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Review Article

Hossam's Secrets of the Glycation-Hyperinsulinemia Interphase in Osteoarthritis with Suggestions of the Root Treatment: US Patents Review

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Abstract: Osteoarthritis is by far the most common disease in the elderly. It has a great impact on the health care system in every nation. Its cost not only includes the price of the medication and surgery but there are other indirect costs in the form of sick leaves, disability, consumption of hospital resources, and others. The traditional treatment depends mainly on analgesics which always have many side effects and almost always fail because the disease usually progresses to a more advanced level. The surgical treatment may cure the pain but it is very expensive and still also has the side effects of the surgery itself. New US patents (US9433798), (US9452297), (US9757583) looked at this disease process from another view. They discovered that osteoarthritis is a small piece of many other parts of a generalized disease affecting the whole body. The root of this condition is in the visceral fat while its summit is the painful osteoarthritic joint. Extensive research was done on the link between the visceral fat and the painful arthritic joint. The visceral fat always occurred before the appearance of arthritis. Therefore, every possible method was exerted to abort this problem at its very early stage. This may even be before the start of the pain which is called the treatment at the root level. This creates a new line of treatment other than medication and surgery. Moreover, this may be physiological, effective, cheaper, and more functional as well.

Keywords: Osteoarthritis, Visceral Fat, Glycation, Hyperinsulinemia, NF-kB, Infra-red Laser, PEMF

1. Introduction

1.1. Osteoarthritis Is the Commonest Chronic Disease in Elderly

Osteoarthritis is *not* an *inflammatory process* as the name implies but it is a degenerative disease in the elderly due to *wear and tear* of the articular cartilage. The pathological process of the transformation of the normal joint to become osteoarthritic is ill-defined. It might be multifactorial which means it depends on genetic, occupational, or even of a lifestyle root. The most considered *current* theory is that the damage of the cartilage is caused by wear and tear of the affected joint (s). This means excessive stress on the cartilage and for a prolonged time leads to its damage. For example, obesity is thought to be the most important risk factor for osteoarthritis because the heavy weight

of the patient allows the wear and tear of the cartilage [1]. The above-discussed patents proved that obesity is a risk factor because of *another mechanism* which is the visceral fat and not the *physical weight* of the patient. It is known that obese patient usually has more fat than non-obese. There is an epidemic of obesity in the western world due to the prevalence of fast foods and highly processed and refined sugar and grains. Thus, osteoarthritis (OA) comes as a result of a *metabolic* process rather than a *physical* one [2].

1.2. Osteoarthritis Is the Endproduct of Visceral Fat

Osteoarthritis (OA) is caused by visceral fat. A granted US patent (*US 9,433,798*) considered the OA as terminal branches of the tree. The trunk of that tree is the interaction between *glycation & hyperinsulinemia*. The root of that tree is visceral fat. Thus, the healing of the OA by treating the joint *only* is insufficient treatment and usually fails. Therefore, the treatment must include all the levels of (OA) which are the root, trunk, and terminal branches [3, 4].

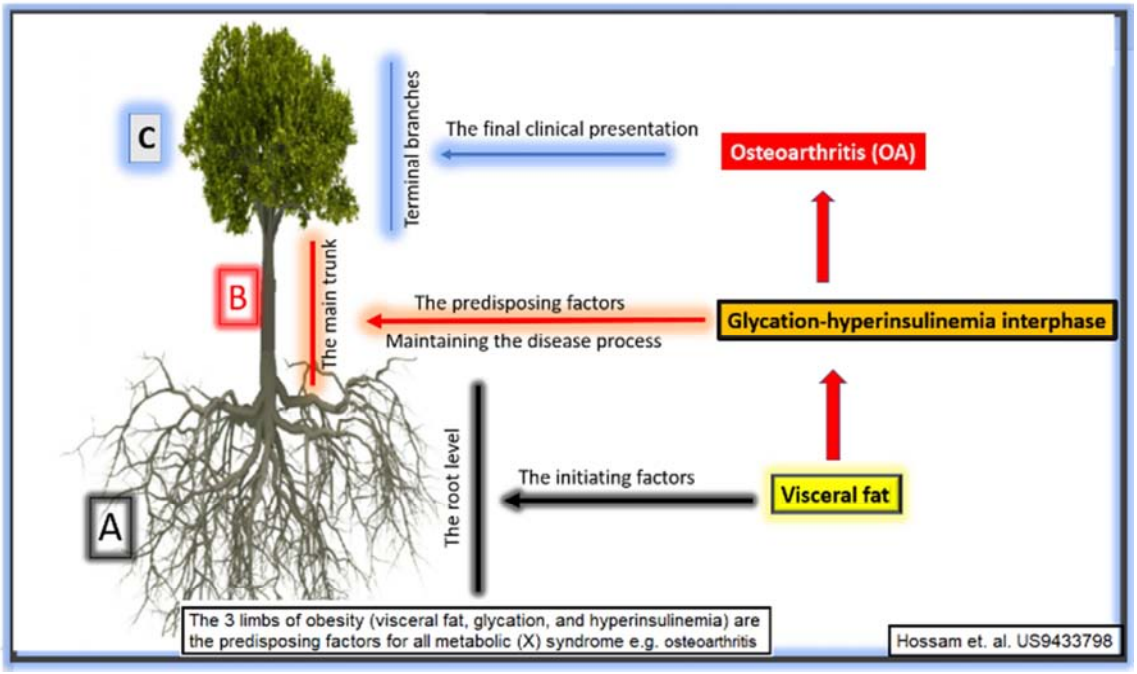

Figure 1. *Obesity is the origin of all metabolic (X) syndrome including osteoarthritis. Visceral fat acts as its roots and glycation & hyperinsulinemia are contributing factors. The terminal branches are osteoarthritis itself (painful joint (s).*

2. The Molecular Mechanics of the Cartilage

Cartilage is formed of 3 main materials. These include synovial fluid, collagen II which is a fibrous protein, and other non-proteinous solid materials.

2.1. The Fluid Content 70%

The collagen is formed mainly of *water called* the synovial fluid. This constitutes about *70%* of the mass of the cartilage. It is believed that it acts as a shock-absorbing mechanism. There is another more important function from the mechanical perspective is that it helps in the nutrition of the chondrocytes (cartilage building cells). It is well-known that the cartilage is *avascular* which means it has mostly no blood supply. Then, the nutrition occurs via the cyclic entrance and exit of the fluid into and out of the cartilage respectively. On its entrance, it brings oxygen and nutrition. On its exit, it takes carbon dioxide & waste products out of the cartilage substance. This could help the chondrocytes to thrive. Thus, they could repair the damage and make maintenance of the cartilage [5].

2.2. The Proteins Content of the Cartilage 15%

Collagen type II forms about 15% of the cartilage substance. It has a fundamental role which is conformation under mechanical stress. The functional collagen shows its role as the internal cartilage machinery. The collagen bends and shows a positive convex side and negative concave side. This phenomenon is called piezo-electricity (PZE) as fully explained in the US9801905 [7]. Chondroitin is a highly negative structure. It is transformed to the positive side of the collagen which is the convex side. This creates an empty space on the concave side. The water rushes to fill the empty space. This creates internal currents of fluid inside the cartilage with each mechanical loading. This distributes oxygen & nutrition throughout the cartilage (figure 3).

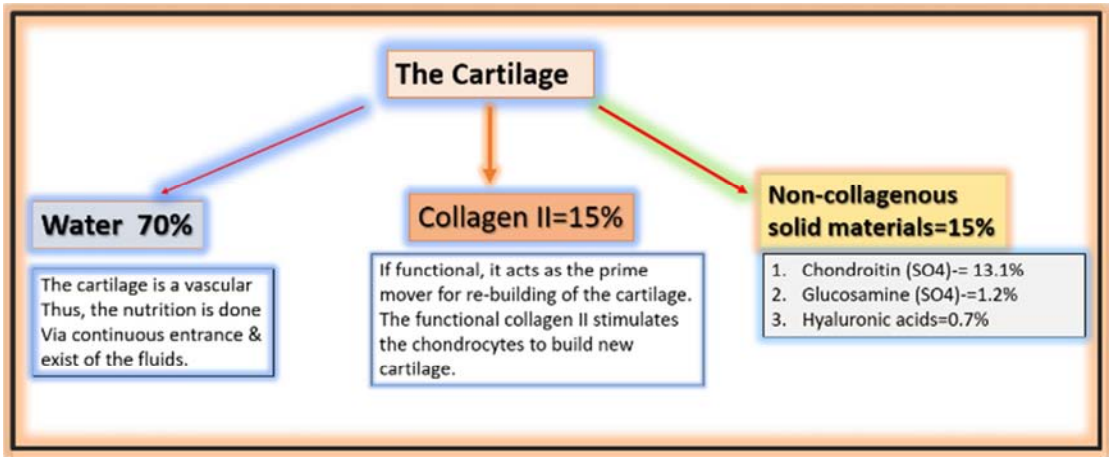

Figure 2. *The 3 main components of the cartilage (fluid 70%+ collagen II 15% + non-collagenous solid materials 15%).*

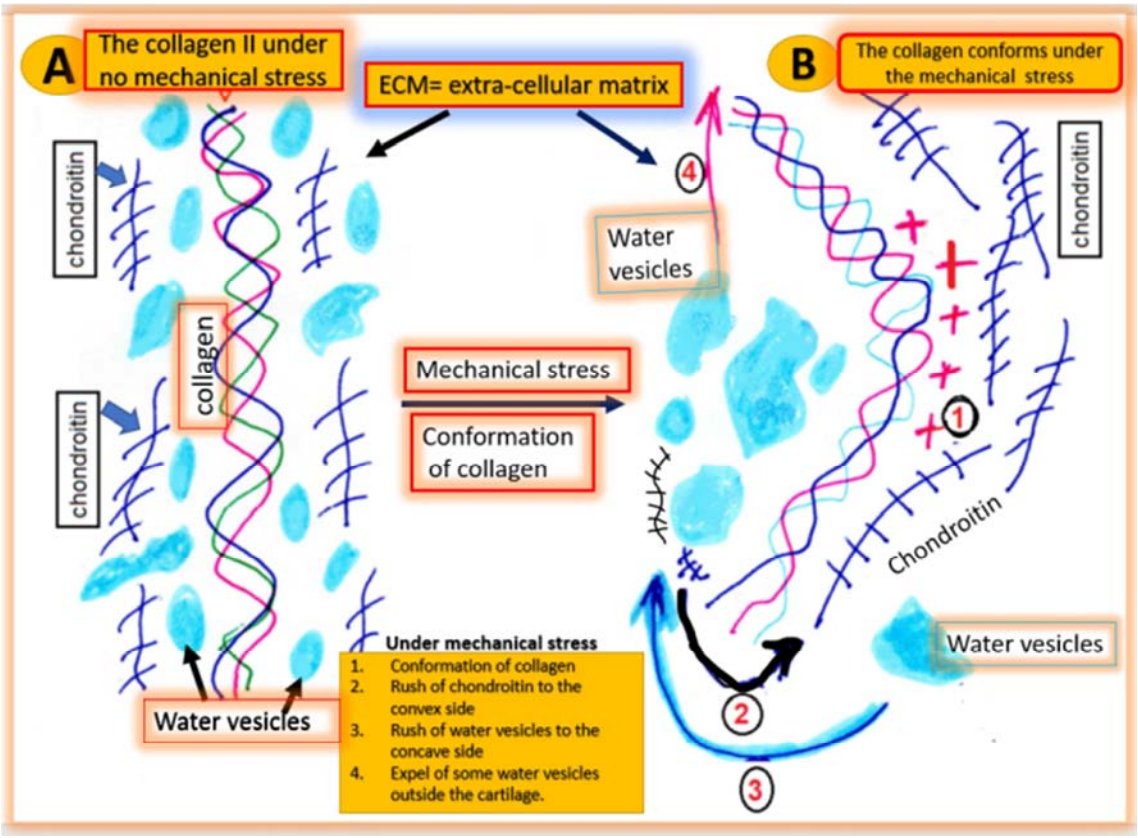

Figure 3. *The molecular mechanic of extracellular matrix. Collagen II is conformed under mechanical stress. 1. It shows a positive convex side & a negative concave side. 2. The negatively charged chondroitin shifts to the positive convex side. 3. The water rashes to the concave side 4. Some fluid is expelled out of the cartilage to the joint space.*

On unloading, all the structures return to the resting state. This means the escaped fluid returns with oxygen and nutrition. The chondroitin becomes evenly distributed again around the collagen. The collagen itself returns to be an un-conformed state and becomes nearly electrically neutral. This cycle is repeated in each loading-unloading. The above cycle occurs only if the collagen is functional i.e non-glycated. On other hand, the glycated collagen (dysfunctional) can not do its proper piezoelectrical role. This means that collagen is the prime mover for the maintenance of the cartilage [6].

NB. Not all the collagen of the cartilage is type II. There is a very small amount of collagen is of type IV in the pericellular matrix (PCM) area (figure 4). This collagen IV is responsible for the stimulation of the chondrocytes to manufacture all the components of the cartilage including chondroitin, glucosamine, and hyaluronic acids (figure 5).

To sum up the types and function of the collagen in the cartilage. There are mainly 2 types of collagen. Collagen II is the predominant type. It is present in the extra-cellular matrix (ECM) and is responsible for the nutrition of the cartilage via the initiation of currents of fluids inside the substance of the cartilage by the loading-unloading cycle. The lesser amount is

collagen IV which is present in the pericellular matrix (PCM) and is responsible for the stimulation of the chondrocytes to manufacture all the components of the cartilage (figure 4) [8].

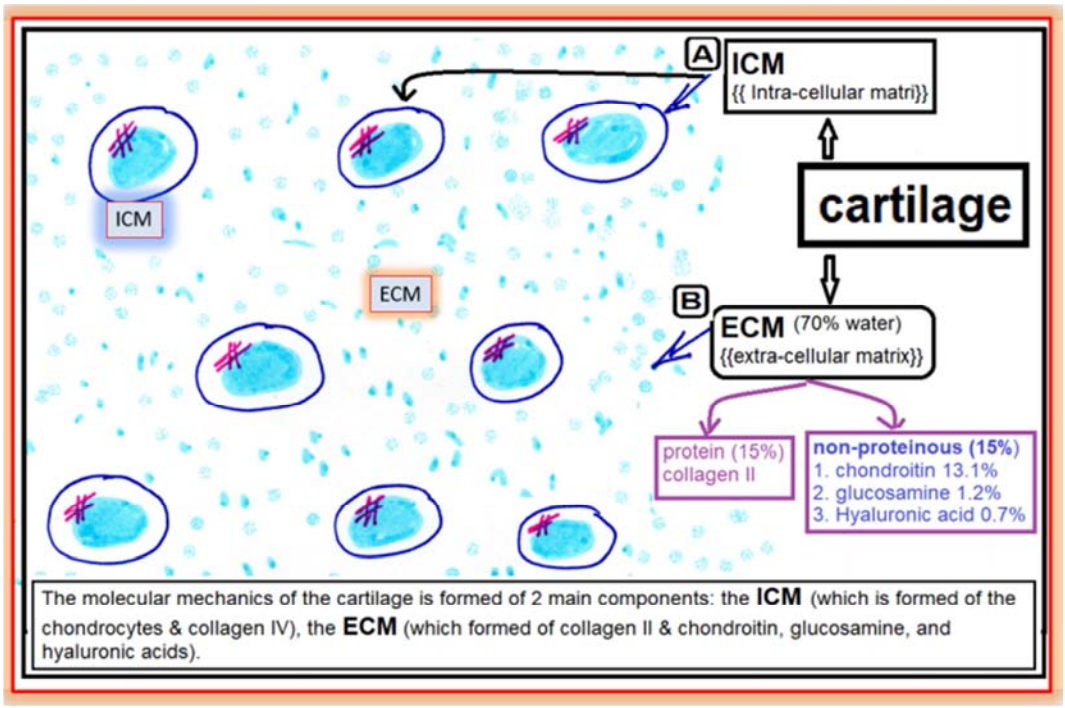

Figure 4. *The cartilage is formed mainly of the extra-cellular matrix (ECM) which has collagen II. The minor amount of the cartilage is the pericellular matrix (PCM) which contains the chondrocyte in a lacuna and contains collagen type IV.*

2.3. Non-proteinous Solid Materials of the Cartilage

2.3.1. Chondroitin Sulfates

It is formed of hundreds or more of the tiny glucosamine units connected together as one long unit. They constitute more than 13% of the normal cartilage mass. Thus, they are the commonest *non-protein structure* of the cartilage. They must be sulfated. Therefore, they are *highly negatively charged* structures. Their main function is to shift to the positively charged part of collagen on loading. Then, it returns to its original site on either side of collagen in an unloading state. This allows the synovial fluid to move in an opposite direction to chondroitin sulfate. Thus, currents of fluid are created inside the substance of the cartilage. Thus, they help in the nutrition of the cartilage [9].

2.3.2. The Glucosamine

Its percentage is slightly more than 1% of the cartilage substance. It may be sulfated or not sulfated. Its function is to act as a semi-valve-like structure. It hinders an easy escape of *all* the synovial fluid from cartilage. Thus, under mechanical loading, some fluid escapes, and some is prevented. The fluid is not allowed to escape by the effect of glucosamine creates tension inside the cartilage. This high pressure acts as a shock-absorbing mechanism and prevents the bone from crushing the terminal cartilage. In other words, the cartilage becomes cushion-like but with tension inside to be able to tolerate the mechanical loading without failure [10].

2.3.3. Hyaluronic Acids

It is of a carbohydrate nature. It is formed of glucosamine plus glucuronic acid. It is the only component of the cartilage that is *never being* sulfated. Each molecule of hyaluronic acid (HA) can catch up to *3000* molecules of water. Therefore, it has a great affinity to water. Its function is the *lubrication* of the 2 surfaces of the cartilage. This means reducing the friction to be minimum. Thus, it also helps in the prevention of osteoarthritis [11].

2.4. Chondrocytes

They are the cells of the cartilage. Their number gradually decreases with age. They are present in lacunae called the pericellular matrix (PCM). The chondrocytes constitute less than 2% of the mass of the cartilage. Its main function is the manufacture of cartilage components. This helps in the maintenance of the cartilage substance in normal conditions. At the time of injury, the chondrocytes have a limited capacity to repair the damage. The above patents exploited this phenomenon by enhancing the reparative power of the chondrocytes. This would be discussed later about mitochondrial & stem cell therapy.

From the above, all the components of the cartilage including the fluid, the collagen, non-collagenous materials, and the chondrocytes are integrated to maintain the cartilage doing its proper function of moving the joint without pain [12].

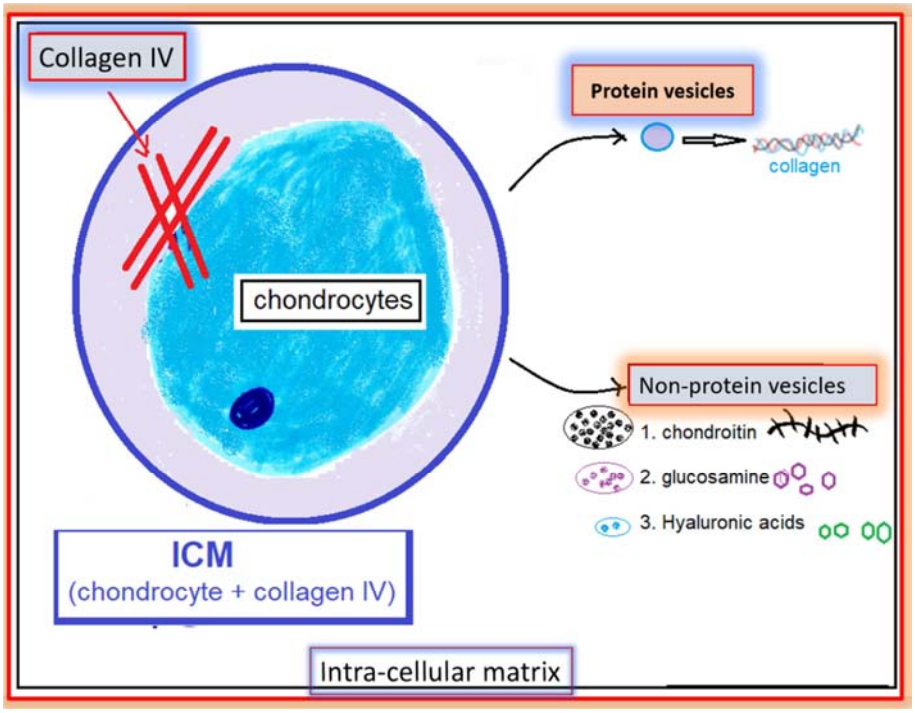

Figure 5. *Pericellular matrix (PCM) contains the chondrocyte & collagen IV inside the Lacuna. The chondrocyte is responsible if stimulated to manufacture all the components of the cartilage materials. It manufactures collagen & noncollagenous materials including (chondroitin, glucosamine, and hyaluronic acids).*

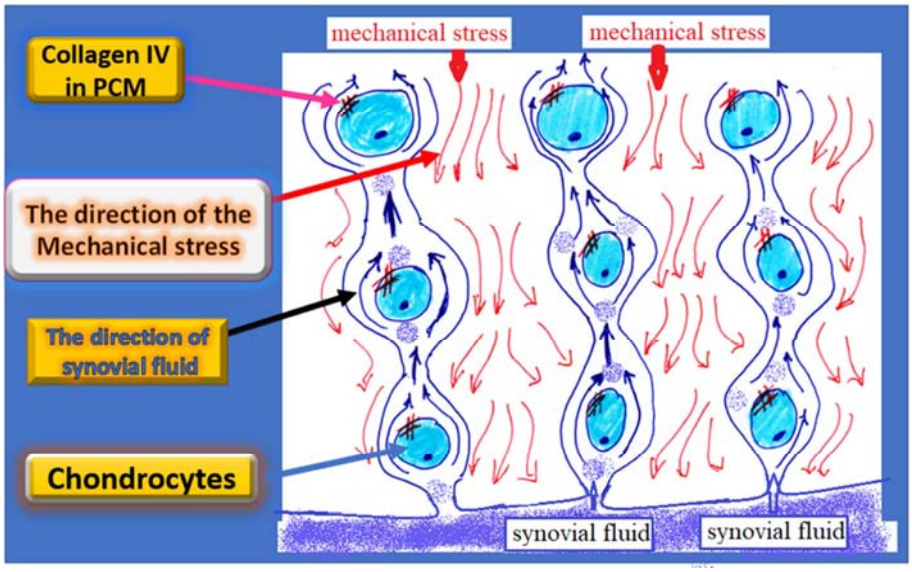

Figure 6. *The direction of the passage of synovial fluid is opposite to the direction of externally applied mechanical stress.*

3. The Degrees of Osteoarthritis & Their Lines of the Treatment

Osteoarthritis (OA) has generally 4 degrees. The 1st is very mild and the 4th is the full destruction of the cartilage. The 2nd and the 3rd are intermediate stages.

3.1. The 1st Degree OA

The joint is fully normal and the arthritis attacks intermittently occur. The attack is exacerbated by more than normal loading on the affected joint. The joint recovers by rest and/or analgesics and the patient think that he is fully normal. If the underlying causes are not corrected, the condition would proceed to the 2nd degree OA. X-ray shows a very mild manifestation like osteophytosis and/or slight narrowing of the joint space [13].

3.2. The 2nd Degree OA

The attacks occur more frequently. The attacks may be exacerbated by normal movement. For the pain to subside, it would take a longer time than the 1st degree OA. X-ray shows more damage to the joint like more osteophytes and more

narrowing of the joint space than that of stage I. The chance for a complete cure is not much but the chance to proceed to a 3td degree is higher [14].

3.3. The 3rd Degree

The pain is almost always present but may subside by the analgesics. Therefore, the patient becomes addicted to analgesics. The normal movement could exacerbate a severe attack. The chance of complete cure is very limited and most of the patients proceed to stage 4. X-ray shows narrowing of joint space, marked osteophytosis, and *sclerosis of the bone under narrowed area. The mechanical axis of the joint may be disturbed [15]*.

3.4. The 4th Degree

There is full destruction of the cartilage of the joint. The pain is always present. The range of movement is greatly limited. The pain is very marked and analgesics are not always enough. X-ray shows complete obliteration of the joint space with marked osteophytosis. The underlying bone shows marked sclerosis due to disturbance of the mechanical stress of the joint. The mechanical axis of the joint is disturbed in most cases. The only hope is surgical intervention [16].

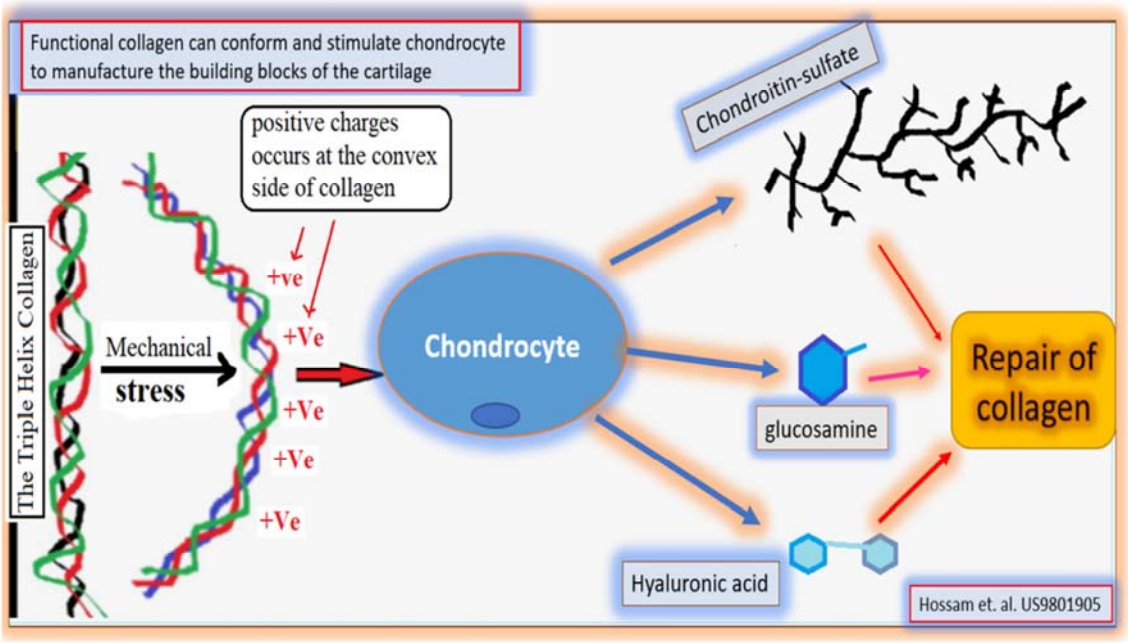

Figure 7. *The functional collagen conforms under mechanical stress and stimulates the chondrocyte. Activated chondrocytes can build all the components of the cartilage materials including (chondroitin, glucosamine, and hyaluronic acids). Thus, the cartilage could be repaired.*

4. The Lines of the Treatment of Arthritic Joints

The treatment of the condition is usually *tailored* to the degree of the damage of the cartilage despite some individual specificity.

4.1. The Medical Treatment

This type of treatment is very efficient in the 1st and to a lesser extent the 2nd degree of OA. It might *not* be sufficient in the 3rd and for sure the 4th degree of OA. It is simply giving the patients analgesic and anti-inflammatory medications. These medications address the pain or more accurately *masking* the pain. The patient can perform his routine life without pain till the affected joint heals. This method is *not* without complications. The commonest medications are non-steroidal anti-inflammatory drugs (NSAIDs). These medications have many side effects, especially on the stomach, kidney, and liver. The most hazardous effects of these medications are on the joints themselves. The complications on the joints include-:

1. They give the patient a *false sense of security*. The patient feels as if the joint is healed and not painful anymore. The patient can do his/her routine life and this may destroy the joint. Resting the joint is one of the most important parts of the healing process.
2. They also block certain types of prostaglandin (PGs) that are necessary for the healing process of the joint.

To sum up the medical treatment with NSAIDs must be used with a very limited period and telling the patient this is not the ideal line of treatment. It is just a temporary before the main line of treatment starts [17].

4.2. The Surgical Treatment

It is usually elective surgery and not urgent. It is needed most in the 4th stage of OA and to a lesser extent in the 3rd stage. For sure, the 1st and 2nd stages of OA should be given a *chance* of medical treatment. The complications of this type of treatment are the complication of the surgery *itself* like the complications of anesthesia, wound infection, loosening of the

prosthesis, damage of surrounding vital structures like nerve, blood vessel, muscle, and so on [18].

4.3. Supplemental Medications

This line of treatment is excellent in the 1st and 2nd stages of OA. This depends on the molecular mechanic of the cartilage. Thus. it is more physiological in repairing the cartilage. It is not analgesic and has no side effects from masking the pain or prevention of prostaglandin formation (PGs). This method depends on supplying the patient with the non-proteinous components of the cartilage.

4.3.1. Chondroitin Sulfate Supplementation

This forms more than 13% of the cartilage mass. Therefore, it is most important. Moreover, because it has negative charges, they move to the positive side of collagen on mechanical loading. This enforces the fluids to move in the opposite direction.

It creates currents of synovial fluids inside the substance of the cartilage mass. Its only drawback is its very large size that hinders its absorption. Its absorption rate is about 15% [19].

4.3.2. Glucosamine

Its size is very small regarding chondroitin sulfates. Therefore, its absorption is very excellent. Its only drawback is its percentage inside the cartilage is very limited. It is just more than 1% of the cartilage mass. Thus, its efficacy in healing is not marked. This means the early few doses may have some improvement and tolerance would occur after that. The detail would be in the discussion [20].

4.3.3. Hyaluronic Acids

It is carbohydrates in nature. It might be digested in the stomach. Therefore, it is better to be given by injection into the joint. Again, its percentage in the joint is very limited i.e. less than 1% of the cartilage mass. The early few doses may show some improvement then tolerance would occur [21]. From the above, there would be no ideal line of treatment that could act on OA from its root.

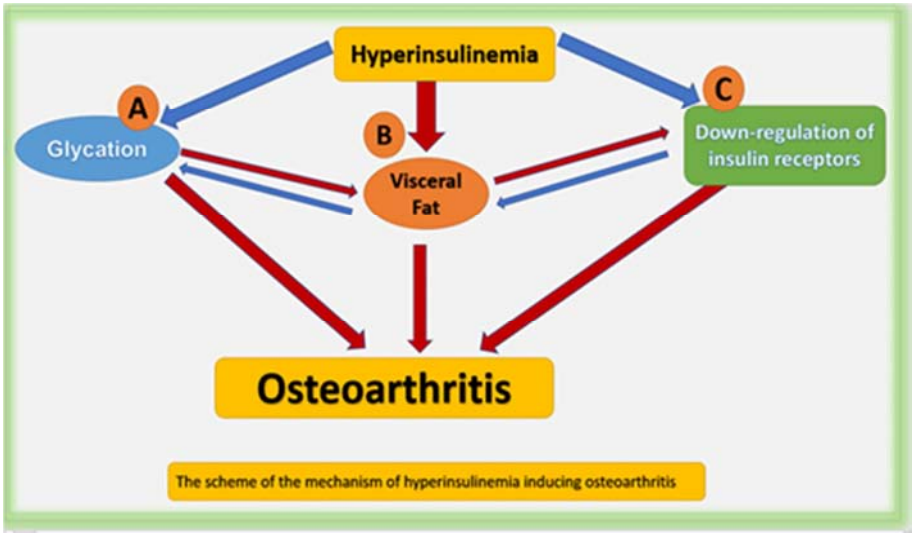

Figure 8. *The 3 limbs of obesity (visceral fat, hyperinsulinemia, and glycation) are the root causes of osteoarthritis. The 3 limbs of obesity come with each other and exaggerate each other. The treatment must include the root causes to be ideal.*

5. Obesity as a Predisposing Factor for Osteoarthritis

Obesity is defined as a body mass index (BMI) is more than 30. Normal weight is from *18-25*. From *25-29.9* is considered overweight. More than 30, the patient is defined as obese. It is strongly believed that the obese person has a higher incidence of joint damage (*osteoarthritis*) due to the higher wear and tear process. Some granted US patents *(US9433798), (US9452297), (US9757583)* looked at obesity from another view. They blamed obesity on *3 main points* and not physical weight that damages the joint by excessive use. These patents consider the obesity of having 3 main limbs that could attack the joints. These limbs are Visceral fat, Hyperinsulinemia, and the Glycation process. These 3 limbs are not only interconnected but also they exaggerate each other. Glycation & Hyperinsulinemia have a direct attack on the cartilage. the visceral fat *indirectly* attacks the cartilage far away through cytotoxic cytokines mainly through the Tumour Necrosis factor (TNFs) pathway (figure 10).

5.1. Glycation & OA

Obesity is always associated with excess glucose inside the tissues. This process is aggravated by *sulfur deficiency*. It is well known that sulfur *non-enzymatically* attaches to collagen. Thus, in the case of sulfur deficiency, glucose could occupy the same site of sulfur on the collagen leading to glycation [7]. Therefore, the definition of glycation is the non-enzymatically attachment of glucose to the *collagen* of the cartilage. This causes the collagen to be dysfunctional. This means that collagen can not do its proper job in the

issuance of synovial current inside the cartilage. As said earlier, the synovial current is responsible for the nutrition of the chondrocytes. Thus, the cartilage can not be maintained to go in line with the normal wear and tear process. Thus, the cartilage starts to lose some of its material gradually. In the long run, osteoarthritis develops [22]. The glycation also occurs in the *collagen IV* that is present in the peri-cellular matrix (PCM). However, this collagen IV is of a very small amount compared to that of *collagen II* of the extra-cellular matrix (ECM), it has a fundamental function in the activation of the chondrocytes to secret all the building blocks of the cartilage (figure 5). Therefore, the glycation of collagen IV results in less production of all the components of the cartilage by chondrocyte. The normal shedding of the cartilage material is not compensated anymore. This explains the effect of glycation on both collagen II of (*ECM*) & collagen IV of (*PCM*) the cartilage.

5.2. Hyperinsulinemia & OA

Obesity is almost always associated with hyperinsulinemia. Moreover, obesity without the occurrence of *DM II* is explained by hyperinsulinemia. This means there is excess sugar in the body but the pancrease *compensates* and succeeds in pushing all excess sugar into the tissue. Thus, hyperinsulinemia is far more common than DMII. Roughly, in the US, *Hyperinsulinemia* is 3 times more common than DM II. Hyperinsulinemia has a *negative feedback* mechanism in lowering insulin receptors on the surface of chondrocytes (figure 9). In the early stage, this mechanism acts as a protective one. It defends the chondrocytes from the excess sugar in the synovial fluid. Later, the chondrocytes start to suffer from starvation. Some chondrocytes start to show degenerative changes or even to die. The chondrocytes are the main producers of cartilage materials. Therefore, their sickness or even death causes the cartilage raw materials to start to become less and less. The normal maintenance of the cartilage is stopped. The normal shedding of the surface of the cartilage is not replaced. The OA is borne at the end of this vicious cycle [23].

5.3. Visceral Fat & OA

As said earlier, obesity means that the BMI is more than 30. The higher the degree of obesity, the more the body fat. It must be noted that not all fat is equal. The subcutaneous fat is inert and has no metabolic problem. This is the fat that could be removed surgically via liposuction. On the other hand, visceral fat is the fat inside the viscera like the liver, pancrease, kidney, the omentum, intestinal wall, and even the pericardium. This type of fat is metabolically active. It is the basis of all metabolic syndrome like DM II, Alzheimer's, coronary artery diseases, osteoporosis, tendinitis, and osteoarthritis which is the subject of this paper. The worst criterion of this type of fat is that it is not accessible to surgery. The only solution for this type of fat is a complete cut of carbohydrates & prolonged fasting to allow the body to use this fat as a source of energy. The main problem of this visceral fat is the production of an excessive amount of inflammatory products namely tumor necrosis factors (TNFs) and others (figure 10). These initiate a chronic subclinical inflammation far away from the original site of the visceral fat.

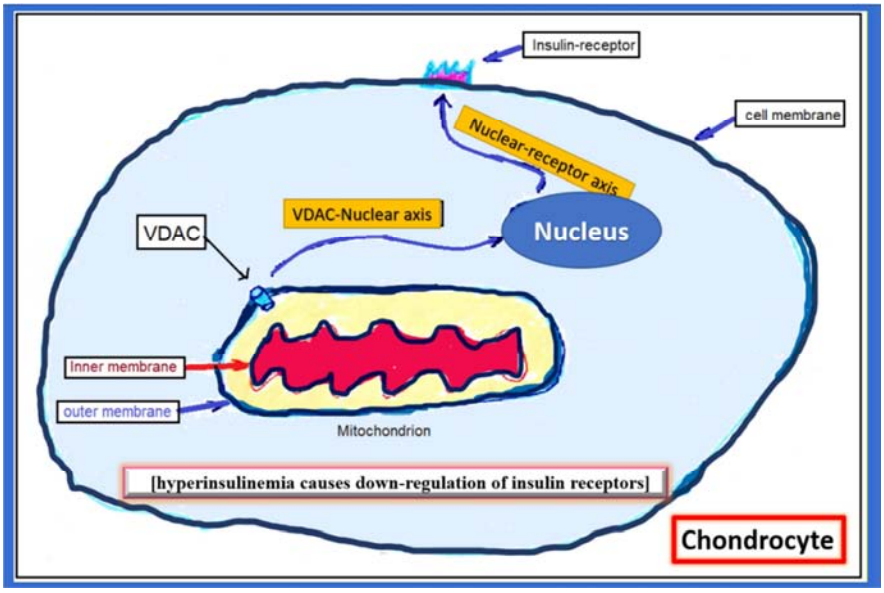

Figure 9. *Hyperinsulinemia causes down-regulation of insulin receptors in the chondrocytes. The chondrocyte becomes sick and even suffer from starvation. This is accomplished via retrograde VDAC-Nuclear axis.*

The disease process differs according to the affected site. For example, in the case of the brain, Alzheimer's would occur, in the case of bone, osteoporosis would occur. The example of this paper is the affection of cartilage where chronic inflammation occurs in the synovial membrane of the joints. A prolonged low-grade (sub-clinical) chronic inflammation of the cartilage leads to scaring and its damage. In the long run, the cartilage becomes defective and eroded and osteoarthritis develops [24].

6. The Treatment OA at the Root Level

This new modality of the method of the treatment needs to fulfill the following criteria:

1. Safe
2. Effective
3. More physiological
4. With no side effects
5. Accessible, affordable, easy to be conducted

The criteria above are considered ideal. According to the above-mentioned patents, this could be achieved by the concentration on stem cell therapy, mitochondrial medicine, and the recovery of glycated collagen.

6.1. The Role of Stem Cells Therapy in OA

The stem cells are dormant and not active. On their activation, they could proceed to form new types of cells that could repair the damaged tissues. The newly formed tissue would be very similar to the original one. There are many types of stem cells the most famous ones are the adult and the juvenile ones. The adult stem cells could repair only a certain type of tissue. For example, stem cells of the heart can manufacture only heart cells, the stem cells of the brain can manufacture only neurons, and so on. On the other hand, juvenile stem cells could repair any tissue. This means that on their activation, they circulate in the blood and patrol the tissues, and are implanted into the damaged area and start the repair process. Therefore, the repair of the damaged cartilage can be done better with juvenile stem cells. These cells are not present everywhere and they are also reduced in number in the elderly. They are most abundant in the bone marrow and deep in association with visceral fat [25].

The stem cells could be activated by the pulsed electromagnetic field (PEMF), infrared laser therapy, or the best by the hybrid system which is the top. The hybrid system is the combination of both the infra-red laser and pulsed electromagnetic field in one device. These new patents (US 9,452,297) & (US 9,757,583) succeeded to make the above 2 forces of energy together as one unit. This device is developed at Ottawa university Canada [26]. The detailed stem cells activation is the discussion chapter.

6.2. The Role of Mitochondrial Medicine in OA

The mitochondria are the powerhouse of the cells. They are responsible for energy production the via complete burning of glucose to carbon dioxide and water. This mechanism of energy is called *oxidative phosphorylation* or the *Krebs cycle*. All the recent studies show that aging, in general, is *not* more than dysfunction of mitochondria in the elderly. This includes Alzheimer's, coronary artery diseases, osteoporosis, osteoarthritis which is the subject of this paper. The mitochondrial damage occurs mainly in the inner membrane which is exposed to enzymes responsible for the burning process. The metabolites of the burning process are called free radicals which are not stable and have a great affinity to get an extra electron from other tissue causing their damage. The most successful method of the recovery of the mitochondria is via strong *anti-oxidants*. Thus, the methods of the treatment of osteoarthritis at all levels including the root must contain strong anti-oxidants. These would help in the recovery of the mitochondria and allow them to do their proper job of energy production again [27]. The details of mitochondrial medicine are in the discussion section.

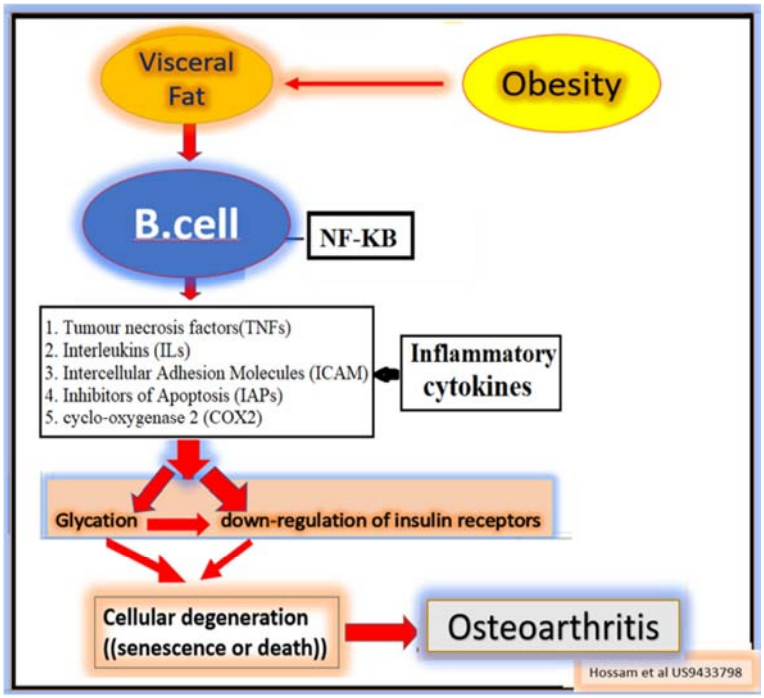

Figure 10. *The obesity has 3 limbs that causes osteoarthritis which include (viceral fat, hyperinsulinemia, and glycation). These limbs interact with each other and exaggerate each others.*

6.3. The Recovery of the Glycated Collagen

As known earlier that collagen is the prime mover of repair of the damaged cartilage. The functional collagen conforms under mechanical stress and stimulates the chondrocytes to secret the new building blocks of the cartilage. If the collagen is glycated i.e dysfunctional, it can not do this important function. The normal wear and tear of the cartilage are not compensated by the new building block. Thus, every effort is exerted to recover the glycated collagen to be functional again. This can be done via anti-oxidants, certain amino acids like lysine, and organic sulfur-like MSM.

7. Discussion

All the different methods of the treatment of OA are discussed here with the *pros and cons* for each one. As shown earlier OA is not a *pure joint disease*. Its root may be far away in visceral fat, obesity, excess carbohydrate intake, sedentary life, lack of exercise, and others. Therefore, for the treatment to be *perfect*, attention must be paid to the root causes of this disease even before the joint can be affected. This new method of thinking has the advantage that the other *non-affected joints would be saved* and also it prevents the *recurrence* of the OA in the already treated joint. Sometimes, the disease process may be aborted at its early stages even before the start of the pain of the joint. Very special attention must be given to the *3 limbs* of obesity which are *visceral fat, hyperinsulinemia, and the glycation* process. The new eras of treatment of OA through stem cells, mitochondrial medicine, and the deglycation of the collagen would also be discussed in detail.

7.1. The Traditional Method of Treatment of OA

These methods of treatment look at OA as only a disease of the affected joint. These methods ignored the root causes of the disease. they also *do not* consider the new methods of treatment like mitochondrial, stem cell therapy, or deglycation of the collagen.

7.1.1. Traditional Medical Therapy

These methods are effective only in the 1st & 2nd stage of OA. It may fail in the 3rd stage of OA but it has no role in the 4th stage. These methods of treatment could alleviate the pain of arthritis at the expense of blocking *the natural healing power* of the body. The healing of the inflammatory part of arthritis could be repaired by certain cytokines called prostaglandins (PG). Thus, the long run of medical treatment may be associated with accelerated damage of the joint. Therefore, the patient who is addicted to NSAID analgesics is associated with accelerated damage of the joint. The worst drawback of analgesics is that they have many side effects which include gastritis, hepatorenal toxicity, gastrointestinal upset, and others. They are also contraindicated in pregnant patients especially in the 1st trimester, in end-stage renal failure, and end-stage hepatic failure [28].

7.1.2. The Traditional Surgical Treatment

This is needed for the 3rd & 4th stages of OA. The line of treatment is surgical replacement of the affected joint. The commonest joint to be replaced are the knees followed by the hips. If the surgery is done perfectly, the patient could return to his routine life. The complications are usually limited to the surgical intervention as infection, tissue damage like artery, nerve, important muscle. Rare complications also could occur as shock or hypotension, fat or blood embolism. The main drawback of this procedure is that the artificial joint has a certain lifespan and may need revision after 15-20 years of utilization. Therefore, They must not be done in young patients especially if they are active. They would need to change their joint after a few years. the worst complication *ever* for joint replacement is an infection in the prosthesis of the joint with or without loosening. The only solution is the surgical removal of the prosthesis with surgical adding of long-term anti-biotics. Multiple surgeries for the removal of the necrotic tissue may be needed. A complete cure of the infection is very rare. Therefore, a new joint replacement *can NOT* be done for a very long time or sometimes forever. It would be a catastrophe for the patient that he/she might not walk again. Although this complication is very rare, it must be taken into a consideration and explained fully for the patient that it might occur but it is rare [29].

7.1.3. The Traditional Supplements

It is the supplementation of non-collagenous components of the cartilage. Namely, Chondroitin, Glucosamine, and Hyaluronic acids. This type of treatment is generally considered safe (*GCS*) by FDA. There are no major side effects as that of the other above traditional methods of treatment. There are some drawbacks to this method that differ according to the type of supplement.

Chondroitin-sulfate is the commonest non-collagenous solid material of the cartilage. It is about 13% of the mass of the cartilage. It is very *negatively charged* due to its attachment to *sulfate* molecules. Its main function is to coordinate with collagen to create currents of synovial fluids inside the cartilage substance under mechanical stress. Thus, It helps in the nutrition of the cartilage. It has 2 main drawbacks, the 1st one is its function depends on the vitality of the collagen. This means that *dysfunctional collagen* would not allow the chondroitin to do its proper function in the issuance of currents in the synovial fluids. Thus, the chondrocytes would not get their nutrition and can not manufacture the cartilage components. The 2nd drawback is its very large size. Thus, its absorption is very limited which is about 15% only [30].

Glucosamine-sulfate may be sulfated or not. Its main job is to act as a Hemi valve-like structure. It *hinders the full* escape of the synovial fluid. This simply means some synovial fluid is allowed to escape but the majority is retained inside the cartilage substance. Thus, it allows the increase in *tension* inside cartilage on loading. Simply, its function in the joint acts as a cushion to protect the cartilage from the vigorous effect of nearby bone. Thus, it prevents the bone from crashing

the underlying cartilage. The only drawback is its percentage is very small in the cartilage slightly more than 1%. It also needs the collagen to be functional for the glucosamine to properly work. Its small percentage causes it to fully saturate the cartilage with the early doses. The patient may not show any improvement with later supplementation. Therefore, its effect is good in the early few doses only but later tolerance would occur. This is because the cartilage becomes saturated [31].

Hyaluronic acid is a carbohydrate in nature but acts as a lubricant. This is because each particle can catch *3000 molecules* of water. Thus, it is highly hydrophilic (loving water). It helps the cartilage to retain its water contents. As said earlier, the synovial fluid forms 70% of the cartilage mass. It acts as a lubricant for the cartilage to move upon each other without friction. Therefore, hyaluronic acid is very essential for the cartilage. Its drawback is its cartilage content is less than 1% of the cartilage mass. Thus, the 1st few supplementations may give a result but later supplementations may not be effective as the cartilage is fully saturated by its small percentage of hyaluronic acid in the joint which is called tolerance [32].

7.2. Obesity as a Predisposing Factor for OA

As said earlier, obesity has 3 main limbs namely visceral fat, hyperinsulinemia, and glycation. These 3 limbs are interacting with each other to aggravate the OA. This explains the idea that OA is *not* due to the physical wear and tear of the cartilage. Many athletes are heavily weighted but do not complain of arthritis. This is because these people have zero visceral fat.

Visceral fat is the starting point of the damage of the cartilage (OA). This type of fat is metabolically active because it releases certain inflammatory products namely the (*TNFs*). Visceral fat does not come alone. It must be associated with Hyperinsulinemia & the glycation process. This is because the person who eats a lot of carbohydrates always has visceral fat. After all, the liver has a limited capacity to store fat. It has to export this fat to surrounding tissues namely the pancrease, omentum, intestine, kidney, and pericardium. This is the mechanism of visceral fat formation. It must be noted that subcutaneous fat is not metabolically active and does not secret any metabolites. This type of fat is benign and it is the only type accessible for surgery via liposuction [33].

hyperinsulinemia is always associated with visceral fat. This is because the origin of both of them is one thing which is eating a lot of carbohydrates. Hyperinsulinemia is blamed to be the origin of all metabolically active syndrome (X) which are DM II, Coronary artery diseases, Alzheimer's, osteoporosis, tendinitis, and osteoarthritis which is the subject of this paper. Hyperinsulinemia simply means that the sugar intake is much more than needed. The pancrease secrets excess insulin to compensate for the high blood sugar. Thus, the sugar may be within the normal level in blood but it becomes in an excess amount inside the tissues. one statistic in the US suggested that hyperinsulinemia is 3 times more common than DM II. This means that DM II is 11% of about 31 million while hyperinsulinemia is about 36% of about 86 million [34].

Glycation is the 3rd limb of obesity. It means the non-enzymatic attachment of glucose to collagen and other proteins. This results in dysfunctional proteins that can not do their proper jobs. It is the translation of hyperinsulinemia that is associated with visceral fat. All the 3 limbs have a common origin which is eating a lot of carbohydrates especially refined sugar and grains. As the collagen is the prime mover for stimulation of the chondrocytes to manufacture the cartilage components, its glycation causes it to be dysfunctional and could not stimulate the chondrocytes. This means a decrease in the cartilage materials with subsequent no repair of normally damaged cartilage materials. finally, OA occurs in the end [35].

7.3. The New Eras for the Treatment of OA

The mitochondrial and stem cell therapies are new modalities for the treatment of OA. They are characterized by being with almost no side effects.

7.3.1. Infra-red Laser Therapy

It is of increasing popularity because it is very safe, effective, and has almost no side effects if properly used. There are 2 main types of infrared laser: near infra-red laser (*NIR*) and far infra-red laser (*FIR*). NIR is more commonly used because it has more penetration capacity of 3-5 cm depth. FIR may be more effective but less commonly used because of its limited capacity of penetration to the tissue. The difference is mainly in the wavelength i.e. NIR laser is of a range of (*700-2500nm)* while the FIR laser is between (*4000 nm-1.000.000 nm*). Both are more or less similar except as said above in the wavelength and the capacity of tissue penetration. FIR has superiority in the stimulation of the (*RUNX2*) gene. This was an earth-breaking discovery in the treatment of osteoporosis. later, RUNX2 has great benefits on osteoarthritis and many other diseases in the elderly. infra-red therapy, in general, has the following benefits in the treatment of OA:

1. They increase the blood supply to the exposed area
2. Stimulation of the stem cells
3. They stimulate more collagen formation
4. They stimulate the mitochondria to produce more ATPs necessary for the repair of the damaged tissues including the cartilage.
5. They open fat channels for the fat to be utilized as a source of energy instead of glucose.

The increased blood supply to the exposed area has major healing power. The improved circulation brings more oxygen and nutrition to the ischemic or damaged tissues. Also, there is an increase in the venous return causes the washing effect of the waste products, carbon dioxide, lactic acid, and all other metabolites that cause the pain. Thus, the pain will dramatically subside and the joint would be repaired. The stimulation of the stem cells causes the repair of the damaged tissues. By far, the most important effect of infrared laser is the stimulation of the mitochondria. The enhanced ATPs production improves the repair of the damaged cartilage [36].

7.3.2. PEMF Therapy

This is the abbreviation for *pulsed electromagnetic field therapy* which is a new modality of treatment of damaged tissue. This is very effective for the joints by exposing them to PEMF. Its mechanism of action is via enhancing the mitochondrial production of the ATPs. The surplus energy is used for the repair of the damaged tissues. It is known that OA is not more than the damaged tissue of the cartilage. Thus, the new method is very safe, effective, and non-invasive at the same time. The 1st to discover that is NASA's patent. Later, our patent came to bring the hybrid system discussed later [37].

7.3.3. The Hybrid System (US9,452,297)

This is by far is considered the top because it combines the benefits of *both infra-red laser* and the *PEMF*. It is not just a combination but is a *synchronization* between the 2 sources of energy. The linkage between the infrared laser & PEMF occurs at the hydrogen atoms of the fluid of the human body. As it is well-known that more than 60% of the human body is water, This new idea can be used in all human tissues. This granted US patent has a dual effect on the mitochondria, stem cells, and blood vessels. Thus, it is expected that the healing power would be much better than infrared laser alone or PEMF alone. It must be noted that the Hybrid system must have a magnetic field of a unipolar system. Therefore it is a unipolar pulsed electromagnetic field (UPEMF) to be able to arrange the hydrogen atoms. The critical point of the hybrid system is to consider the hydrogen atom as odd number atoms. This may update the theory of stimulated emission (figure 11) [38, 39, 42].

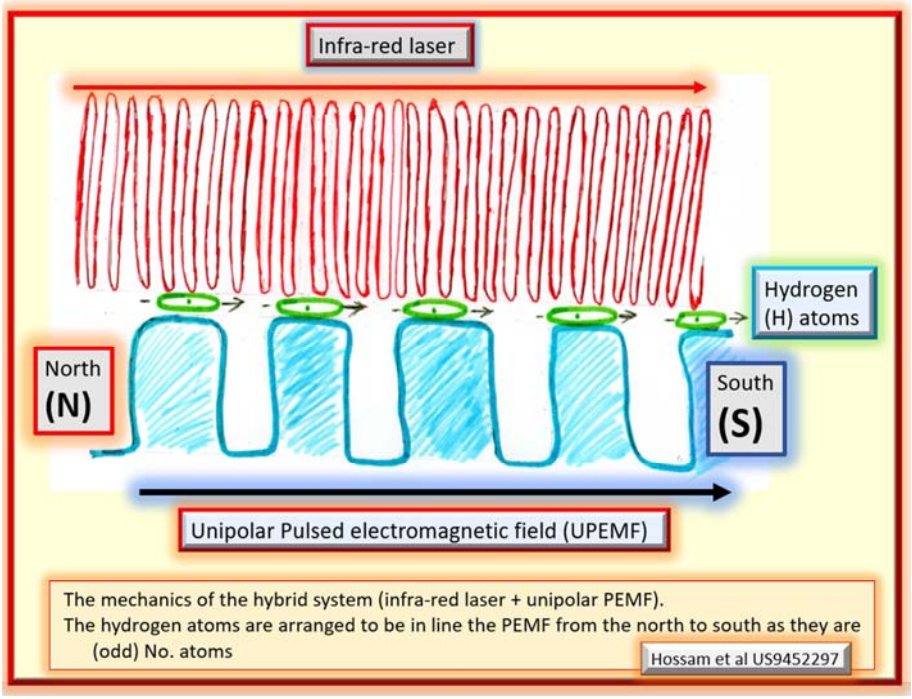

Figure 11. *The Hybrid system is a new granted US patent that succeeded to combined the infrared laser & PEMF via the hydrogen atom orienation.*

7.3.4. Non-traditional Supplements

Some supplements have great healing benefits of the articular cartilage other than those that we called earlier the traditional supplements. These include strong antioxidants, Taurine, MSM, and certain amino acids. Examples of one of these regimen include:

1. Anti-oxidants {alpha-lipoic acid (ALA) and/or N-acetyl cysteine (NAC)}
2. Taurine
3. MSM
4. Amino acids (Lysine and/or citrulline)
5. Mineral like Zinc
6. Vitamin (K2 and or vitamin D3)

The combination of 2 or more of the above components has a very great benefit of the joint. This regimen is created by the reversal of the exact process of OA. For example, *anti-oxidants* block the effect of (NF-kB) which is the main inflammatory product of the human body [40]. *Taurine* is considered the best to protect the mitochondria via its blocking effect of mitochondrial calcium uniport (MCU). This port allows calcium to enter the mitochondria and causes their damage. Thus, blocking this port is associated with cytoprotective [41]. *MSM* is the source of organic sulfur to protect the collagen from glycation and also it can stimulate (RUNX2) as said earlier. The selected amino acid as *Lysine* is very essential for the cross-linking of the collagen. *Citrulline* is a non-essential amino acid but it is very important for the production of nitric oxide (NO) which plays a major role in mitochondrial activation. Zinc is a metal that is deficient in tissue damage and is needed for the repair of the damaged tissue. Lastly, certain vitamin as K2 is responsible for the transfer of calcium from the cartilage to the bone. Recently discovered that the calcium precipitation inside the cartilage is

one of the initiations of cartilage damage. Thus, vitamin K2 via its activation of MGP (M Gla Protein) is capable of transferring calcium from the cartilage to the bone again.

8. Conclusion

Osteoarthritis (OA) is a catastrophic disease and is considered the most prevalent all over the world in the elderly. Its predisposing factors are multiple may be genetic, environmental, occupational, lifestyle, and others. Therefore, its exact causes are not well understood. The traditional treatment divided it into 4 stages and each stage would be treated accordingly. The traditional treatment looks at OA as only a joint disease. Thus, the cure must only be concentrated on the affected joint. This paper review multiple granted US patents that look at the OA as a generalized disease all over the body. Its root may be in the visceral fat and its end is in the joint. Thus, the treatment depends on the *excision of the disease from its root up to its summit in the joint.* Attention must be paid to the distance between the root (visceral fat) and the summit (OA joint). Paying special attention to the intervening area between the root and summit which is obesity. The traditional treatment usually has side effects and the cure may not be perfect. The methods of treatment at all levels; the root, the joint, and the intervening area of the joint damage are usually *more safe, effective, and without side effects*.

9. Future

OA may be considered DM type V. This is because OA could occur without the presence of hyperglycemia. This means a high degree of *hyperinsulinemia* that preferentially affects the chondrocytes more than the other cells of the body. Infrared laser injection therapy & a hybrid system of infrared laser & PEMF could be the non-invasive method that could repair the cartilage without the side effects of either the medical treatment or total joint replacement.

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