Frontiers
2022; 2(1): 22-33
http://www.sciencepublishinggroup.com/j/frontiers
doi: 10.11648/j.frontiers.20220201.13

Review Article

Hossam (Y) Site Theory of Collagen Type I Decrypts the Origin of Metabolic Syndrome (X) in the Elderly with a Suggested Conjecture of Cure: Granted US Patent Review

Hossam Mohamed[1, 2, *], Houda Almansour[1, 2], Dalal Alsaadoun[3], Mariam Almansour[4], Yasmin Almansour[5], Sawsan Samy[1], Sulaiman Alnassera[6]

[1]Medical & Research Department, Huda Health INC, Ottawa, Canada

[2]Medical & Research Department, Houda Almansour Global Medical Device & Designs INC, Ottawa, Canada

[3]Internal Medicine Department, College of Medicine, King Faisal University, Alahsa, Saudi Arabia

[4]Department of Endocrinology, AlFaisalia Hospital, Alhafouf City, Saudi Arabia

[5]Department of Palliative Care, Specialized King Fahad Hospital, Dammam, Saudi Arabia

[6]Department of Pharmacology and Toxicology, Unaizah College of Pharmacy, Qassim University, Qassim City, Saudi Arabia

Email address:

hossamortho@gmail.com (H. Mohamed), halmansour@csnnottawa.ca (H. Almansour), Dalsaadoun@kfu.edu.sa (D. Alsaadoun), Maryam17757@gmail.com (M. Almansour), Yahalmansour@moh.gov.sa (Y. Almansour), arssammi@aol.com (S. Samy), sm.alnasser@qu.edu.sa (S. Alnassera)

[*]Corresponding author

To cite this article:

Hossam Mohamed, Houda Almansour, Dalal Alsaadoun, Mariam Almansour, Yasmin Almansour, Sawsan Samy, Sulaiman Alnassera. Hossam (Y) Site Theory of Collagen Type I Decrypts the Origin of Metabolic Syndrome (X) in the Elderly with a Suggested Conjecture of Cure: Granted US Patent Review. *Frontiers*. Vol. 2, No. 1, 2022, pp. 22-33. doi: 10.11648/j.frontiers.20220201.13

Received: December 27, 2021; **Accepted**: January 12, 2022; **Published**: January 20, 2022

Abstract: Collagen is the commonest protein in mammalian. Its function is thought to be only of structural support. New US patents claimed that it has another very vital role in the human body which is piezoelectricity. Most of the chronic diseases in the elderly are caused by the disturbance of this newly discovered function. The exact site of disturbance is defined as the site (Y) of collagen. Profound molecular and biomechanical studies were done at the site (Y) to determine its mechanical disturbance from the pathological point of view. As collagen is present all over the human body like bone, cartilage, the heart, brain, blood vessels, skin, even the sclera of the eye, its correction would recover most of the tissues of the human body. This paper discusses the site (Y) and its effect on piezo-electricity and its glycation. It discusses also all the factors that may affect the site (Y) either damaging or recovery in the hope of avoidance of all the destructive factors and enhancing the repairing ones. It is believed that this new method of thinking about the degenerative disease in the elderly could be treated perfectly, more physiological, and also at the root level. This is much better than treating each disease as a separate entity. Lastly and for most, this group of degenerative diseases has a great impact on the health care system and hospital resources of every nation. Thus, the recovery of these patients would save a huge amount of money spent in the health care system for these chronic and almost long-lived diseases.

Keywords: Zero Holes, Gap Zone, Overlapping Zone, (Gly, X, Y), Piezo-electricity, Glycation, Visceral Fat

1. Introduction

1.1. Collagen Is the Commonest Protein in the Human

Collagen is the commonest protein in the mammalian. It forms about 30% of all other proteins of the human. The number of known proteins in the human body is more than 2 million. The collagen alone is about 30% & all remaining 2 million proteins are 70%. This percentage may denote the vital importance of collagen. Moreover, the collagen itself is not one type. It is more than 28 types. Collagen type1 is the commonest. It forms more than 90% of all the collagen of the human body. It is present in the bone, muscles, brain, heart, blood vessels, skin, and sclera of the eye. Collagen is the main

building block of the skeleton of the animal kingdom. It is analog to cellulose in the plant kingdom. As it is a fibrous protein, it is believed that its function is only of structural support to nearby more vital structures. Therefore, it is present in the capsules that support the vital organs like the liver and kidney. It is also present in large amounts in tough structures like bone, muscle, cartilage, tendons, ligaments, and so on [1].

1.2. Collagen and Piezoelectricity

Recently issued patent (US9801905) that profoundly studied the role of collagen in the vitality of the bone. Collagen is the prime mover for tissue remodeling including bone, tendons, cartilage, ligaments, muscles, and so on. Collagen does this fundamental function through its piezoelectric (PZE) property. This simply means that the collagen acts as a transformer that converts the mechanical stress into an electrical gradient difference (EGD) which could send messages to nearby cells to initiate the process of remodeling. The most fundamental property for the collagen, to do its proper job, is to be functional. This means it is not glycated. Therefore, glycated collagen can not do its proper function in tissue remodeling. In other words, the normal tissue damage by the wear and tear process of aging is not compensated by new tissue formation. Therefore, a gradual tissue loss would occur leading, in the end, to complete tissue dysfunction of the affected organ. If the condition is universal all over the body, the aging process occurs which is simply metabolic syndrome (X). This is the subject of this paper [2, 3].

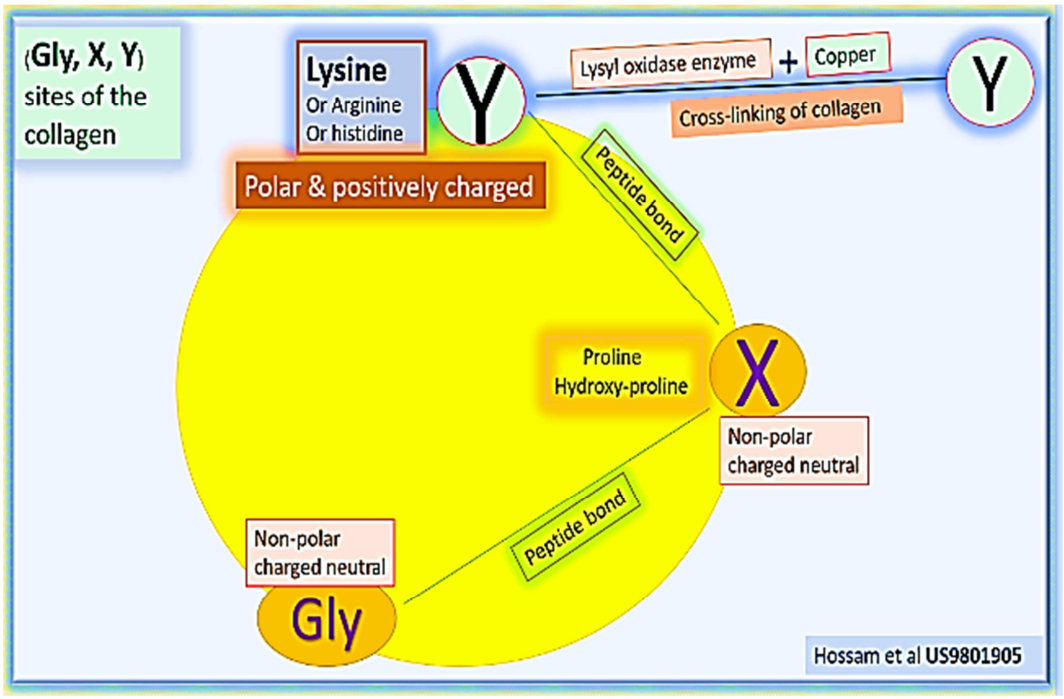

Figure 1. *The cross-section of collagen shows its 3 sites (gly, X, Y). The (Gly & X sites) are non-polar & and electrically neutral while the (Y) site is polar and positively charged. Also, the (Y) site is the only site for the cross-linking of collagen.*

2. The Molecular Mechanic of Collagen

2.1. The Hierarchy of the Collagen

Collagen is formed of the triple helix which is 3 polypeptide chains. They fold upon each other in the form of (α) folding. They are (2 α 1 & 1 α 2). The single thread is formed of about 1050 amino acids. Therefore, each molecule that is formed of 3 threads is about 3150 amino acids. The length of each collagen molecule is 300nm & its cross-section is 1.5 nm. These collagen molecules assemble via cross-linking at the (Y) site which is the subject of this paper. The cross-section of collagen shows 3 sites of amino acids. These are (Gly, X, Y) as in figure 1. The (Gly) is always glycine and it is the smallest and simplest amino acid ever. Therefore, it is always directed to the interior of the collagen. This means that the 3 (glycine) amino acids are facing each other (figure 4). The site (X) is occupied by proline or hydroxy-proline. Proline is the only amino acid in the collagen that has a ring that acts in the periphery to support the structure. The hydroxylation of proline is an enzymatic process and needs (lysyl hydroxylase) and needs also iron and vitamin C as co-factors (figure 5). The bonds between (Gly, X, Y) are peptide bonds. These strong bonds can not yield under mechanical stress. The ones that yield under the mechanical stress are the weaker hydrogen bonds [4, 7].

2.2. The Assembly of Collagen

Each collagen molecule (300nm) is assembled with the other nearby collagen to form collagen fibril (1-3um). The assembly occurs at the site (Y) if it is occupied by lysine amino acids. This is an enzymatic connection that needs the

Lysyl oxidase enzyme (LOX) and copper. Many of the fibrils are connected to form the collagen fiber (10 um) [5].

2.3. The Importance of Zero Holes, Zero Channels

Zero holes are the sites between 2 collagen molecules. It is about 40 nm. This area goes up obliquely to form the zero channel 40 nm. These areas (zero holes & zero channels) have a fundamental physiological role in the bone as they are the site of calcification. This means that it starts in the zero holes then proceeds obliquely to the zero channels. This is because the apatite chips are precipitated in the zero hole 1st then proceed gradually to the zero channel. Each apatite chip has the size of 5X20X50 nm. This means that the apatite chips are oriented vertically at the zero holes & horizontally at the zero channels. Calcium ions would be deposited in the zero holes 1st then proceed to zero channels. The above mechanism is in the physiological situation in bone mineralization. The zero holes have a pathological role in soft tissue calcification. This is the site of phosphate precipitation in collagen. The source of the phosphate crystals is from the cell membrane of nearby structures as a result of tissue damage. The best example is the calcification of arteries as a result of hypertension that damages the blood vessels that release the phosphate crystals to zero holes of the collagen with subsequent calcification. The same mechanism could occur in the valves of the heart [6].

2.4. Folding of the Collagen

The collagen as a polypeptide chain (protein) can not do its proper function except if it is folded. This means the configuration of the shape of the protein. The folding of collagen is of (α) type which means it is *helical* in shape. This occurs at the level of hydrogen bond between the glycine & proline in 2 different planes. The cut section of the same plane shows 3 amino acids (Gly, X, Y). The (Gly) site is always glycine. The (X) site is either proline or hydroxy-proline. The (Y) site is mostly lysine or to a lesser extent Arginine, and to the least extent histidine. The folding is done by the hydrogen bonds at the different planes which are much weaker than the peptide bonds between the amino-acid of the same plane (Gly, X, Y). This is the explanation of the hinge theory. This means that if the structure contains contain 2 types of bonds, the weaker one can be stretched while the stronger one can not. If the theory is applied here, the hydrogen bonds of folding are pliable and stretchable while the stronger peptide bonds remain in their places (figure 3). This is the basis of collagen conformation under the effect of the mechanical stress at the site (Y) [7].

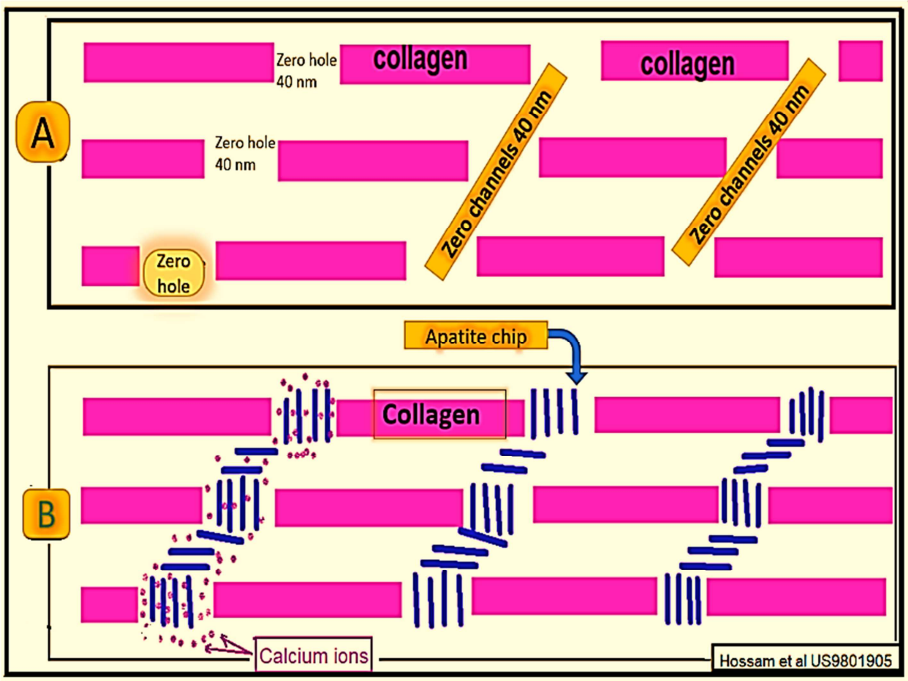

Figure 2. *The Zero Hole & Zero channels are the sites of phosphate precipitation and calcification.*

3. The Sites (Y) of the Collagen

The most important site of collagen is the site (Y) and this is the subject of this paper. This is the site where collagen conformation occurs if mechanical stress is applied, provided that collagen is functional. The (Y) site is different from the other 2 sites (Gly & X) in 4 main points:

1. It is positively changed.
2. It is polar (surrounded by water) i.e it acts as the exterior of the collagen.
3. It is *not* connected with hydrogen (H) bonds of collagen folding.
4. It is the site of cross-linking of collagen if lysine is the occupying amino acid.

From the above, it is the site that can rotate under the effect

of mechanical stress and shift to the convex side of collagen (more capacious). Thus, the convex side becomes positive while the concave side becomes relatively negative. This creates the electrical gradient difference (EGD) that can stimulate the nearby cells to modulate the tissues.

3.1. The (Gly, X, Y) Sites of the Collagen

These are the sites of one collagen thread at the cross-section. They are connected by peptide bonds. The (Gly) site is always occupied by glycine and this may be one 1/3 of sequences of collagen. The (X) site is occupied with either proline (or hydroxy-proline) each of them constitutes about 16% of the amino acid sequence. The site (Y) may be any amino acid but it has a predilection to Lysine, to lesser extent Arginine, and the least extent histidine. It must be noted that these 3 amino acids are the only polar (have an affinity to water) amino acids and also are positively charged.

3.2. Collagen Conformation Under Mechanical Stress

The conformation means a change of the shape of the protein under the effect of mechanical stress. This is exactly related to the change in the concentration of water around the protein structure. Mechanical stress causes some fluid to escape. Thus, the water concentration would subsequently be changed. *The protein is formed of amino acids which are of a different polarity i.e few of them are polar (loving water) and most of them are non-polar (hating water). Therefore, they arrange themselves according to the surrounding water. This arrangement is called protein folding. The change of water concentration around the protein under the effect of mechanical stress is associated with a change in the shape of that protein.* As the amino acids would re-arrange themselves in a new shape according to the new water concentration. This is simply is the conformation of collagen. It must be noted that on unloading, the water concentration returns to its original percentage, and consequently, the collagen also returns to its original shape.

This is because the amino acids regain their original shape. This is the basis of the theory that collagen has a memory related to mechanical stress [29].

3.3. Lysine and Cross-linking of Collagen

This occurs only at the site (Y) provided it is occupied by Lysine. It needs a very important enzyme called the lysyl oxidase enzyme (LOX). This is activated by copper (Cu). The cross-linking causes the collagen to be stronger. It does not occur if the (Y) site is occupied by any amino acid other than (lysine). This explains the importance of supplementation of amino acid lysine in the performance of collagen. Recent studies show that this amino acid could be used to treat osteoporosis. It must be noted that Lysine is essential, polar, and positively charged amino acid. Moreover, it is one of only 2 ketogenic amino acids. This means it would not be converted to glucose like the other 18 glucogenic amino acids. The only 2 ketogenic amino acids are (Lysine & Leucine) [30].

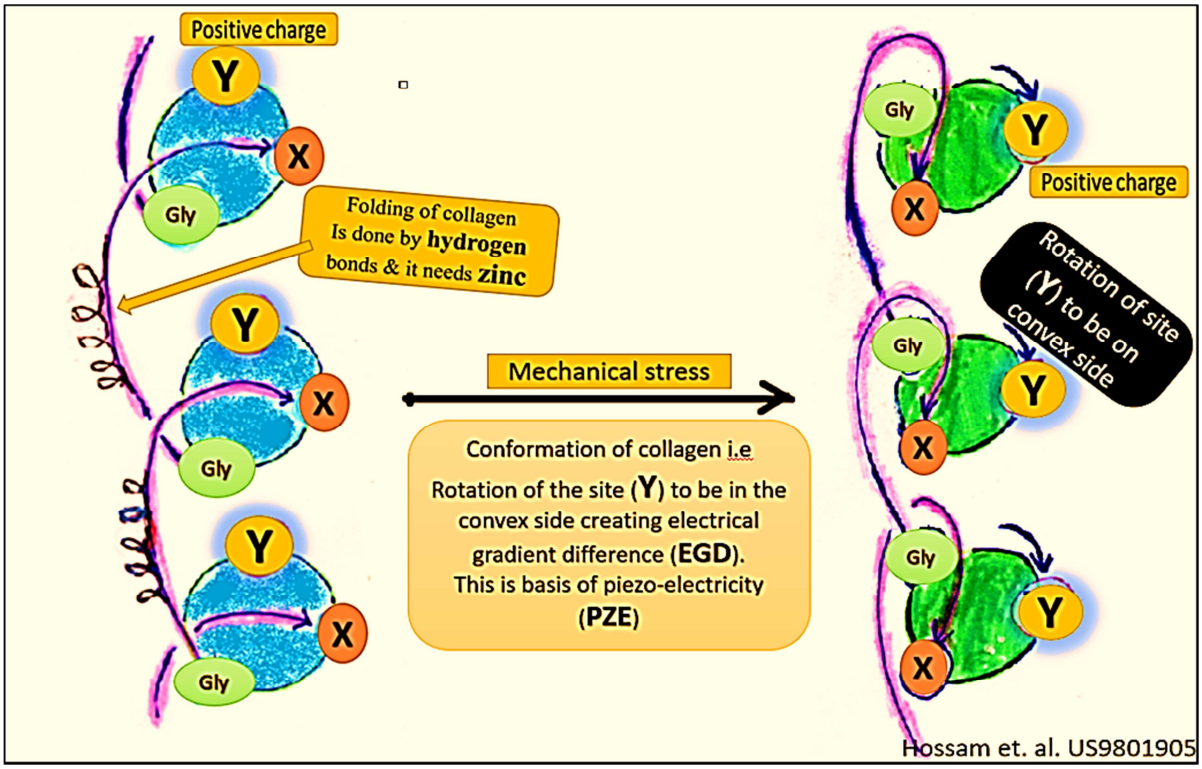

Figure 3. *The mechanics of the conformation of the collagen shows that the (Y) site is shifted to the convex side. As the (Y) site is polar and positively charged, the convex side becomes positively charged.*

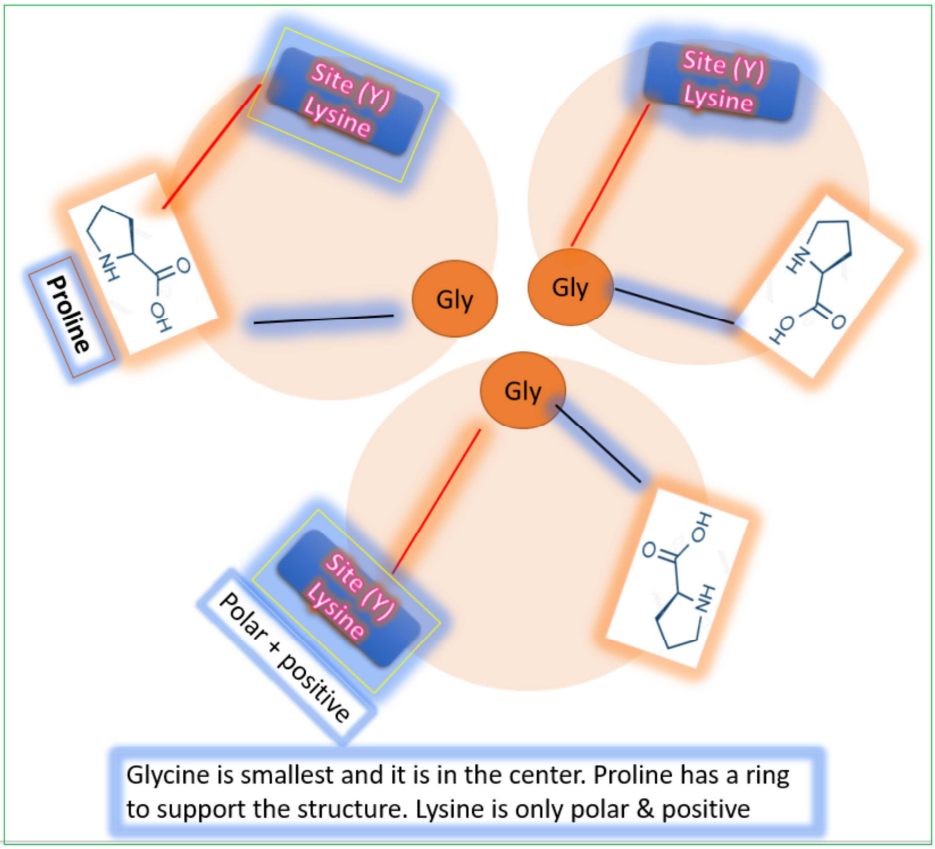

Figure 4. *The glycine is the smallest amino acid and so it is always central. The proline is the only amino acid that has a ring to support the structure of collagen and so it is peripheral. Lysine is the only polar and positively charged amino acid and is surrounded by water.*

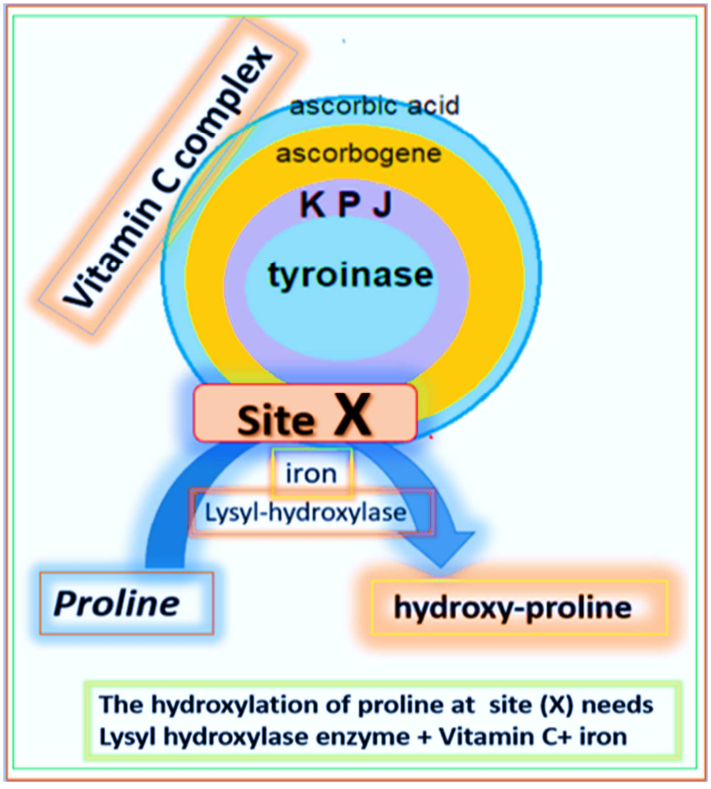

Figure 5. *The hydroxylation of proline to hydroxyproline. This is an enzymatic process that needs Lysyl hydroxylase enzyme that needs vitamin C and iron as co-factors.*

Table 1. *Comparison between the 3 sites of collagen (Gly, X, Y).*

comparison	Site (Y)	Site (Gly)	Site (X)
polarity	Polar (dissolve in water)	Non-polar (hates water) i.e not dissolve in water	
Electrical charge	Positively charged	Neutrally charged	
The type of amino acid	Lysine (commonest) Arginine less common Histidine very rare	Only glycine amino acid which forms 33% of the collagen	Proline 16% & hydroxyproline 16%
Enzymes needed	Lysyl oxidase enzyme (LOX) that needs copper as co-factor	N/A	Lysyl hydroxylase is needed for the conversion of proline to hydroxy-proline
Importance	The site of piezoelectricity The site of cross-linking of collagen.	They are needed in the folding of collagen. The (α) folding of collagen is a hydrogen bond between the glycine & proline (or hydroxyproline) that are not in the same ring	

4. The Glycation of Collagen

The sulfur attaches non-enzymatically to collagen. In case of its deficiency, the empty sites of the sulfur on the collagen are occupied by glucose. This is known as *glycation*. This process causes the collagen to be dysfunctional. In other words, the collagen can not do its proper function of tissue remodeling. It must be noted that the other 2 functions of *cross-linking & conformation* are also inhibited or may be completely stopped. This shows the importance of the site (Y) in tissue regeneration & the effect of glycation in tissue damage. Moreover, recent studies show that glycation is increased via the presence of obesity due to excess inflammatory proteins like (NF-kB). Thus, the reversal of this process needs not only supplementation of sulfur but also supplementation of antioxidants that block the (NF-kB) at the nuclear level. Alpha-Lipoic acid can do block the effect of (NF-kB) at the transcription level [31].

4.1. Glycation Never Comes Alone

As said earlier, glycation is the main process that causes the collagen to be dysfunctional. i.e it can not do its proper job as a tissue modulator except if it is not glycated. On the other hand, if glycation occurs, it needs a local factor as a sulfur deficiency and root factors as visceral fat & hyperinsulinemia. The process is so complicated that all of these factors interact with each other. Moreover, anyone of them exaggerates the others. Therefore, it is a vicious cycle and is needed to be broken at all its levels (figure 6) [32].

4.2. Sulfur Deficiency as the Starting Local Factor of the Glycation

Sulfur deficiency in the elderly is the most important local factor. It allows the glucose to attach to the empty sites that were previously occupied by sulfur. It is known sulfur is an essential element for hair, nail, skin, and insulin. Moreover, the cooking causes sulfur to be damaged at and above 70°. Furthermore, the elderly person usually has malabsorption for sulfur. All these factors predispose to sulfur deficiency. Subsequently, glycation could be predisposed for.

4.3. The Central Factors of the Glycation

Obesity usually does not come alone but it's also associated with excess visceral fat, hyperinsulinemia, and glycation. Obesity is defined as the body mass index (BMI) is 30 or more. The general guideline of the BMI is that a normal person is from 18-25. The overweight is from25-29.9. More than that limit the patient is considered obese and would have excess visceral fat, hyperinsulinemia, and glycation. Visceral fat is present in the viscera like the liver, pancrease, omentum. This type of fat is metabolically active and secrets a large number of inflammatory cytokines namely tumor necrosis factors (TNFs). These inflammatory cytokines are responsible for the initiation of chronic subclinical inflammation. This is the starting point of metabolic (X) syndrome. This is the missing link between glycation & metabolic syndrome. It is also inaccessible for surgery. Its treatment needs to cut carbohydrates and prolonged fasting.

4.4. Glycation and Senescent Cells

The senescent cells are aged cells that similar to zombies that refuse to die and can not do their proper function as well. These cells are very similar to visceral fat in the secretion of inflammatory cytokines like tumor necrosis factors (TNFs). These cytokines can increase the glycation process of the collagen. These cells also secret products that convert the nearby healthy cells to become new senescent cells. In other words, they could infect the nearby cells to become senescent. The hallmarks of these cells are the presence of senescence-associated heterochromatin foci (SAHF). Normally, the chromatin is present just under the nuclear membrane but in the case of senescent cells, they are separated from the nuclear membrane to be seen as (SAHF) [8].

5. The Ingestion of Collagen

Many studies have been done on the supplementation of collagen to improve the internal collagen of the human body. The improvement is minimal because collagen is a very large particle. As said earlier, it is formed of 3150 amino acids. Thus, it must be digested and broken down to its building block amino acids. Then, they could be absorbed as single units. They are rich in the most important amino acids needed for the manufacture of new collagen. As said earlier, collagen is rich in glycine, proline, and hydroxy-proline. Despite all of that collagen is not considered a super-food. Its ingestion has many drawbacks.

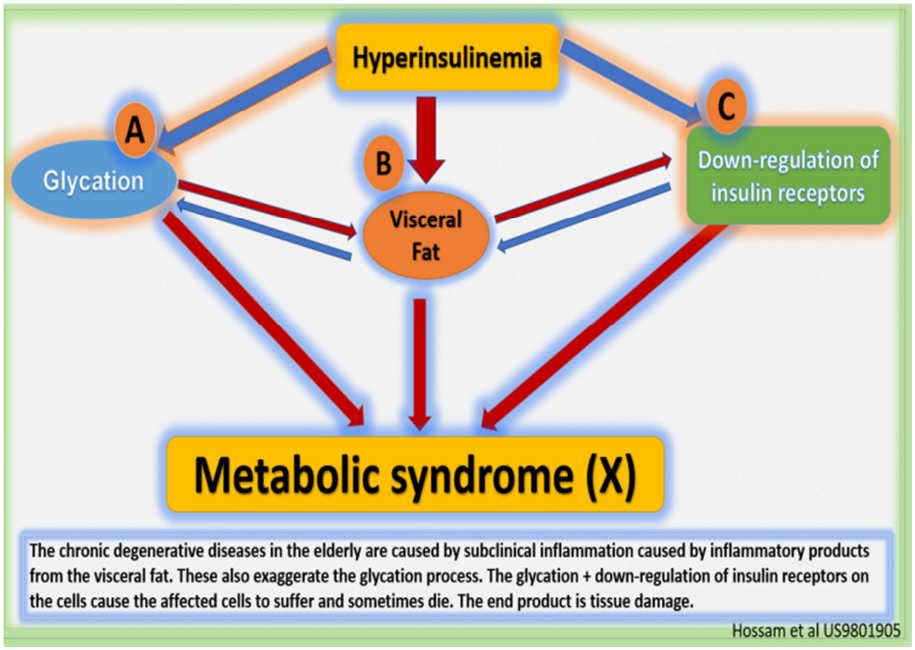

Figure 6. *The relation between hyperinsulinemia, Glycation, obesity (visceral fat) in the initiation of the metabolic syndrome (X).*

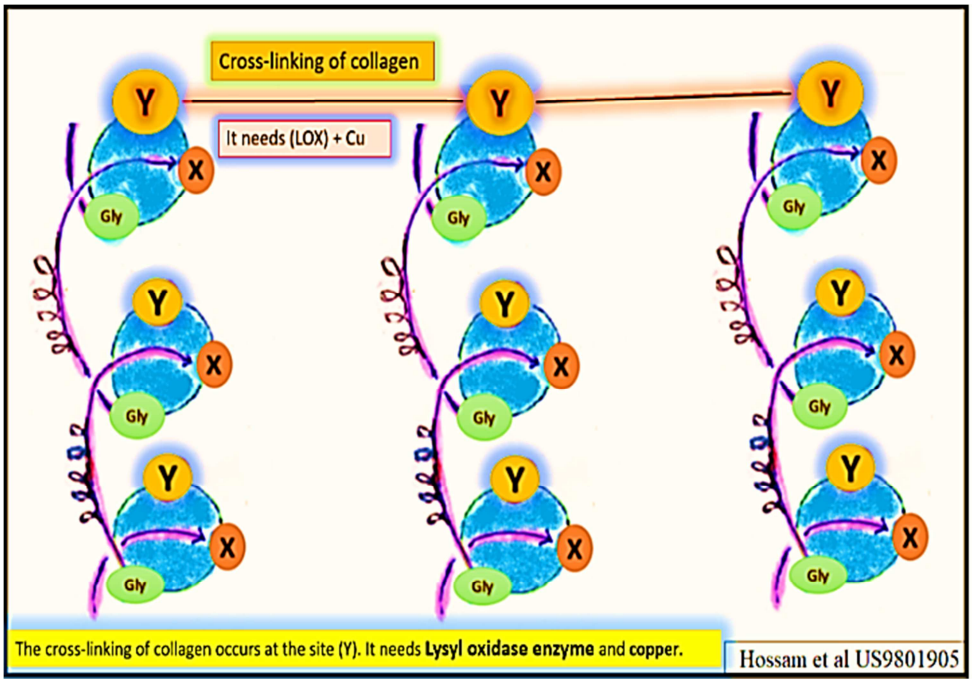

Figure 7. *The cross-linking of collagen occurs at the (Y) sites. via Lysyl oxidase enzyme (LOX). It needs copper as a co-factor.*

5.1. The Drawbacks of Collagen Ingestion

It is deficient in *tryptophan* amino acid which is essential amino acid i.e the human body can not manufacture it and it must be given with foods especially animal products. Tryptophan is needed for the manufacture of 3 vital products which are melatonin, serotonin, and niacin [9]. Collagen is also deficient in cysteine amino acid. However, this is *not* essential amino acid and can be manufactured inside the human body. It can not be manufactured in the elderly or in the case of chronic debilitating conditions. Thus, it must be supplemented. Therefore, it is considered semi-essential amino acid. Cysteine is critically important because it is the amino acid that is the only donor of the *disulfide bonds*. These are necessary for folding for many structural proteins of the human body e.g hairs, nails, insulin, etc. In the case of cysteine deficiency and it is not supplemented as in the case of chronic degenerative disease in the elderly, the body breakdown the muscles to get its requirement of the cysteine. *This explains the muscle wasting that could occur in chronic metabolic syndrome (X)*. It also explains the importance of cysteine supplementation in chronic metabolic diseases in the elderly. Recent studies show that the manufacture of collagen

consumes the cysteine component in the amino acid pool. As cysteine is needed for the disulfide bond formation. This explains the enhanced collagen formation by the supplementation of N.actyl cysteine (NAC) [10].

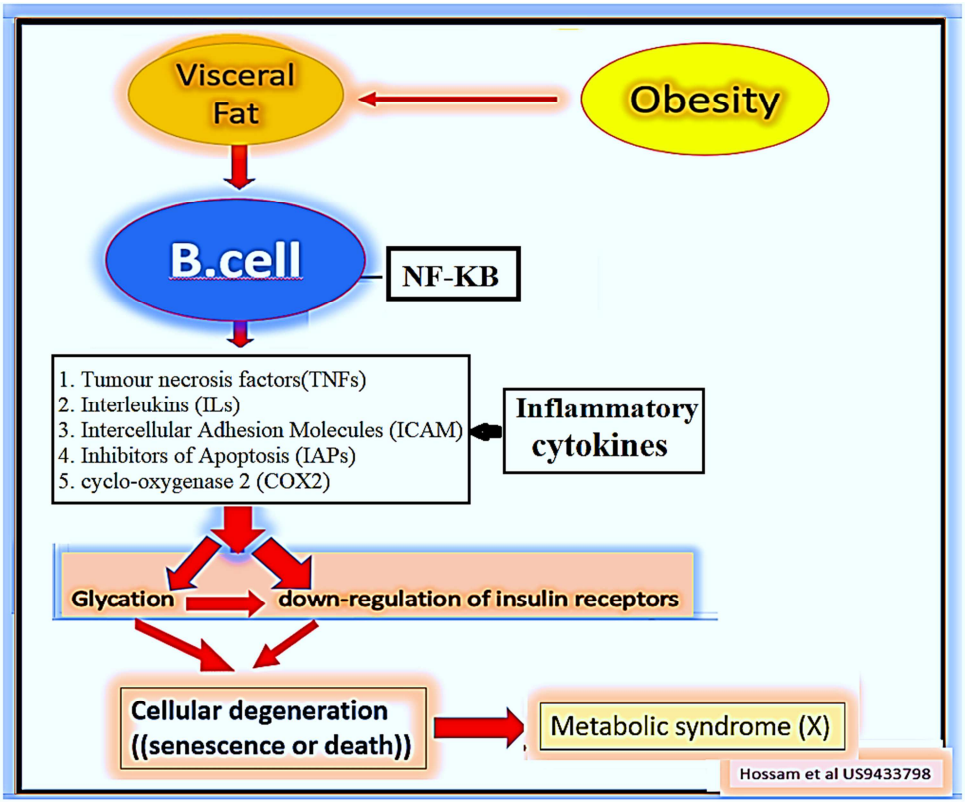

Figure 8. *The relation between visceral fat & glycation and metabolic syndrome (X) of aging {{DM, Alzheimer, coronary artery disease, arthritis, osteoporosis).*

5.2. Collagen Ingestion Has a Neglected Effect on (Y) Site

The collagen has a very small percentage of *Lysine* amino acid which is the key player of the (Y) site. Thus, the effect of collagen ingestion on the cross-linking of collagen is minimal. Collagen is rich in glycine 33% which occupies the site (Gly). It is also rich in proline & hydroxyproline which occupy the site (X). As said earlier, the percentage of each is 16%. Moreover, the collagen must be broken down to its building block amino acids which enter the amino acid pool. They will not be directed specifically to collagen only because the human body has more than 2 million proteins.

Therefore, the ideal method of enhancing collagen is not via its ingestion but through its repair (deglycation). i.e removal of the glucose that is attached to collagen. Removal of visceral fat via prolonged fasting and cutting of carbohydrates. Lastly, adding certain anti-oxidants to block the effect of the inflammatory products (NF-kB) of already present visceral fat. Certain amino acids like Lysine & cysteine also have a beneficial effect on collagen better than ingestion of collagen itself. This is a new method of thinking for the treatment of metabolic syndrome (X) syndrome via the deglycation process [11, 13].

6. Metabolic (X) Syndrome

This is a group of diseases that have a high probability of heart diseases, stroke, hypertension, DM II, fatty liver, Alzheimer's, osteoarthritis, osteoporosis, and others. This group of diseases can be reduced by cutting carbohydrates and increasing exercise and eating healthy non-processed foods. The exact mechanism was not clear but it is more common with an obese person especially with central obesity. It could be predicted if the waist size is more than 85 cm in women or 90 cm in men. The possible explanation is that eating excess carbohydrates and/or highly processed fast food leads to excess fat in the liver. As the liver can store very little amount of fat, it tries to export all the excess fat to the nearby organs i.e the pancrease, omentum, intestinal wall, kidney, and pericardium. This type of fat is metabolically active and secrets a large number of inflammatory products mainly TNFs & and subsequently NF-kB. These are the roots of all subclinical inflammations that are responsible for metabolic syndrome (X) [22].

6.1. The Root Causes of the Metabolic Syndrome

As said earlier, visceral fat never comes alone, it almost always comes with 2 of its sisters namely; glycation and hyperinsulinemia. These are known as biomechanical metabolic triads. Therefore, for the treatment of all the diseases of metabolic syndrome (X) to be optimal, it needs to be treated at all the 3 levels (figure 8). Osteoporosis would be discussed as an example of metabolic disease in the elderly.

6.2. Idiopathic Osteoporosis Is an Example of Metabolic Syndrome (X)

Osteoporosis is a disease of bone weakness that could be broken with milder trauma than expected. It affects usually the elderly. Its scientific definition is the reduction of bone mass per unit volume. It has 2 main types: idiopathic and secondary. The secondary type is out of the scope of this paper because it is caused by another causative disease. Therefore, the treatment of secondary osteoporosis is via the treatment of causative diseases either fracture fixation, cancer, disability, and so on [23]. By far**,** the commonest type of osteoporosis is the (idiopathic) type. It is called the idiopathic because there is no apparent primary factor (s) that may predispose to this type of osteoporosis. It might be genetic, environmental, nutritional, hormonal, occupational, or even lifestyle predispositions. The exact cause is not known. Therefore, it is called idiopathic which means with no known cause [24]. The US patent (US9801905) discovered that osteoporosis's starting point is the *glycation* of its bone collagen. The collagen forms 28% of the bone mass. Its main function was *thought* to be only structural support. The above patent declared out that collagen is a reactive tissue. It acts as a transformer that converts the mechanical stress into an electrical gradient difference (EGD). This is the most important function of collagen. This property is called piezo-electricity (PZE). This fundamental function of the collagen necessitates it to be functional which means it is not glycated. In other words, the glycated collagen is not functional and it could not do its piezo-electric property. Thus, it could not start the bone remodeling and the new bone formation [25].

6.3. Idiopathic Osteoporosis Is Not Idiopathic Anymore

By the above explanation, the idiopathic type of osteoporosis is not considered idiopathic anymore. This is because the predisposing factor is known which is the glycation of collagen of the bone. As said earlier, glycation does not always come alone. It almost always comes with its 2 other sisters: *hyperinsulinemia* that is associated with visceral fat. This is called above the metabolic triads.

Therefore, osteoporosis is considered a metabolic disease. This new concept changes the lines of the treatment of osteoporosis. In other words, attention must be paid to treating osteoporosis at all levels and not only at the bone level. The bone part of osteoporosis is considered as the tip of the iceberg but beneath it, many other factors must be corrected. Special attention is applied to the visceral fat.

As collagen is not only a protein of structural support as was thought. It has another very fundamental function as the starting point of tissue remodeling. It can stimulate or inhibit nearby cells to remodel the surrounding tissues. This job can be only done if the collagen is functional and not glycated [12].

The sulfur deficiency acts as an important point of collagen dysfunction. This is because the sulfur is non-enzymatically attached to collagen. In case of its deficiency, the glucose gets access to the collagen and the glycation occurs [26].

6.4. Hyperinsulinemia and Osteoporosis

Hyperinsulinemia exaggerates osteoporosis. The recent studies that show the mitochondrial-nuclear axis could down-regulate the number of insulin receptors on the osteocytes. This is a simple negative feedback mechanism. In the early stages, this would have a protective role for the osteocytes to be saved from the high insulin level. Later, the affected cells may suffer from starvation up to death. As the osteocytes act as the maestro that controls all other bone cells namely the activation of osteoblasts and/or inhibition of osteoclasts. The remodeling of the bone is greatly disturbed. This means that new bone formation is reduced while bone resorption may be enhanced. This is because the osteoclasts are released from their inhibition. Thus, osteoporosis may issue [27].

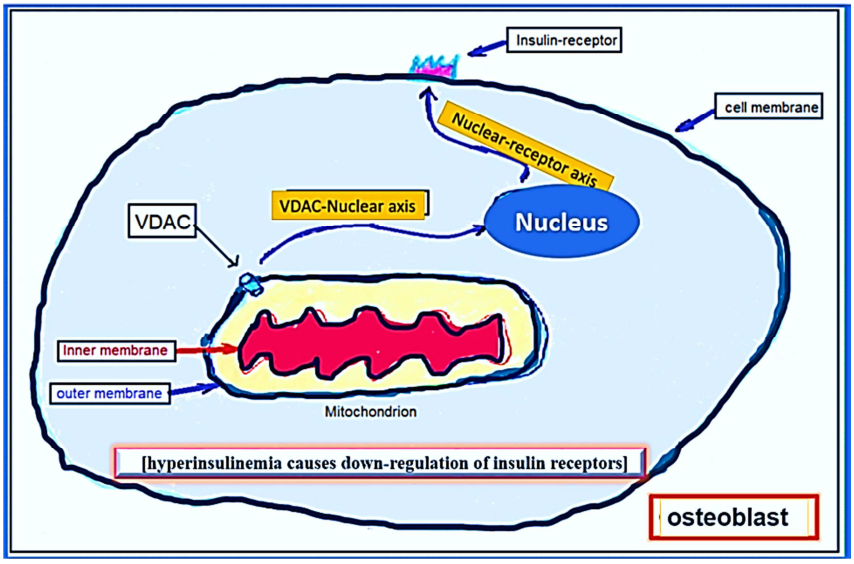

Figure 9. *Hyperinsulinemia down-regulates insulin receptors on the osteoblast (VDAC-Nuclear axis).*

6.5. The Visceral Fat and Osteoporosis

Visceral fat is the 3rd limb of the metabolic syndrome. It affects mainly the 3rd type of bone cells which are the osteoclasts. Visceral fat secrets (TNFs) enhance the formation of (NF-kB) pathway. Subsequently, Reactive Activators of Nuclear factor (RANK)-(RANK-L) interaction (figure11). These are the main stimulators of osteoclasts (bone-eating cells). This exaggerates bone resorption with subsequent osteoporosis formation [28].

From the above, morbid obesity has 3 limbs namely; *visceral fat, hyperinsulinemia, and glycation.* Every limb could attack a certain part of the bone cells for osteoporosis to occur. Therefore, idiopathic osteoporosis is a metabolic disease of known causes and its correction needs to deal with all these factors to treat bone osteoporosis at the root levels.

7. Discussion

The (Y) site has a critical role in collagen function. It has the following criteria:

1. The site of piezo-electricity.
2. It is a polar site (surrounded by water i.e loving water).
3. It is the only positively charged site of collagen.
4. The site of cross-linking of collagen (if lysine is the occupying amino acid).

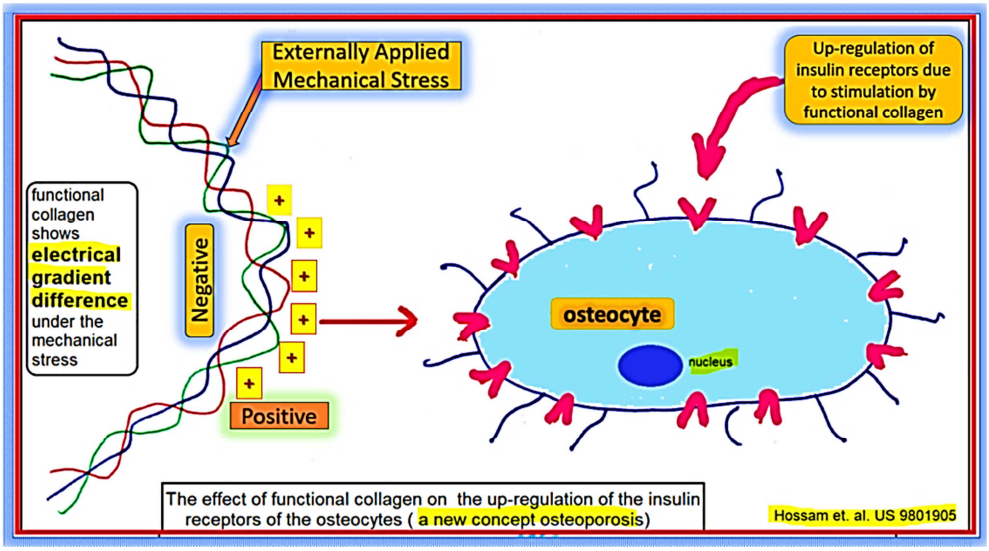

Figure 10. *The Functional collagen has an electrical gradient difference (EGD). This up-regulates the insulin receptors of the osteocytes.*

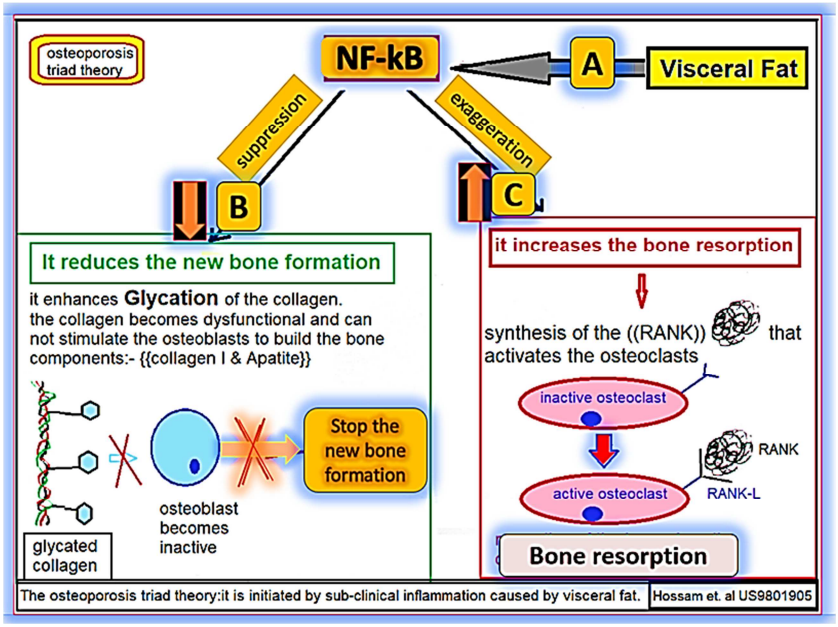

Figure 11. *The 3 limbs of morbid obesity could attack the bone at 3 levels. These are visceral fat, hyperinsulinemia, and glycation. Thus, Idiopathic osteoporosis is considered as one of the metabolic syndrome (X).*

5. It does not attach to hydrogen bonds of collagen folding. (it is not in the hinge of the rotation)

As collagen is not only a protein of structural support as was thought. It has another very fundamental function as the starting point of tissue remodeling. It can stimulate or inhibit nearby cells to remodel the surrounding tissues. This job can be only done if the collagen is functional and not glycated [12].

The sulfur deficiency acts as the starting point of collagen dysfunction. This is because the sulfur is non-enzymatically attached to collagen. In case of its deficiency, the glucose gets access to the same places i.e non-enzymatic attachment to collagen. Then, the collagen becomes dysfunctional and it can not do its role in the activation of nearby cells to remodel the surrounding tissues. thus, the supplementation of MSM as a source of organic sulfur could be essential in the prevention of this starting point [14, 15].

potent anti-oxidants have a very important role in the prevention of the glycation process. e.g. Alpha-lipoic acid, N. acetylcysteine, or taurine could prevent the glycation process via inhibition of the effect of (NF-kB) which is the main inflammatory product of the human body. Recent studies show that (NF-kB) predisposes to the glycation process. Also, from the (RANK)-((RANK-L) interaction pathway, the osteoclasts could be activated to aggravate the condition of osteoporosis [16].

As said earlier, visceral fat is the main source of (NF-kB). This type of fat is present in the liver, omentum, intestinal wall, pancrease, kidneys, and even the pericardium. This fat is metabolically active and always manufactures the inflammatory products that cause glycation of collagen with subsequent gradual tissue damage that leads at the end to the chronic metabolic diseases of the elderly. This type of fat is not accessible for surgical removal. It needs prolonged fasting and completely cutting the intake of carbohydrates [17].

Hyperinsulinemia is a silent catastrophic disease. the patient has a false sense of security that he is not yet diabetic as blood sugar is still within the normal levels. The pancrease can compensate to push sugar inside the tissues. high blood sugar is dangerous but excess sugar inside the tissues is more dangerous. Recent studies show that hyperinsulinemia is associated down-regulation of insulin receptors. This is a protective mechanism at the early stages but later, the cells suffer from starvation. It must be noted that hyperinsulinemia does not come alone. It must be associated with obesity and excess visceral fat. Thus, there would be an excess (NF-kB) of the visceral fat. Hyperinsulinemia is roughly 3 times more than that of DM II. In the US, the percentage of hyperinsulinemia is about 36% of the population which is about 86 million. On the other hand, DM II in the US is about 11% of the population of about 31 million [18].

Lastly, certain amino acids are very essential for collagen function. the human body has 20 amino acids. Nine of them are essential which means that they can not be manufactured by the human body. They must be supplemented by food. The other 11 amino acids are non-essential and the body can manufacture them in case of their deficiency [19]. Regarding collagen (Gly, X, Y) sites, the glycine & proline are non-essential amino acids. Thus, the body can manufacture them in case of their deficiency. On the other hand, the site (Y) is occupied by Lysine mainly, and to lesser amount arginine, and very rare histidine. Lysine & histidine are essential and must be supplemented in the foods. Arginine is not essential and can be manufactured by the human body. It must be noted that arginine is the main source of *nitric oxide* for the body. Arginine has some side effects on the gastrointestinal tract. Citrulline is the best alternative for arginine and is even more effective and has no side effects [20].

Collagen supplementation has no or very minor effect on the (Y) site of the collagen. Moreover, collagen has another disadvantage of the deficiency of tryptophan amino acid that is essential and needed for melatonin, niacin, and serotonin. It is also deficient in cysteine amino acids. Although cysteine is non-essential, it is needed for supplying the body with disulfide bonds. In the elderly with chronic metabolic diseases, the body breakdown the muscles to get its requirement of cysteine. This explains muscle wasting in chronic metabolic diseases. Therefore, collagen supplementation is not the ideal solution for the (Y) site diseases [21].

8. Conclusion

Collagen is a protein that means it is a polypeptide chain. The cross-section of one collagen thread shows 3 amino acids at 3 sites (Gly, X, Y). The (Y) site is different from the other 2 sites in being polar, positively charged, the site of cross-linking of collagen, and the piezo-electricity. Moreover, it is the site of the glycation of collagen. The group of amino acids that may occupy this critical site may be Lysine, to a lesser extent arginine, and very rare to be histidine amino acids. It is known that Lysine & histidine are essential amino acids while arginine is not essential. It is strongly believed that collagen as a fibrous protein has only a structural support function. Recently discovered that collagen has another very fundamental function which is its piezo-electricity (PZE). This means that collagen is the prime mover for tissue remodeling. It acts as a transformer that converts some of the mechanical stress into an electrical gradient difference (EGD). This is the very important function of collagen depending on its (Y) site. Therefore, the recovery of the (Y) site could allow tissue repair to occur and to compensate for the natural loss of the tissue as a result of wear and tear. On the other hand, the dysfunctional (Y) site stops the piezoelectric effect with subsequent loss of the repair of the damaged tissues. every effort is exerted in this paper to recover the site (Y) again to correct the metabolic syndrome (X). This could be done by certain materials which include organic sulfur, certain amino acids, some anti-oxidants, and change of the lifestyle of the patient, cut carbohydrates especially refined sugar and grains.

References

[1] Sylvie Ricard-Blum, 2011. The Collagen Family. Cold Spring Harbour perspective in biology. Volume 3. Article004978.

[2] 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.

[3] 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.

[4] Olena S. Rabotyagova. 2008. Collagen structural hierarchy and susceptibility to degradation by ultraviolet radiation. Materials Science and Engineering: C. Volume 28, Issue (8), Pages 1420-1429.

[5] K E Kadler, 1996. Collagen fibril formation. Biochemical Journal Volume 316 (1): Pages 1–11.

[6] Michael Meyer. 2019. Processing of collagen based biomaterials and the resulting materials properties. BioMedical Engineering OnLine volume 18, Article number: 24.

[7] Collin M. Stultz, 2006. The folding mechanism of collagen-like model peptides explored through detailed molecular simulations. Protein Science. Volume 15 (9): 2166–2177.

[8] Katherine M. Aird, 2013. Detection of senescence-associated heterochromatin foci (SAHF). Methods Molecular Biology. Volume 965: 185–196.

[9] Cristiana Paul, 2019. Significant Amounts of Functional Collagen Peptides Can Be Incorporated in the Diet While Maintaining Indispensable Amino Acid Balance. Nutrients. Volume 11 (5): 1079.

[10] Andrew S. DiChiara. 2018. A cysteine-based molecular code informs collagen C-propeptide assembly. Nature Communications volume 9, Article number: 4206.

[11] V. V. Emel'yanov, 2017. Glycation, antiglycation, and deglycation: Their role in aging mechanisms and geroprotective effects (literature review). Advances in Gerontology volume 7, pages 1–9.

[12] 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.

[13] 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.

[14] Abdulhakim Elosta, 2017. Aged garlic has more potent antiglycation and antioxidant properties compared to fresh garlic extract in vitro. Scientific Reports volume 7, Article number: 39613.

[15] Qiushi Wang. 2015. Hydrogen Sulfide Prevents Advanced Glycation End-ProductsInduced Activation of the Epithelial Sodium Channel. Oxidative Medicine and Cellular Longevity, Article ID 976848, 10 pages.

[16] Rodrigo Rodrigues Franco, 2018. Antioxidant and anti-glycation capacities of some medicinal plants and their potential inhibitory against digestive enzymes related to type 2 diabetes mellitus. Journal of Ethnopharmacology volume 215: Pages 140-146.

[17] Nikolaos Alexopoulos. 2014. Visceral adipose tissue as a source of inflammation and promoter of atherosclerosis. Atherosclerosis. Volume 233 (1): Pages 104-12.

[18] Dylan D Thomas. 2019. Hyperinsulinemia: An Early Indicator of Metabolic Dysfunction. Journal of Endocrinal Society. 3 (9): 1727–1747.

[19] Clare-AnnCanfield. 2019. Amino acids in the regulation of aging and aging-related diseases. Translational Medicine of Aging. Volume 3, Pages 70-89.

[20] Anton V. Persikov. 2005. Prediction of Collagen Stability from Amino Acid Sequence. Journal of biological chemistry. Vol. 280, (19), pp. 19343–19349.

[21] Simon N. Young. 2013. Acute tryptophan depletion in humans: a review of theoretical, practical and ethical aspects. Journal of Psychiatry Neuroscience 38 (5): 294–305.

[22] A López-Candales. 2001. Metabolic syndrome X: a comprehensive review of the pathophysiology and recommended therapy. J. Med. Volume 32 (5-6): 283-300.

[23] Tümay Sözen, 2017. An overview and management of osteoporosis. European Journal of Rheumatology. Volume 4 (1): 46–56.

[24] Ibrahim Akkawi. 2018. Osteoporosis: Current Concepts. Joints. Volume 6 (2): 122–127.

[25] MiguelCerrolaza. 2017. Analysis of Bone Remodeling Under Piezoelectricity Effects Using Boundary Elements. Journal of Bionic Engineering. Volume 14, Issue 4, Pages 659-671.

[26] Yahtyng Sheu. 2011. The Role of Bone Marrow and Visceral Fat on Bone Metabolism. Current Osteoporosis Reports volume 9 (2), pages 67–75.

[27] Xinshui Wang. 2021. Association Analysis of Insulin Resistance and Osteoporosis Risk in Chinese Patients with T2DM. Dove Press. Volume 2021: 17 Pages 909—916.

[28] Taishin Akiyama. 2012. RANKL-RANK interaction in immune regulatory systems. World J Orthop. Volume 3 (9): Pages 142–150.

[29] Yuye Tang. 2010. Deformation micromechanisms of collagen fibrils under uniaxial tension. J R Soc Interface. Volume 7 (46): 839–850.

[30] Mitsuo Yamauchi, 2012. Lysine post-translational modifications of collagen. Essays Biochemical. Volume 52: 113–133.

[31] Chang-Keun Lee, 2008. Alpha-lipoic acid inhibits TNF-alpha induced NF-kappa B activation through blocking of MEKK1-MKK4-IKK signaling cascades. International Immunopharmacology. Volume 8, Issue 2, Pages 362-370.

[32] Hossam Mohamed, 2022, Hossam's Secrets of the Glycation-Hyperinsulinemia Interphase in Osteoarthritis with Suggestions of the Root Treatment: US Patents Review. Frontiers. Volume 2, Issue 1, Pages: 1-14.