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Deciphering the Hidden Secrets between the Early Skin Wrinkling & the Metabolic (X) Syndrome with the Possible Reversal of This Process at the Molecular Level

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Abstract

The aging process is a group of degenerative changes that physiologically occur in most of the people in the elderly. This affects one or more of the human body systems. The treatment of diseases related to the aging process has a huge impact on the economy of all nations. Aging of the skin comes on the top and despite that, the results of the already present lines of treatment are not always satisfactory. This acts as a stimulus for us to dig deeper to discover the root causes of the premature aging of the skin. This was simply caused by the accumulation *of repeated minute damage* to the internal structure skin. In other words, if the degree of minute damage is more than the capacity of the skin to repair, the repeated micro-damage is presented in the long run as a skin wrinkling. Moreover, the skin acts as a *mirror* that reflects the internal structures of the human body. Thus, the more degenerative changes in the human body systems, the more the skin could become wrinkled. Our strategy to prevent or at least slow down the aging process of the skin depends on 2 main steps; the 1st is to reduce the micro-damage as can as possible, and the 2nd is to enhance the capacity of tissue regeneration to be able to reverse the already present damaged skin. As the 2 processes are synchronized with each other, this strategy would be considered the ideal for prevention of skin wrinkling especially premature ones. This not only reverses premature skin wrinkling but also protects it from future wrinklings. This review sharply pointed out the role of the *functional collagen* of the dermal layer of the skin in the prevention of skin wrinklings. Therefore, it would be the target to study how collagen works in the complex machinery of the dermal layer of the skin. This concept deeply believes that the recovery of dermal collagen has a much better effect than

simply ingesting collagen or receiving a topical collagen booster.

Keywords

Collagen, Skin Wrinkling, Glycation, Hyper-Insulinemia, Hidden Obesity, Visceral Fat, Inflammatory Cytokines

1. Introduction

The skin is the largest organ of the human body. It acts as a barrier between internal organs and the external environment [1]. Moreover, it has many other functions like the production of vitamin D from its cholesterol content *i.e.* 7dehydro-cholesterol on exposure to type B of ultraviolet rays [2]. Furthermore, it has an essential role in regulating the body temperature via the change in the vascularity of the skin [3]. One of the most important functions of the skin but it may not be given the perfect attention is that it reflects the integrity and function of the internal organs [4]. For example; jaundice may reflect liver and/or biliary tree dysfunction [5]. Pale skin may reflect anemia, and so on. Lastly, it is one of the most important organs for the beauty and youth of the human. This means that smooth healthy skin reflects a healthy body and subsequently healthy internal organs. On the other hand, thin and wrinkled skin may reflect the aging of the person which also may denote active degenerative changes in the internal organ(s). This is why pharmaceutical companies spend multi-billion dollars on research in the industry for skin regeneration. The most successful industry is the oral ingestion of collagen to induce smoothness of the skin [6]. The others use either oily or creamy ointments that are applied topically to the skin to induce its smoothness. As no one completely discovered the exact mechanism of the aging of the skin, most of the methods of treatment of the aging of the skin have some degree of imperfection [7]. Recently discovered that the effect of the glycation of the collagen of the dermal layer of the skin is the true hidden predisposing factor for skin aging and its wrinkling. This means that there is a hidden relation between the functional collagen of the dermis and the other components of the skin as will be discussed later. In this review, we studied collagen at the molecular level. There is a hypophysis that functional collagen could stimulate the nearby organ to manufacture new tissues. On the other hand, if the collagen is glycated *i.e.* to be dysfunctional. Subsequently, the collagen would not stimulate the nearby structures which end with the thinning of the skin and its wrinklings [8]. This, also, means that the glycation of *dermal collagen* is the predisposing factor for the preliminary skin wrinkling. Therefore, the deglycation process *i.e.* removal or at least the prevention of attachment of glucose to collagen would be the cornerstone in the prevention or at least reducing the wrinkling to a minimum. To sum up, the above point, for the dermal collagen to do its proper function in the prevention of skin wrinkling, it has to be functional *i.e.*

not glycated. This guides us to the next step which is the question about the factor(s) that may increase the glycation. By far, the most common causes of glycation are diabetes, prediabetes, obesity, and/or hyper-insulinemia [9]. Obesity may be not so accurate term because some obese patients may not develop glycation and wrinkling of the skin. The most accurate term is *hidden obesity* which is characterized by excess *visceral fat* with or without generalized obesity as will be explained later [10]. The layers of skin are coordinated with each other in a synergetic manner and the collagen would act as prime-mover in the integrity and functionality of the skin provided that it is functional. This will be explained in the next chapter.

2. The Structural Component of the Skin

2.1. The 3 Main Layers of the Skin Namely: The Epidermis, Dermis, and Hypodermis

It is well known that the skin is formed of 3 main components; *epidermis, dermis, and subcutaneous tissues as in* **Figure 1**. The study of the aging process of the skin at the molecular level shows that the dermis which is the middle layer is the blamed layer of skin wrinkling and its aging process as in (**Figure 1**). It forms about 85% of the skin thickness [11]. To be more accurate, the culprit of the aging process of the skin is the glycation of the collagen component of the skin. The dermis has a variable amount of collagen which may be 50% - 60% of the dermal structure. The percentage of collagen in the dermis is maximum in adolescents and middle age [12]. The reduction of collagen content in the dermal

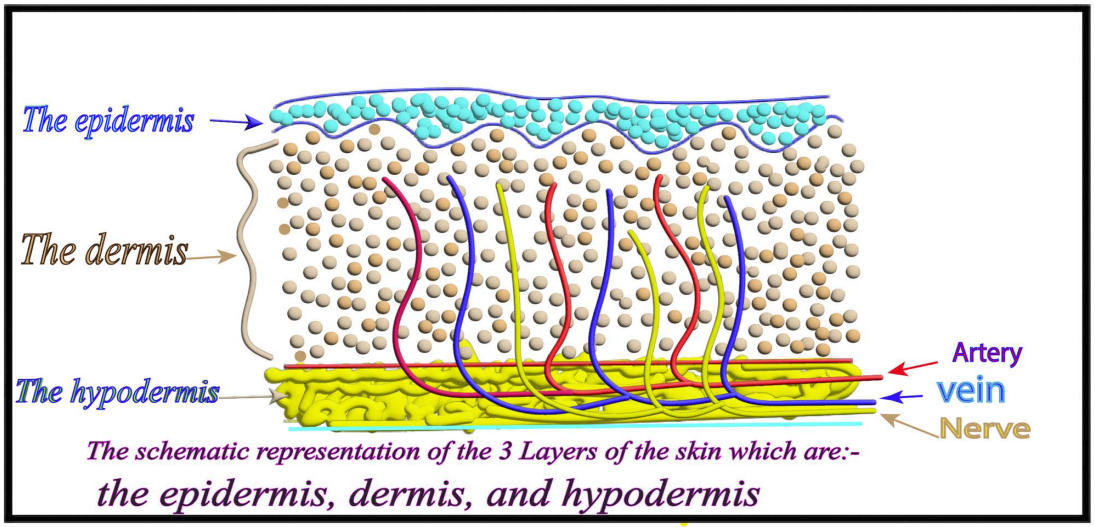

Figure 1. The 3 Layers of skin are the epidermis, dermis, and hypodermis. The epidermis is the thin most superficial layer of the skin and it is mainly formed of keratinocytes. The dermis is the main thickness of the skin more than 85% of the skin thickness. The collagen fibers are the main component of the dermis and they act as the internal machinery of the skin. There are other components of the dermis that include elastin fibers, Hyaluronic acids, fibroblasts, and mucopolysaccharide ground substances. The blood vessels, lymphatics, and nerves perforated the dermis from the underlying hypodermis. The hypodermis is the fatty deep layer of the skin and it has the main blood, lymph, and nerve supply of the skin.

layer of the skin becomes obvious after the age of 40 s with subsequent development of skin wrinkling. Recent studies show that the *quality* of the collagen may be more important than its quantity. In other words, the dermal collagen may not be reduced in its substantial amounts *i.e.* it may become within its normal percentage but the skin wrinkling would occur and this would be due to the loss of the active physiological function of the collagen [13]. *i.e.* the collagen becomes glycated or simply dysfunctional and cannot do its proper job in maintaining the manufacture of all the components of the dermis. Subsequently, dermal collagen cannot do its role in the rejuvenation of the skin and the prevention or at least the slowing down of its wrinkling. The healthy collagen is functional due to its piezo-electric properties which means that mechanical stress could be converted into an electrical gradient difference that can stimulate the fibroblast cells of the dermal layer to secret further collagen, elastin protein, hyaluronic acids that can regain the water contents of the skin to make it smoother and healthier. Thus, the functional non-glycated collagen fights against skin wrinkling [14]. On the other hand, if the collagen is glycated, it becomes dysfunctional and it becomes not reactive to the externally applied mechanical stress. This means that it loses its piezoelectric property. The collagen fails to create the electrical gradient difference on the application of mechanical stress during its conformation. Subsequently, the fibroblasts in the dermal layer lose the *drive* that can stimulate them and they finally fail to synthesize the components of the dermal layers of the skin namely; the collagen, the elastin, and the hyaluronic acids. The skin starts to lose its water contents, strength, and elasticity and becomes thin, weak, and wrinkled. This is the exact presentation of the aging process of the skin [15]. The epidermis of the skin is a very thin layer and is about 7% - 8% of the skin as in (**Figure 1**). It is formed mainly of keratinocytes. The hypodermis is also a very thin layer which is about 7% - 8% of the skin as in **Figure 1**. It is the deepest layer of the skin and is formed mainly of subcutaneous fat that covers underlying structures of the skin either muscle, tendons, ligament, cartilage or even bone. It has the blood, lymphatics, and nerve supply of the skin [16]. The middle layer is the *dermis* and as is said earlier, it forms the main bulk of the skin and is the most important biomechanical active structure of the skin. It must be noted that the dermis is penetrated by the blood supply, nerves, and lymphatics from the hypodermis as in **Figure 1**. On the other hand, the epidermis, the superficial layer, has no blood supply or lymphatics but it still has nerve endings. Therefore, the skin is sensitive. From the above each layer of the skin has a special role and function. The middle zone, the dermis, is the thickest zone and its collagen forms the main component. The collagen may reach up to 50% of the whole mass of the skin. Therefore, great attention must be paid to collagen and its dermal layer for their role in the integrity of the skin in a healthy state. Also, they have a critical role in the initiation of wrinkling in the aging process. Thus, collagen and the dermis will be discussed in full detail in the next chapter.

2.2. The Biomechanical Machinery of the (Dermis) in the Prevention of the Skin Wrinkling

The dermis forms 90% of the skin mass. This is the most important segment of the skin. Its components integrate with each other in a synergetic manner to prevent skin wrinkling provided that its collagen is functional and not glycated. The components of the dermis are formed of collagen, elastin, hyaluronic acid, water, fibroblasts, and other minor polysaccharides.

1) The collagen; is mainly formed of collagen type 1 (*collagen I*). The collagen is the main component of the dermal layer. It was thought that collagen is responsible *only* for the strengthening of the skin via its structural support because it is a tough and strong protein. Recent studies show that collagen has another fundamental role in the prevention of skin wrinkling provided that it is physiologically functional and not glycated. This could be achieved via the stimulation of fibroblasts. Subsequently, they could be able to manufacture all other components of the dermal layer provided that the collagen is functional and glycated.

2) The elastin; is the protein that from its name has a recoil or elastic property. This is a very important criterion of juvenile skin that on its stretch, it could recoil again. However, this protein has a very small percentage of the dermal layer but its presence even in a small amount causes the skin to appear young, stretchable, and without wrinkling. In the case of the aging process, the elastin fibers become scarcer. Moreover, it could be damaged by the free radicals that become prominent during the aging process. Therefore, the elastin will be reduced both in quality and quantity. The net result is that the skin loses its elasticity and stretchability which aggravates the skin wrinkling. The physiologically active collagen could stimulate the fibroblasts to secret more elastin fibers. This clearly denotes the relation between the collagen fibers and the elastin [17].

3) Hyaluronic acid: is a certain type of disaccharide that is formed from a combination of *glucoronic acid and glucosamine*. The skin contains a very small amount of hyaluronic acid in young and juvenile skin but with the aging of the skin, its amount gradually becomes less till it completely disappears [18]. The main function of hyaluronic acid is to catch the water content of the skin. Recent studies show that hyaluronic acid has a great affinity to water particles. This means that each molecule of hyaluronic acid could catch 3000 pieces of water. Thus, the skin appears smooth and shiny due to its water content. In the case of the aging process, the skin loses much of its hyaluronic acid with subsequent loss of its water contents. The skin appears thin, atrophic, and less shiny. Therefore, the processes of skin wrinkling become aggravated. The physiologically active collagen can stimulate the fibroblasts to secret hyaluronic acid. Thus, there is an indirect but very important relation between collagen activity and the percentage of hyaluronic acid. This also means that maintaining the collagen physiologically active and not glycated acts as the main mechanism in keeping hyaluronic acid in a good percentage in the skin and preventing or at least delaying

its wrinkling [19].

4) The fibroblasts; are the main cell components of the dermis. These cells are responsible for the secretion of all components of the dermis which include collagen, elastin, hyaluronic acid, and the other polysaccharides. The fibroblasts could not manufacture these dermal components except if they are stimulated by the functional collagen. If the collagen becomes glycated in the elderly, all the components are reduced in amount with subsequent exaggeration of the wrinkling of the skin. Furthermore, in the elderly, many of the fibroblast cells either die or become scarce which also allows the skin to become more wrinkled. The vitality of these cells depends on some vitamins like vitamins C, E, D, and A. This will be fully explained later in the reversal process of skin wrinkling. Moreover, these cells suffer greatly from the free radicals that become predominant in the elderly. Therefore, anti-oxidant therapy like N. acetly cysteine, alpha-lipoic acid, taurine, and others would enhance the vitality of these cells and save them from death. This would be taken into consideration in the protocol for the prevention of skin wrinkling later on. This also clearly denotes the complex and deep relation between the physiologically active collagen and the vitality and integrity of the fibroblasts [20]. From the above, the physiologically active collagen has a mutual role with elastin fibers, hyaluronic acid, and fibroblasts. Thus, the collagen fibers will be discussed in more detail at the structural, molecular, and functional levels in the next chapters.

3. The Molecular Structure of Dermal Collagen

The collagen of the skin is mainly concentrated in the dermal layer. It is mainly formed of collagen type 1 (collagen I) which is the most common type of collagen of the human body. *i.e.* more than 90% of the collagen in the human body is collagen I. The exact percentage of collagen in the dermal layer is variable according to age which means that collagen percentage is higher in young and middle age than the elderly population [21].

3.1. The Assembly of Collagen Molecules into Collagen Fiber

Collagen is the most common protein structure in the human body. In the case of the skin, it is concentrated in the dermal layer. Each collagen molecule is a *triple helix* which means that it is formed of 3 strands of proteins that folded upon each other (as in **Figure 2**). The folding type in all of the strands is alpha (*a*) type which is helical in shape as in **Figure 2**. Each molecule is *300 nm* in length and *1.5 nm* in diameter. The terminal part of the collagen molecule is not folded and is called (telopeptide). The remaining part of the collagen molecule is the folded part *i.e.* triple helix [22]. The function of collagen is done, as will be explained later, by the *folded part* of the collagen. For the collagen molecules to be assembled into a single collagen fiber, they are arranged in layers according to the thickness of the collagen fiber. Each 2 collagen molecules are separated from each other via a small distance called the *zero hole* which is about 40 nm in

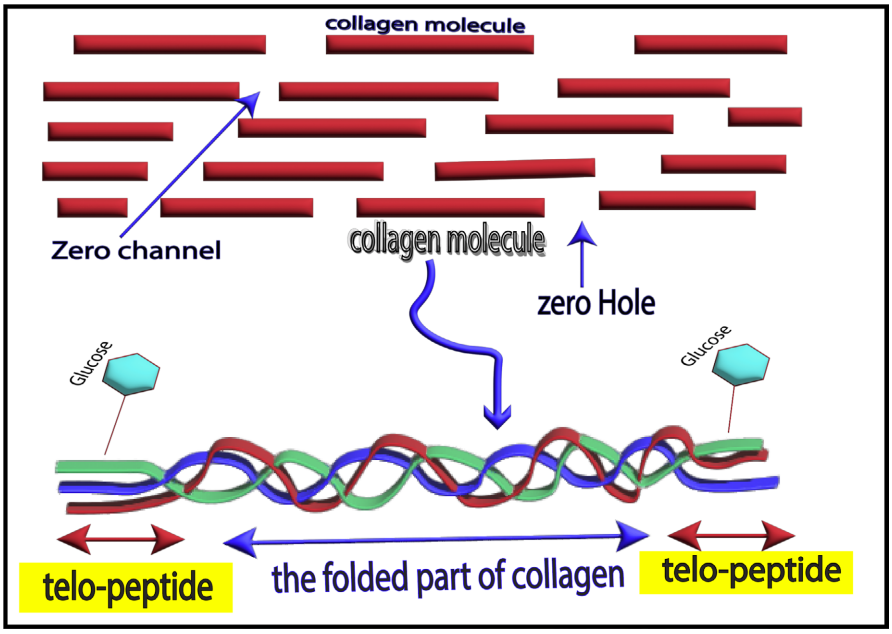

Figure 2. The upper part of the picture shows the *triple helix* of one collagen molecule. İt must be noted that the terminal part of collagen is not folded and it is called the telopeptide which is the site of glycation. The main part of collagen molecule is the folded part and it is the part that can perform the collagen function. The lower part of the picture shows the alignment of collagen molecules with each other to form one collagen fiber. The zero holes and zero channels are the important part of the mechanics of the collagen. As shown the zero channels are obliquely oriented which is the characteristic of the collagen fibers. This has an important role in the strengthening of the collagen fibers (27).

length. It must be noted that the collagen molecules are oriented in a special manner that makes them consistent with their proper function. However they are parallel to each other, in each layer, the collagen molecules precede slightly more than the layer below. This creates an *oblique orientation* of the zero channel between the layers of the collagen molecule [23]. This oblique orientation of the zero channels is very important in the strength and durability of collagen. This also would affect the function of the collagen because the non-folded part of the collagen is the area that is more susceptible to the glycation process. Furthermore, there is a cross-linking between each 2 the nearby collagen molecules. The cross-linking causes an extra strengthening of the collagen fibers and gives them durability in the resistance to the externally applied mechanical stress. The cross-linking occurs at the site (Y) if it is occupied by the amino acid lysine as in **Figure 3**. This will be explained later that it needs a very important enzyme called *lysyl oxidase enzyme* (LOX) which only acts at *lysine* amino acid as its name denotes. This enzyme also needs copper (Cu_{29}) as a cofactor as in **Figure 3**. We can benefit from the above idea in the supplementation of Lysine amino acid and copper as part of our strategy for the recovery of collagen [24]. The big picture of the strategy of all our lines of treatment of skin wrinkling will appear by the end of this review.

3.2. The Piezoelectric (PZE) Property of Collagen

The collagen was thought to have only a structural support to the surrounding medium. Recent studies show that collagen has a more fundamental function than just supporting structure which is piezoelectricity (PZE). This simply means that on the external application of mechanical stress on collagen fibers, they could initiate an electrical gradient difference (EGD) [25]. This means that collagen if it is functional and not glycated, acts as a functional structure that responds to the mechanical stress and transforms some of the mechanical energy into electrical energy. Subsequently, this newly generated electrical energy could modify the surrounding tissue via the stimulation of the fibroblasts which can secret all the components of the dermis namely; new collagen, hyaluronic acids, elastin, and the mucopolysaccharide ground substance. As said earlier, hyaluronic acid could absorb more water leading to the expansion of the dermis and giving the skin its smooth texture which also means the prevention of skin wrinkling. The elastin fibers are responsible for the elasticity of the skin. To sum up the above point, collagen does not have just a structural support function but it acts as a t*ransformer* that could help in remodeling the surrounding structure. This could be achieved only if the collagen is functional and not glycated [26].

3.3. The Orientation of the Amino Acids Sequence at the Cut-Section of Collagen

The above chapter discussed the longitudinal section of collagen. This chapter will study the transverse section of the collagen. Thus, a comprehensive picture would be collected about the collagen molecule. On taking a cut-section of each thread of the collagen molecule, we would find (*3 amino acids)* which are arranged in the form of (*Gly, X, Y*) as shown in (**Figure 3**). This sequence of amino acids symbolizes the following amino acids: the symbol (Gly) is *always* referred to the *glycine* amino acid, the symbol (X) is referred to either proline or hydroxyproline, while the symbol (Y) may be referred to either Lysine (60%), or Arginine 30%, or very rare to be histidine amino acid which is about 10% or very rarely any other amino acid [27]. This (Gly, X, Y) orientation is in one thread only but the collagen molecule is formed of a triple helix which is 3 threads folded upon each other in *an alpha (α) folded* manner. As in **Figure 5**, the site (Gly) glycine amino acids are oriented in the center of the triple helix because they are the smallest amino acids. The site (X) which is either Proline or hydroxy-proline is the only amino acid that has a ring that supports the structure. The site (Y) is the only polar site and it is always peripherally situated to be near to the water in the surrounding medium. This is because the amino acids that may occupy this (Y) site are always hydrophilic *i.e.* water-loving as in **Figure 5**.

3.4. The Piezoelectricity of the Collagen Occurs at the Hossam (Y) Site of Collagen

As said earlier, the (Y) site is the situation of mainly 3 amino acids namely;

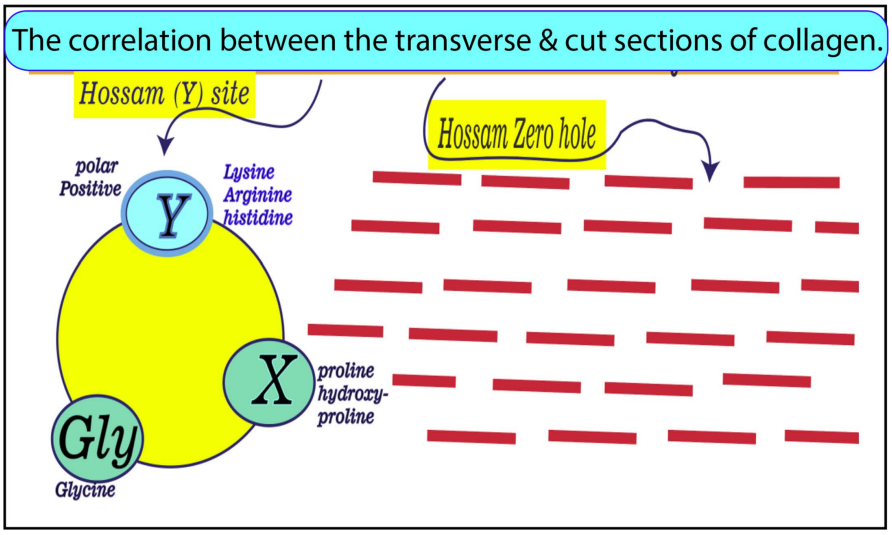

Figure 3. A cut-section of one collagen thread showing the arrangement of amino acids in the form of (Gly, X, Y). (Gly) is always glycine amino acid. (X) is either proline or hydroxy-proline. The site (Y) is either Lysine, and to a lesser extent Arginine, or very rare to be histidine. The site (Y) is the only site that is polar and positively charged (27).

Lysine, or to a lesser extent *arginine*, or to the least extent *histidine*. This site has special criteria that make it functionally different from the other 2 sites (Gly & X).

The criteria of the site (Y) include:-

- It is the only *polar* site (hydrophilic) *i.e.* loving water as the amino acids that may occupy this site are polar amino acids (lysine, Arginine, or histidine).
- This is the only site that is *positively charged* as the amino acids that may occupy this site are all positively charged.
- This is the site of the *cross-linking* of collagen via lysyl oxidase enzyme (LOX) between the 2 nearby (Y) sites as in **Figure 3**.

The process of the *cross-linking* of the collagen is extremely important in the stabilizing of the collagen. This is because it connects the 3 collagen threads into one collagen molecule *i.e.* the triple helix in **Figure 2**.

The cross-linking only occurs at the (Y) site and it needs a very important enzyme called lysyl oxidase enzyme *i.e.* LOX [28]. This enzyme needs copper (Cu_{29}) as a co-factor.

On the other hand, the other 2 sites namely *(Gly & X)* are:-

- *Non-polar* (cannot dissolve in water) because the amino acids that occupy them are non-polar. *i.e.* glycine for the site (Gly) and proline or hydroxyproline for the site (X) are non-polar.
- *Neutrally charged* because the amino acids occupying these sites are neutrally charged.
- There is *no cross-linking* at these sites (Gly & X).

This discrepancy between site (Y) and sites (Gly & X) leads us to discover the cause of collagen piezoelectricity (PZE). This occurs at site Y [27]. This could be explained by the mechanical stress of collagen, it would conform, and because

the site (Y) is the only site that is both polar and positive, it rotates under the mechanical stress to be on the convex side of the collagen as in Figure 4. This created electrical gradient difference (EGD) which can stimulate the fibroblasts to produce all the components of the dermal layer of the skin including collagen, elastin, hyaluronic acid that adsorb to water, and the mucopolysaccharides. The skin appears thick and shiny and the wrinkling disappears. It cannot be stressed enough that all the above cascades would not occur if the collagen is glycated and not physiologically functional. This would help us in the reversal of wrinkling later.

To complete the *full-blown* picture of the collagen molecule, the cross-section of the 3 threaded polypeptide chains of collagen together as in (Figure 5) shows the following point:-

- *Glycine* is always central because it is the smallest amino acid.
- *Proline or hydroxy-proline* has a ring to support the triple helix
- *Lysine* is peripheral and it is the only amino acid that is both *positively charged* and *polar* (loving water)

Therefore, the collagen molecule is studied *longitudinally* (Figure 2), at the cross-section of one thread (Figure 3), and the cross-section of the 3 threads together *i.e.* one molecule (Figure 5). This novel study of the collagen structure at both longitudinal and transverse levels could help us in a better understanding of the collagen molecule mechanics at the molecular level. This also may help us

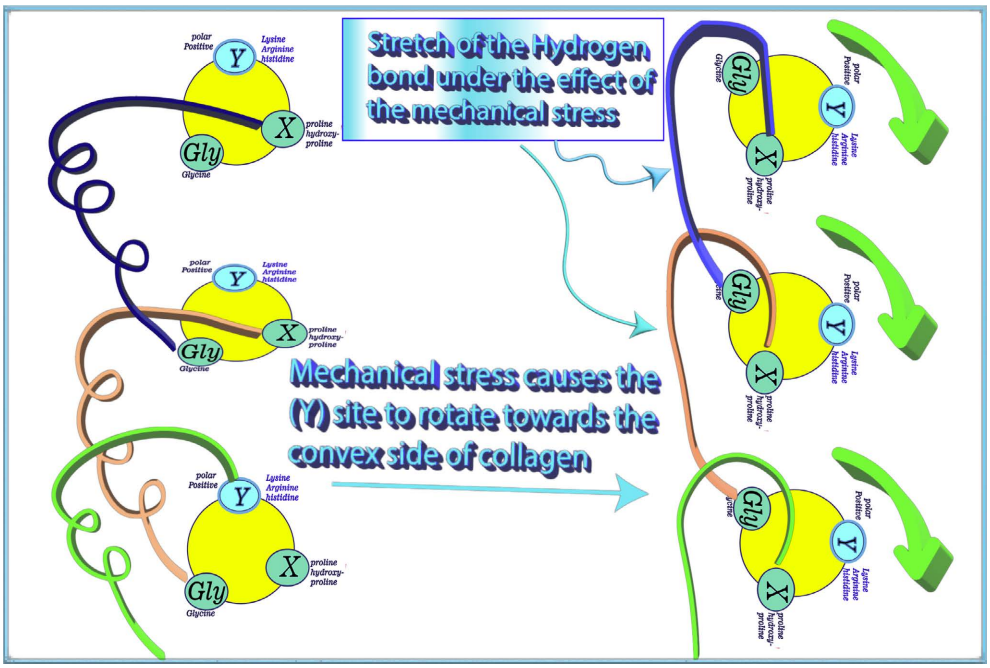

Figure 4. It shows the effect of the mechanical stress on the collagen molecule. The (Y) site which is only the polar and positively charged site is shifted towards the convex side of the collagen. This is the explanation of the piezoelectricity (PZE) of the collagen. This means that the collagen would show an electrical gradient difference (EGD) on its either side on the application of the mechanical stress. This (EGD) can stimulate the fibroblasts to remodel the skin and prevent its wrinkling. This only happens if the collagen is physiologically functional and not glycated (27).

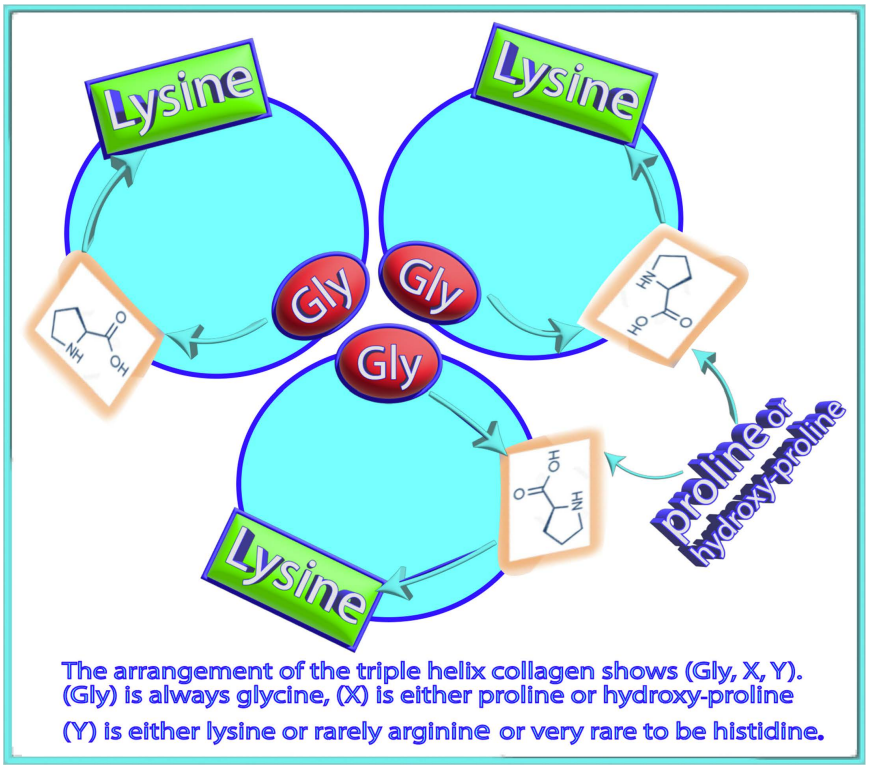

Figure 5. A cut-section of one collagen molecule (the triple helix). The (gly) *i.e.* Glycine site is the smallest amino acid and it is always inside. The site (X) which is either proline or hydroxy-proline has a ring to support the structure. The site (Y) is always in the periphery to allow bending in the collagen (27)

in the reversal of the aging process of the skin. *i.e.* skin wrinklings.

4. The Hidden Relation between the Metabolic (X) Syndrome & Glycation

Metabloc (X) syndrome is a wide variety of conditions that are associated with sub-clinical inflammation of many tissues of the body leading to their permanent damage. The metabolic syndrome occurs in the process of the conversion of food to energy. In other words, this syndrome is mainly due to dysfunction of the mitochondria (the powerhouses of the cell). This condition is considered the root cause *of most if not all* degenerative diseases in the elderly which include obesity, diabetes Mellitus type 2 (DM II), insulin resistance, hyperinsulinemia, osteoporosis, osteoarthritis, coronary artery diseases, Alzheimer's, autoimmunity, and even some cancers. This is why recent studies considered Alzheimer's as 3rd type of diabetes mellitus (DM III) [29]. Also, all recent studies considered cancer as a metabolic disease [30]. As metabolic syndrome is considered the root cause of all degenerative diseases in the elderly, it has a profound effect on skin wrinkling which is considered the hallmark of the aging process [31].

4.1. The Role of Visceral Fat in the Metabolic Syndrome

It is well-known that obesity is blamed for the acceleration of the aging process

in the elderly. This may not be very accurate because some obese patients may be healthy and they may not suffer from metabolic syndrome in the future [32]. Obesity can be calculated by *body mass index* (BMI) which takes into consideration both body weight and length. Simply it can be divided into:-

- 18% or less is underweight
- 18% - 24.9% is normal
- 25% - 29.9% is overweight
- 30% - 34.9% is obese
- 35% or more is morbid obesity.

The higher the percentage, the more the liability of the metabolic syndrome [33]. The fat in the human body does not have the same metabolic effect. The subcutaneous fat is metabolically inert. The visceral fat, on the other hand, is metabolically active and secretes many inflammatory cytokines that are responsible for the metabolic syndrome. The visceral fat, as in **Figure 6**, is deposited mainly in the liver, pancreas, wall of the intestine, and the mentum [34] [35]. This means that it is concentrated mainly inside the abdomen. Thus, visceral fat is usually associated with an increase in the circumference of the abdomen at the umbilicus. Normally, it is 80 cm in women and 85 cm in men. More than that, visceral fat is predicted [36]. The visceral fat can be only seen by C.T. scan [37].

4.2. The Role of Mitochondrial Dysfunction in the Metabolic Syndrome

The mitochondria are the powerhouse of the cells. They are responsible for the

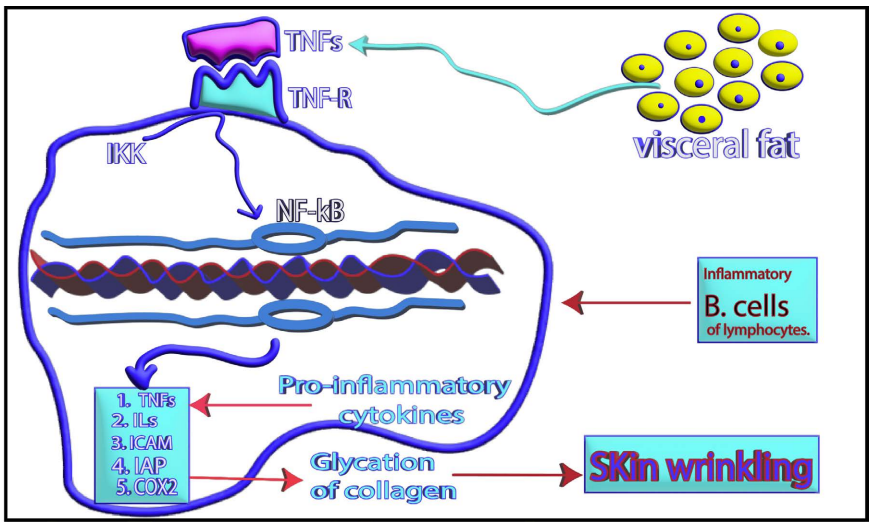

Figure 6. The mechanism of obesity and/or visceral fat in the induction of the aging process. One hallmark sign of aging is the wrinkling of the skin which is initiated by pro-inflammatory cytokines that initiate chronic and subclincal inflammation of the affected tissues. This is the main cause of the glycation of collagen by the effect of the advanced glycation end-products (AGEs). The most common inflammatory cytokines that are released from the visceral fat are; Tumour necrosis factors (TNFs), Interleukins (ILs), Intercellular adhesion molecules (ICAM), inhibitors of apoptosis (IAP), and cyclo-oxygenase 2 (27).

conversion of food into energy for the production of ATPs that are necessary for every activity of the human body [38]. The inner membrane of mitochondria is damaged as a result of the accumulation of oxidative stress in the form of reactive oxidative species (ROS) which are simply free radicals. ROS are considered the most common cause of tissue damage with subsequent downregulation of protein synthesis including insulin receptors on the cell membrane of the fibroblasts. This could be done via the Voltage-Dependent Anion Channels (*VDAC*) on the mitochondria as in (**Figure 7**). These materials are very active and try to damage the affected tissue by receiving electrons from the nearby structure [39]. The free radicals could be neutralized by *anti-oxidants* that prevent them from damaging the tissues [40] [41]. This is very important for us to get benefits from this phenomenon to reduce or minimize the aging process in general and skin wrinkling in particular. Recent studies show that the whole aging process may be only caused by mitochondrial dysfunction in the elderly. Refined sugar is blamed as an important risk factor for damaging the inner membrane of the mitochondria with subsequent mitochondrial dysfunction [42].

4.3. Hossam Retrograde Mitochondrial-Nuclear Axis

There is a new theory of *cross-talk* between the mitochondria and the nucleus. There are 2000 types of protein in the mitochondria only 13 of them are transcripted in the mitochondria. The remaining are transcripted in the nucleus. This suggests a continuous cross-talk between the mitochondria and the nucleus. In the case of the aging process, the cross-talk is reduced or even stopped with

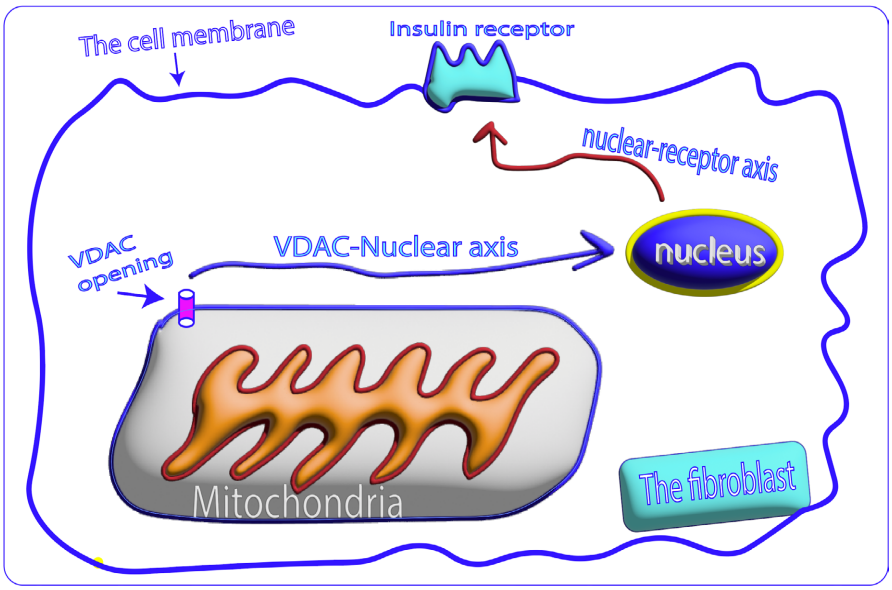

Figure 7. The effect of hyper-insulinemia in the down-regulation of insulin receptors of the fibroblasts with the subsequent insulin resistance. The mechanism could be explained through the communication between the Voltage-Dependent Anion channels (VDAC) and the nucleus. This mechanism is explained via the Hossam retrograde mitochondrial axis. The preservation of the cross-talk between the mitochondria and nucleus is the main preventive mechanism of the aging process (27).

the subsequent development of the metabolic (X) syndrome [43]. The process is initiated in the mitochondria and not in the nucleus because all the process of metabolism which is the conversion of food into energy occurs in the mitochondria. The mitochondria have 2 membranes, the outer is permeable and the inner is impermeable to control what exactly needs to enter and exit from the mitochondria [43]. The dysfunction of the mitochondria occurs in the inner membrane. There are different ports on the inner membrane of the mitochondria which are; the mitochondrial calcium uniport (MCU), carnitine shuttle, and pyruvate-dehydrogenase enzyme. The (MCU) is the port that allows calcium to enter the mitochondria. The accumulation of calcium inside the mitochondria causes their damage. Therefore, the blockage of this port could activate the mitochondria again. The best material that blocks that port is *Taurine* amino acids. Therefore, Taurine supplementation is cytoprotective via protection of the mitochondria through this mechanism [44]. On the other hand, the Carnitine shuttle is responsible for the burning of fat. Thus, the carbohydrate-burning machinery would be saved because the energy could be obtained through the fat-burning machinery that does not cause damage to the mitochondria [45]. *Lysine* amino acid is essential for the building of the carnitine shuttle [46]. Lastly, the *pyruvate-dehydrogenase enzyme* is essential for lowering blood sugar by enhancing its utilization by the mitochondria. This could be enhanced by supplementation of Alpha-lipoic acid [47]. To sum up the above point, the supplementation of Taurine, Lysine amino acid, and Alpha lipoic acid would protect the inner membrane of the mitochondria and prevent their dysfunction with subsequent restoration of the cross-talk between the mitochondria and the nucleus. This is put into consideration in our strategy for the prevention of the aging process and skin wrinkling.

5. Discussion

To stop or at least slow down the skin wrinkling process, the exact pathological process of its occurrence must be known and every effort must be made to find all the possible ways of the reversal of the pathological process. The steps that are followed in this paper are as follows:-

- Studying the layers of the skin at the molecular level
- Studying the biomechanical and structural aspects of collagen at the longitudinal and cross-sectional levels.
- Studying the effect of the metabolic (X) syndrome on the glycation of collagen and mitochondria and making them dysfunctional.

The process of the prevention of wrinkling needs to be done at the root causes which has the following targets; maintaining the collagen function and if it is possible to improve it in quality and quantity, repairing the dysfunction of the mitochondria, with every possible trial to get rid of metabolic (X) syndrome.

5.1. Supplementation of Certain Amino Acids

Studying collagen shows it is a protein structure that is formed of *amino acids*

connected via peptide bonds. It is known that there are 20 amino acids in the human body that form the building blocks for the manufacture of all the proteins in the human body. Only 6 amino acids are highly needed in the manufacture of collagen as will be explained now. The cross-section (in **Figure 3**) shows that there are 3 sites at which the amino acids are situated (Gly, X, Y). This means that the manufacture of collagen needs the following amino acids; glycine at site Gly, proline or hydroxyproline at site X, Lysine, Arginine, or histidine at site Y. These 6 amino acids are the most important building blocks of the collagen.

Not all the above *6 amino acids* are of the same importance. This is because Glycine, proline, and hydroxy-proline are non-essential amino acids which means that if they are deficient in food, the body can manufacture them. Thus, there is no deficiency of these amino acids at the sites (Gly & X).

Regarding site (Y), *Lysine and histidine* amino acids are essential which means that the body cannot manufacture them and their deficiency in food causes the body to suffer. Arginine, on the other hand, is considered *a semi-essential* amino acid which means that the body can partially manufacture it. It could be concluded that the *Lysine and histidine* amino acids are the most important amino acid building blocks for the manufacture of collagen. Since histidine is very rarely needed, Lysine amino acid is by far the most important amino acid in collagen synthesis [48]. Also, lysine acts as the site of the lysyl oxidase enzyme (LOX) which is the most important enzyme in the cross-linking of collagen and making it strong [49]. Lastly, the Lysine amino acid is very important in the manufacture of carnitine which is essential for the integrity of the mitochondria [50]. As said earlier, mitochondrial dysfunction is one of the most important factors for the exaggeration of metabolic syndrome. Therefore, Lysine supplementation would help the collagen directly as it is one building block amino acid and indirectly via the manufacture of carnitine that lessens the effect of metabolic syndrome.

5.2. Supplementation of Certain Anti-Oxidants

Antioxidants are substances that can neutralize free radicals *i.e.* Reactive Oxygen Species (ROS). As said earlier, damage to mitochondria or their dysfunction could be the most important factor in the metabolic syndrome with subsequent exaggeration of the aging process. Therefore, the supplementation of these anti-oxidants may play an important role in the prevention of the tissue damage associated with dysfunctional mitochondria. The most important antioxidants that could be used for tissue rejuvenation are:-

- **N. Acetylcysteine** (NAC) is considered the strongest antioxidant because it can be converted to glutathione (GHS). This can perfectly remove all the free radicals from the body and detoxify them [51].
- **Alpha-lipoic acid (ALA)** is considered a universal antioxidant because it can work on both aqueous and fatty media. It also can stimulate pyruvate dehydrogenase enzyme a very important mitochondrial protein for carbohydrate

metabolism. Thus, it helps in reducing blood sugar, insulin resistance, and metabolic syndrome in general. Moreover, it can replenish all the remaining antioxidants like vitamin C, and vitamin E [52].

- **Taurine** is not a true amino acid because it has *no codon* to be incorporated in protein synthesis. It has a strong antioxidant property in the neutralizing the free radicals. It has a special characteristic in blocking mitochondrial calcium uniport (MCU). This has a very strong protective effect on the mitochondria. Thus, it has a very beneficial effect on the metabolic syndrome and aging process in general [53] [54].

5.3. Supplementation of Methylating Agent(s)

The methylating agents are the supplements that could supply the already damaged tissue by adding a *methyl group* (CH3). This is why this group of supplements is called methyl donors. As said earlier, free radicals are very active substances that try to steal electrons from the tissues leading to their damage. Methylaing agents (methyl donors) could repair the damaged part especially if the damaged part was in the DNA [55]. Moreover, the methyl donors could prevent the hazardous effect of a very dangerous by-product called homocysteine. This is an intermediate metabolite of methionine amino acid because it accelerates the aging process by blocking the action of glutathione (GHS). Thus, the mechanism of action of the methylating agents on Homocysteine is to convert it into functional other products like methionine or cysteine and both are natural amino acids [56] [57]. The most common methylating agents are:-

- Methyl sulphonyl methane (MSM)
- S. Adenosyl Methionine (SAMe)
- Trimethylglycine (TMG)
- Choline
- Folic acid (one member of the vitamin B complex).

5.3.1. Vitamin Deficiency Related to the Aging Process

- *Vitamin D deficiency* is very common, especially in the northern atmosphere above the 37 parallel due to reduced sun. This is because ultraviolet B (UVR-B) could convert the cholesterol under the skin into vitamin D precursor that could be activated later in the liver and kidney. Vitamin D has a very important role in controlling the T. regulatory cells of the immune system [58]. This type of cells from their name regulate the immune system and prevent continuous subclinical inflammation that may exaggerate the aging process. Recent studies show that vitamin D by itself has an anti-aging effect on the skin [59], [60].
- *Vitamin K2 (menaquinone)* is always associated with vitamin D because it acts as an accessory for vitamin D. This is because vitamin D causes the absorption of calcium and vitamin K2 redirects the calcium from soft tissues into the bone and teeth. Thus, there is always a synergism between vitamin D and vitamin K2 [61].

- *Vitamin C* is considered the backbone of all anti-oxidants. This product is mainly of plant origin especially citrus and green leafy vegetable. Other than the anti-oxidant effect, vitamin C has a fundamental role in the conversion of *proline to hydroxy-proline* in the site (X) of collagen synthesis as **Figure 8**. Therefore, vitamin C has a very essential role in collagen synthesis [62]. It is well known that vitamin C deficiency causes scurvy which is the disease of soft tissues. Moreover, it has an antiaging property by neutralization of free radicals [63] [64].

5.3.2. Mineral Deficiency Related to the Aging Process

- *Zinc* (Zn) is by far one of the most important minerals to the vitality of the skin [65]. Zinc is needed in the proper folding of collagen and it also stimulates the fibroblasts to secret more collagen [66]. Zinc also has a fundamental role in the regulation of nitric oxide synthase enzyme (NOS). This enzyme is essential in the production of nitric oxide (NO) which has a stimulatory effect on the mitochondria for energy production [67]. As in **Figure 9**, zinc connects 2 subunits of nitric oxide synthase (NOS). It can fix the oxygen atom (O) into the nitrogen atom (N) that is generated from the Arginine amino acid. Thus, nitric oxide (NO) is produced **Figure 9**.
- *Copper (Cu)* has an antiaging property in lengthening the telomere which is the terminal end of the chromosomes [68]. The longer the telomere, the more the probability of a longer age of a person [69]. Another very important function of copper, as explained in **Figure 3**, is that Lysyl Oxidase Enzyme (LOX) uses copper as a co-factor for cross-linking of collagen [70]. The cross-linking is very important for the strengthening of the collagen.

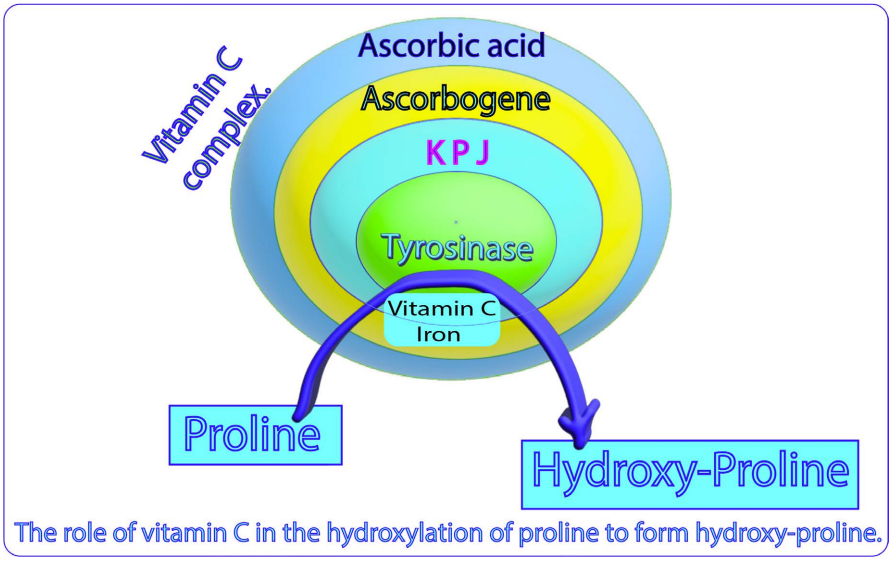

Figure 8. The effect of vitamin C in hydroxylation of proline. This occurs at the (X) site. This process needs an important enzyme called *lysyl hydroxylase* enzyme and *iron* as a co-factor. Thus, vitamin C is very essential in the integrity and function of collagen and its deficiency causes scurvy. This also shows the 4 main components of the vitamin C complex which are tyrosinase, KPJ, Ascorbogene, and ascorbic acid (27).

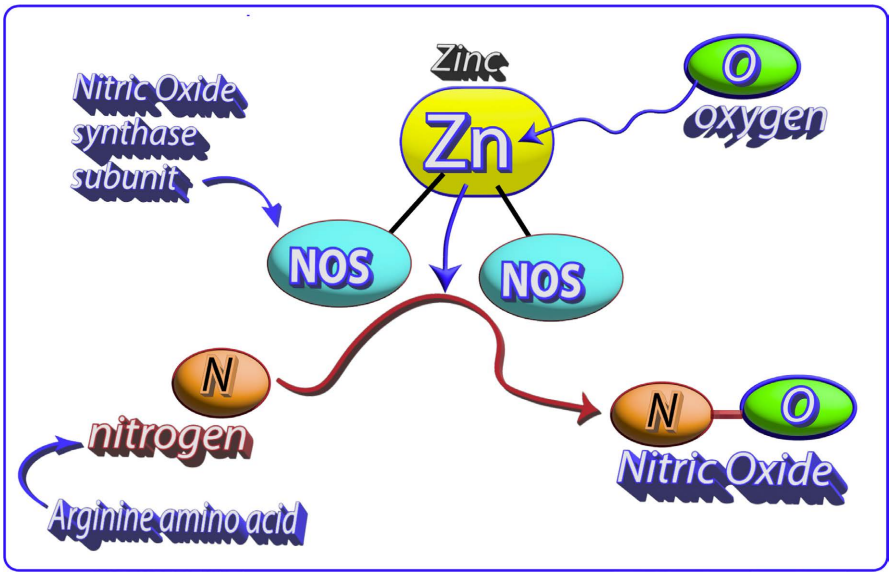

Figure 9. The role of Zinc in the combination of 2 sub-units of 2 nitric oxide synthase (Nos) to form a nitric oxide (NO). The exact mechanism of zinc is to fix oxygen (O2) into the nitrogen (N2) from arginine amino acid to form a nitric oxide (NO). This substance is very important in the healing mechanism because it has a powerful vaso-dilator effect that enhances the blood supply to the skin and removes the free radicals. Thus, skin wrinkling would not occur. Moreover, it has a stimulatory effect on the mitochondria to perform their proper function (43).

6. Conclusion

Wrinkling of the skin is considered the hallmark feature of the aging process, especially in the elderly. Many studies were executed to fight or at least slow down the process. Many pharmaceutical companies use multi-billion dollar industries in the form of either *cosmetics* and/or *collagen* ingestion claiming that would have a beneficial effect on reducing skin wrinkling. This article goes in a different direction to search for the root cause of skin wrinkling with every possible trial to stop or even reverse the exact pathological process. This was accomplished by studying the layers of the skin at the molecular level. The skin is formed from 3 main layers namely epidermis, dermis, and hypodermis. The epidermis is the most superficial layer and forms about 7% - 8% of the skin thickness. It is formed mainly of keratinocytes. The deepest layer is the hypodermis which is also thin and is about 7% - 8% of the skin mass. It is formed mainly of a fatty layer that carries the blood, nerve, and lymphatic supply of the skin. Both epidermis and hypodermis have little or no essential role in the process of skin wrinkling. On the other hand, the dermis has the most important role in the formation of the skin wrinkling. Thus, the dermal layer and its components are studied in full and minute detail. The dermis forms about 85% of the skin thickness. The dermis is formed of collagen fibers, elastin fibers, hyaluronic acid, fibroblasts, and some mucopolysaccharides. Collagen forms the main component of the dermal layer which may reach up to 50% of dermal mass. There is a deep and complex relationship between collagen and the other

dermal components. The physiologically active collagen is needed for optimal integrity and function of other dermal components. Therefore, this review deeply studied collagen at the structural and molecular levels. Moreover, it shows its hidden role in the aggravation of skin wrinkling if the collagen loses its physiological function. Therefore, collagen is studied at the biomechanical aspect of view at the *longitudinal* and *cross-sectional levels*. The longitudinal structure of the collagen shows the terminal part of the collagen which is a non-folded part and it is called telo-protein. This is the site of the glycation of the collagen. The remaining collagen molecule is a folded area *i.e.* the triple helix which is part that the collagen molecule can perform its function. The longitudinal section also shows the zero holes and zero channels of the collagen fibers which have a fundamental function in the integrity of the collagen. The study of the collagen at the transverse section shows the amino acid orientation at the (Gly, X, Y). This shows amino acids that form the building blocks of the collagen. These amino acids namely; (Gly) which is always referred to as glycine, and (X) is referred to as proline or hydroxy-proline. Site (Y) is either Lysine or to a lesser extent arginine and very rare to be histidine. This is very important in the protocol of the amino acids supplementation. The studying the effect of the metabolic X-syndrome on the glycation of collagen and making it dysfunctional. It is believed that this paper would open a new path for the prevention of skin wrinkling and also would help the researcher to dig deeper for the root cause of the disease instead of dealing with the superficial symptoms of the disease process. This is also important because the metabolic (X) syndrome could affect most of the systems of the human body if not all of them. Furthermore, collagen is the most common protein in the human body and constitutes about 30% of the protein of the whole body system. Linking the *commonest* root cause of metabolic diseases with the *commonest* protein in the body which is collagen would lead us to *more new concepts* of the mechanism of action of the aging process. Subsequently, the management of the aging process is anticipated. Lastly, this review suggests that the aging process in general and skin wrinkling as a mirror of it *i.e.* skin wrinkling reflects the exaggeration of the degenerative changes in the internal organs. Therefore, it put a suggestion of certain lines of defense against the aging process which include antioxidants that neutralize the free radicals. Also, the supplementation of certain vitamins and minerals is necessary to allow the body to recover from the minute and accumulated aging process. Because collagen is a protein structure, its building blocks are amino acids. This review studied the amino acids that are essential for the recovery of collagen. The combination of these supplement antioxidants, essential amino acids, and certain vitamins and minerals would be a new strategy that contributes to the prevention of skin wrinkling according to the above molecular study of the skin components. This may be more effective in the prevention of the early type of skin wrinkling or the condition of premature aging.

Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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