteoporosis is seen from a different angle and hyperinsulinemia is considered its primary cause. Hyperinsulinemia has 3 limbs to cause osteoporosis. The glycation of collagen, the (NF-kB)-(RANK) pathway, and down-regulation of insulin receptors. Moreover, these 3 limbs are interconnected with each other. This gives a chance for a better understanding of the mechanism of occurrence of osteoporosis. Furthermore, it helps in discovering the lines of treatment of osteoporosis in a more efficient way. It must be stressed that the best lines of treatment of osteoporosis must reverse the exact pathological process of the above 3 limbs of hyperinsulinemia. By this review, osteoporosis is not idiopathic anymore because its underlying causes are discovered. It is well known that all the already present lines of treatment of osteoporosis are not effective and have many side effects. This is because all previous lines of treatment of osteoporosis deal with it as if it is a disease of an increase in bone resorption. Therefore, all the previous lines of treatment concentrate on fighting the osteoclasts (bone-eating cells). As the method of treatment is directed in the wrong way, the results of the treatment are not perfect. However, the produced bone shows some increase in the bone mineral density (BMD), it is still liable to fracture. The best example is Atypical fracture which is a life-threatening fracture that may occur in bisphosphonates which are the commonest medications in the markets. On the other hand, the benefits of lines of the treatment suggested by the patent (US9801905) are physiological because they just reverse the pathological process. They are formed of supplementations that are necessary for the deglycation of collagen, restoring the mitochondrial nuclear axis, and prevention of the effect of the (NF-kB)-(RANK) pathway on the bone.

Lastly, there is a close link between hyperinsulinemia and osteoporosis. However, osteoporosis may occur without the occurrence of diabetes II, it is suggested that metabolic osteoporosis is a certain type of diabetes better called DM IV.

8. The Recommendation for Future Studies

Hyperinsulinemia is a very common silent disease that is the root of all metabolic diseases. The effect of hyperinsulinemia has to be further deeply studied on the bone. It is suggested that osteoporosis be called diabetes mellitus type IV (DM IV).

The Hossam Osteonic circulation (HOC) has to be further studied to show its role in osteoporosis.

The sacrificial bonds (hidden length theory) of the bone that absorbs 75% of the externally applied mechanical stress has also to be further studied. Its relation to osteoporosis must be more clear.

The piezo-electricity (PZE) of the bone has to be more deeply studied to show its exact role in osteoporosis.

The role of antioxidants like alpha lipoic, taurine, NAC, certain amino acids like lysine, citrulline, certain vitamins like Vitamin D & K2, minerals like Calcium and zinc, and organic sulfur supplementation all have a great benefit in the reversal of osteoporosis, especially in its early stages (US9801905).

The measuring of insulin levels in the blood is difficult & it is more difficult to be interpreted in the lab. results. So, the C-peptide could be used as a marker of hyperinsulinemia in the future.

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