Thesis: The metabolic syndrome and AGEs and their incidence in the aging process

Capstone Project

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The Metabolic Syndrome (MetS) and Advanced Glycation End-products (AGEs) have increasingly been implicated in the onset of many metabolic diseases and the acceleration of ageing. MetS is comprised of several metabolic disorders that include excess upper-body fat, high cholesterol levels, high blood sugar levels or insulin resistance (IR), and hypertension. On the other hand AGEs or Advanced Glycation End-products are a group of highly oxidant compounds that have an incidence in the onset of diabetes, heart disease and other illnesses. Numerous researches and investigations have been conducted to establish these relationships. And even though they have clearly proven the incidence of MetS and AGEs in the onset of some of the conditions mentioned above, there is still the need of more research to help clarify certain doubts that have been exposed by some researchers. The author believes that it is necessary to draw clear lines as to when MetS or AGEs are the culprits of any metabolic disease. And when other factors such as genetics or environment are the cause. Also if there exists the possibility of a combination of those etiological factors. The literature available today suggest that oxidative stress and inflammation play a major role in the formation of several metabolic diseases and the stimulation of ageing and even though some of these illnesses have a multifactorial etiology AGEs and MetS are still considered the major culprits in their development. The present investigation is geared to prove the connection between MetS, AGEs and the acceleration of ageing.
INTRODUCTION

After the introduction of the Seven Countries study by Ancel Keys in 1958 there were new scientific discoveries that linked diet with prevalent diseases such as cardiovascular disease (CHD) (Kromhout, 1999). Then in 1966 J.P. Camus (a French physician) introduced for the first time the concept of the metabolic syndrome (The trisyndrome metabolique) (Eriksson, Taimela, & Koivisto, 1997). But it was only until late in the 1980s that Gerald M. Reaven finally presented the metabolic syndrome as the main culprit in the formation of metabolic diseases including diabetes, heart disease, and stroke (Eriksson, et al., 1997).

**What is the metabolic syndrome?**

The metabolic syndrome or MetS concept was first introduced by J.P Camus in 1966, to refer to a group of conditions that induced rheumatism and arthritic problems (Morley, 2015). Years later in 1988 Gerald M. Reaven re-introduced the concept as Syndrome X, and then it was later renamed as the metabolic syndrome or MetS (Eriksson, et al., 1997). In reality MetS cannot be considered a disease but rather a group of risk conditions that can induce illnesses such as heart disease, diabetes, and stroke (Mayo Clinic, 2015). These disorders include hypertension, high blood sugar levels (insulin resistance or IR), increased or abnormal cholesterol levels, and excess fat around the waist (Mayo Clinic, 2015). The two most important factors in the development of the metabolic syndrome are related to obesity and they are insulin resistance or IR, which is the inability of the body to use and control blood sugar, and excessive fat around the middle and upper parts of the body (Western Washington University, 2014). MetS have long
been linked to the acceleration of the aging process and this relationship is discussed further in
the results section. Another factor that is thought to be involved in the acceleration of ageing is
advanced glycation end-products or AGEs.

**What is AGEs?**

Advanced glycation end products or AGEs, also known as glycotoxins are substances formed after the heating process of foods in modern diets (Uribarri et al. 2010). Glycation needs to be distinguished from glycosylation (Gkogkolou & Bhom, 2012). While the first is produced by a non-enzymatic reaction between reducing sugars like glucose, and proteins, lipids and nucleic acids, glycosylation is the product of an enzymatic reaction that attaches glycans (polysaccharide carbohydrates) to proteins, lipids and other molecules (Gkogkolou & Bhom, 2012). Glycation was first described by Maillard in 1912. And reintroduced by Hodge 50 years later due to its role in food browning during thermal processing (Gkogkolou & Bhom, 2012).

AGEs are known to induce the formation of increased oxidant stress or OS and inflammation (Uribarri et al., 2010). Glycotoxins are a group of highly oxidant compounds with pathogenic activity and are thought to be active in the aging process and the onset of several diseases including diabetes, cardiovascular disease, Alzheimer’s disease, and stroke (Uribarri et al., 2010). It appears that the literature regarding the acceleration of the aging process linked to AGEs regard this disorder as the main or at least one of the major components of the acceleration of aging. A complete discussion of this condition is presented in the result section. A co-factor involved in the production of both the metabolic syndrome and AGEs is inflammation. Some researchers consider inflammation as the result of either MetS or AGEs while others believe it is an independent risk factor.
What is inflammation?

Western Washington University (2014), contends that inflammation is closely related to the metabolic syndrome and can be considered an independent risk factor in the onset of many diseases including heart disease, diabetes, stroke, etc., and the stimulation of the ageing process. Inflammation is thought to be the underlying cause of diseases like diabetes, cardiovascular disease, and insulin resistance (IR) and if we can stop its formation we may be able to prevent these diseases and premature ageing at its early onset Western Washington University, 2014). However this is a very hard task to determine because the etiology of inflammation is deeply rooted in the so called western diet (Western Washington University, 2014). The western diet is based on excessive amounts of refined foods including the use of refined white sugar in great quantities, low consumption of fresh fruits and vegetables, lots of processed foods which contain additives that induce permanent or chronic inflammation and lack of exercise among other factors (Western Washington University, 2014).

When there is a permanent low-grade inflammation in the body this condition is considered an immune system response due to a damaging stimuli in our bio system (Western Washington University, 2014). Several inflammatory substances are produced by our body including cytokines, tumor necrosis factor-alpha, interleukins, etc., that respond to the stimuli and since this stimuli is permanent on account of western’ society feeding habits then a chronic inflammation develops (Western Washington University, 2014). A complete discussion of how chronic inflammation induces the onset of many of the common metabolic diseases and premature ageing affecting the western world is exposed in the results section. Another final co-factor related both to AGEs and MetS in the formation of metabolic illnesses and ageing.
acceleration is oxidative stress. Which is produced by the accumulation of oxidant by-products in our cells and tissues.

**What is oxidative stress?**

When the protective mechanisms of our biological system called antioxidants fail to eliminate the oxidant products of our metabolism which include free radicals and reactive metabolites an imbalance is generated creating a condition called oxidative stress (Reuter, Gupta, Chaturvedi, & Aggarwal, 2010). These oxidant products are called reactive oxidant species or ROS and the imbalance they cause affect the normal functioning of molecules and cells of the whole body system affecting their DNA (Reuter et al., 2010). In the initial stages ROS produce inflammation and changes to the DNA (Reuter et al., 2010). These gene mutations and DNA structural changes will eventually induce the formation of inflammatory conditions that cause the formation of illnesses such as diabetes, cancers, heart disease, etc., and the ageing process acceleration (Reuter et al. 2010). During the lifetime of an individual the accumulation of the oxidant-induced somatic mutations in the mitochondrial DNA (mtDNA) contribute to damage in the mitochondria bioenergetic function leading to ageing stimulation or acceleration (Bonomini, Rodella, & Rezzani, 2015). Oxidative stress has been strongly connected to the development of diabetes.

**Oxidative Stress and Diabetes**

Hyperglycemia is thought to be the main cause of diabetic complications. Diabetes mellitus or DM is characterized by hyperglycemia resulting in short term metabolic changes in lipid and protein metabolism and long term irreversible changes in vascular and connective tissue (Nowotny et al., 2015). Oxidative stress plays an important role in the formation of
hyperglycemia-induced tissue injury as well as in early processes of the development of type 2 diabetes. The formation of Advanced Glycation End products or AGEs is considered one contributing factor (Nowotny, et al., 2015). Oxidative stress plays also an important role in the onset of cardiovascular disease.

**Oxidative Stress and Cardiovascular Disease**

Cardiovascular disease or CVD is a leading cause of mortality in Western societies. The production of AGEs and their interaction with their receptor RAGE, are thought to play an important pathogenic role in the development of CVD (Ward, Fortheringham, Cooper, & Forbes, 2013). The AGEs-RAGE axis is considered to induce a proinflammatory environment that creates cellular dysfunction cascading towards pathology (Ward et al., 2013). Mitochondrial dysfunction creates the environment for the proinflammatory response presenting excess reactive oxygen species or ROS, another name for oxidative stress (Ward et al., 2013). Oxidative Stress also has implications in the formation of other diseases where inflammation is present and has an incidence in ageing stimulation including cancer (Reuter et al., 2010)

**Oxidative Stress and Cancer**

ROS or reactive oxygen species also called oxidative stress is known to induce a wide array of diseases including chronic inflammation which in turn leads to the formation of several cancers (Reuter et al., 2010). The relationship between inflammation and cancer has been established in numerous epidemiological and experimental research investigations and these findings are validated by anti-inflammatory therapies that have proven to be effective in the management and prevention of cancer (Reuter et al., 2010).
During the aging process an impairment of body functions is developed as we age (Reuter et al., 2010). This dysfunction is increasingly caused by the formation of accumulated damage in DNA, proteins, and lipids and also by the increase in intracellular oxidative stress due to a decreased in the antioxidant fight against ROS intracellularly (Reuter et al., 2010).

METHODS

Databases such as PubMed, InfoTract, ProQuest, Google Search, and others were included in the investigation. Two medical books related to the topic were used in the research literature. Thirty peer-review, full text investigations were consulted during the research investigation.

Keywords used included: metabolic syndrome, MetS, Advanced Glycation End-products, AGEs, aging, diabetes, cancer, inflammation, oxidative stress, obesity, atherosclerosis, cardiovascular disease, CVD, hypertension, insulin resistance, hyperlipidemia, western diet

RESULTS

The metabolic syndrome and aging

MetS has a definitive incidence in aging. Mets is explained in the ATP III or the Adult Treatment Panel III issued by the National Cholesterol Education Program or NCEP in 2001. This was an expert panel in the evaluation, detection, and treatment of high blood cholesterol in adults for the prevention of coronary heart disease or CHD and this publication was intended to provide guidelines for the control and testing of cholesterol (myhealthywaist.org, 2015). The NCEP- ATP III also considered MetS, for the first time as a second in importance risk factor after high LDL cholesterol in the onset of CHD and a target for its prevention and development (myhealthywaist.org, 2015). Obesity is considered the foremost leading cause of MetS, especially upper-body obesity, but it is also heavily associated with several metabolic disorders.
including atherogenic dyslipidemia, which consist of sebaceous or fatty cysts that form in the inner lining of the arterial walls and also beneath them (myhealthywaist.org, 2015). MetS is also associated with a pro-thrombotic and a pro-inflammatory profile, insulin resistance IR, and hypertension (myhealthywaist.org, 2015).

The NCEP-ATP III, asserts that certain ethnic groups and individuals have a genetic tendency to develop MetS. It has been found that some people with common genetic variants, and rare single gene disorders are more prone to develop some MetS characteristics (myhealthywaist.org, 2015). But people who have good lifestyles, who are not obese, do not smoke, and maintain beneficial practices such as regular exercise, a healthy diet that includes fruits, vegetables, whole grains and no-to moderate alcohol intake are rarely affected by the metabolic syndrome (myhealthywaist.org, 2015). Aging is considered an important factor together with insulin resistance IR, abdominal fat, no physical activity and hormonal imbalance in the onset of MetS (myhealthywaist.org, 2015). An increased use of the western diet all over the world has resulted in an increase of the negative conditions this lifestyle carries with it (Monteiro & Azevedo, 2010). Which includes stress, an excessive energy intake coupled with low physical activity, low-quality food ingestion that is low in micronutrients and high in fat and dense carbohydrate energy (Monteiro & Azevedo, 2010). And finally, a disruption of chronobiology, which is an alteration of the living rhythm and the effect of time (Monteiro & Azevedo, 2010). Inflammation is closely associated with MetS and some researchers agree that they are not sure which precedes which (Esposito & Giugliano, 2004). The discussion is still open to this date.
The Metabolic Syndrome and Inflammation

Inflammation produced by the metabolic syndrome typically consists of high levels of tumor necrosis factor-alpha, interleukin-6, and C-reactive protein, all of them markers of the immune system inflammatory reactions (myhealthywaist.org, 2015). Western Washington University (2014), affirms that a low grade inflammation is an immune system response that is associated with the body’s detection of any injurious foreign agent. This response is determined by a body’s reaction such as fever, or a blood or metabolic response (Western Washington University, 2014). It is important to mention that low grade inflammation is clinically considered a two to four times the elevation of the circulating levels of proinflammatory and anti-inflammatory cytokines, which are nonantibody proteins that act as intercellular mediators, and also the increment of other markers that indicate immune system activity (Western Washington University, 2014). Monteiro and Azevedo (2010), also contend that this “low-grade” inflammatory state is unique to the metabolic syndrome and promotes premature cellular ageing. However its particular features and mechanism of action are not well understood. A considerable amount of the health disorders associated with inflammation are linked to lifestyles especially feeding habits of people of western societies (Western Washington University, 2014). Hence it is necessary to discuss how lifestyle patterns affect the development of inflammation.

Lifestyles and the Development of Inflammation

Low grade inflammation can be affected by many activities that can disrupt the normal functioning of the body and induce its formation (Western Washington University, 2014). Our western lifestyle is one of those activities that may induce the formation of chronic inflammation (Western Washington University, 2014). Western Washington University (2014), explains that in a study conducted among healthy middle-aged women, high glycemic loads were related to high
levels of C-reactive protein, which is a known serum globulin pro-inflammatory marker that is produced in the liver, independently of their weight or their caloric intake. A low consumption of omega-3 fatty acids-containing foods, which are very important for healthy cell membrane functioning, is shown in the western diet, which induces inflammation especially in the cells of blood vessel walls (Western Washington University, 2014).

Omega-3 is a polyunsaturated fatty acid found in food such as fish, flaxseed, and nuts and is directly related with reducing the levels of pro-inflammatory substances that include interlukin-6, tumor necrosis factor-alpha, C-reactive proteins, and increasing the levels of antioxidant markers (Western Washington University, 2014). However the mechanism through which omega-3 interacts in the reduction of pro-inflammatory markers are not very clear yet (Western Washington University, 2014). Even though it is well known the important role omega-3 fatty acids play in the normal functioning of membrane cells in the whole body, especially blood vessels wall cells (Western Washington University, 2014).

Another factor to be considered is that a reduced consumption of foods containing B vitamins leads to B vitamin insufficiency (Western Washington University, 2014). This B vitamin deficiency induces blood vessels harm and inflammation, creating blood clotting, oxidative stress, and possible interactions with white blood cells (Western Washington University, 2014). Also a deficiency in magnesium and low consumption of antioxidant vitamins such as vitamin E and C, together with high meat intake can also lead to chronic inflammation due to the constant production of free radicals in the blood (Western Washington University, 2014). Inflammation is very closely related to diabetes. Which is one of the world’s leading metabolic diseases (Western Washington University, 2014). A detailed discussion of the incidence of inflammation in diabetes is thus imperative.
Inflammation and diabetes

Esposito and Giugliano (2004), suggest that chronic inflammation has an incidence as a triggering factor in the development of the metabolic syndrome which induces diabetes. Overnutrition, lack of exercise, and aging are powerful stimuli for the hypersecretion of cytokines that may induce insulin resistance (IR), and diabetes especially in people with a genetic predisposition and or a metabolic conditioning (Esposito & Giugliano, 2004). Insulin creates an anti-inflammatory reaction-resistance in the body and this reaction induces an increase in cytokine production which in turn produces a persistent low-grade inflammatory condition (Esposito & Giugliano, 2004). However there is a wide spread debate about the use of diagnosing the metabolic syndrome in clinical practice (myhealthywaist.org, 2015). Because of this debate the American Dietetic Association ADA and the European Association for the Study of Diabetes EASD published jointly in 2005 a statement in which they exerted caution in diagnosing the metabolic syndrome and its clinical use and added that more research was needed before all the disorders that encompass the metabolic syndrome could in fact be called “a syndrome” (myhealthywaist.org, 2015).

Morley (2015), explains that diabetes leads to DNA damage. Thus if the metabolic syndrome, which induces diabetes, is treated at its early onset it is possible to reduce the progression of cell damage that activate the acceleration of ageing (Morley, 2015). Morley (2015), also conveys that in order to combat the appearance of the metabolic syndrome (MetS) it is necessary to establish new healthy dietary patterns coupled with exercise, particularly resistance exercise. This slows the progression of the metabolic syndrome and thus the acceleration of ageing (Morley, 2015).
In a cross-sectional study conducted by Dallmeier et al., (2012), that included 2570 participants nine inflammatory biomarkers related to the metabolic syndrome were studied. The most important inflammatory biomarkers tested included, C-reactive protein (CRP), interleukin-6, tumor necrosis factor alpha, and tumor necrosis receptor-2, among others (Dallmeier et al., 2012). The study results showed that there was a significant interaction between C-reactive protein in relation to the metabolic syndrome and insulin resistance (Dallmeier et al., 2012). In people who did not have metabolic syndrome the presence of insulin resistance (IR) was associated with higher concentrations of C-reactive protein (CRP) (Dallmeier et al., 2012). However people who were metabolically obese but had normal weight presented higher concentrations of CRP, interleukin-6, tumor necrosis factor alpha, and tumor necrosis receptor-2, among others compared to people who had normal healthy weight (Dallmeier et al., 2012). These results suggest that the metabolic syndrome including diabetes or insulin resistance is associated with an inflammatory state, which induces the acceleration of ageing (Dallmeier et al., 2012). This inflammatory state also has an incidence in heart function (Western Washington University, 2014). Hence it is important to discuss how inflammation affects heart activity that leads to cardiovascular disease, which is directly related to increased stimulation of ageing (Esposito & Giugliano, 2004).

**Inflammation and Cardiovascular Disease**

Inflammation is a necessary body function for normal health. Because without it injuries and infections will go undetected by our immune system and will not heal them (Harvard Medical School, 2007). But when inflammation is permanent or chronic is called low-grade inflammation and can be the cause of many disorders including cardiovascular disease (Harvard Medical School, 2007). Chronic inflammation can lead to the formation of atherosclerosis, which
induces cholesterol-clogged arteries that in turn affect heart function (Harvard Medical School, 2007). This therefore indicates a close relationship between inflammation and the many blood circulatory problems that include heart attack, stroke, peripheral arterial disease, and even vascular dementia (Harvard Medical School, 2007). Years ago atherosclerosis was considered as a lipid build up on the surface of arteries that with time would reduce or block the blood supply to tissues inducing a cardiovascular event (Libby, 2006). Today this mechanism of atherosclerosis formation is viewed differently. Inflammation plays an important role in its development and the formation of the atheromatous plaques (sebaceous cyst) in the clogging process is initiated in the interior of the artery in the artery’s wall cells rather than on the external surface as was previously thought (Libby, 2006). In a healthy individual endothelial cells (ECs), which comprise the innermost surface of the artery walls, will resist the adhesion of leukocytes (Libby, 2006). But if elements that trigger atherosclerosis are present such as a high saturated fat diet, hypertension, hyperglycemia, smoking, insulin resistance IR, or obesity, they can initiate the expression of adhesion molecules by ECs permitting the adhesion of leukocytes to the endothelial walls thus inducing the formation of inflammation through the initiation of several immune processes (Libby, 2006). Hence inflammation is considered pivotal in the onset of cardiovascular disease. And it is a progressive process that goes from the formation of fatty streaks to the accumulation of complex plaque that induces atherosclerosis which in turn causes heart disease increasing the ageing process (Libby, 2006).

Inflammation has also been tied to the formation of cancer. Inflammation could be the result in this case of a genetic expression or an accumulation of lifestyle and environmental factors or a combination of them (Reuter et al., 2010). In the following section we will examine how these agents affect its formation and also how cancer is related to the acceleration of ageing.
Inflammation and cancer

Chronic inflammation is considered one of the culprits in the formation of several cancers. It is linked to the development of various steps in carcinogenesis that include cellular transformation, promotion, survival, proliferation, invasion, angiogenesis, and metastasis (Reuter, et al., 2010). The causes of inflammation are due to an array of factors that include microbial and viral infections, exposure to allergens, radiation and chemicals, autoimmune and chronic diseases, obesity, high alcohol consumption, tobacco use, and a high calorie diet (Reuter et al., 2010). If the inflammatory condition persists for a long period of time (chronic inflammation) the probability of cancer formation increases (Reuter et al., 2010). When inflammation lasts for long periods of time, several chemical reactions are produced at the inflamed site and mast cells and leukocytes arrive at the damaged area creating a “respiratory burst” which is connected to a high oxygen uptake that generates an increased accumulation and released of ROS at the affected site (Reuter, et al., 2010). Several substances such as cyclooxygenase, inducible nitric oxide synthase, tumor necrosis factor-alpha, interleukin-1, IL-6, chemokines, and alterations in the expression of specific ribonucleic acids, all contribute to maintain a state of inflammation (Reuter et al., 2010). When this condition is maintained for longer periods of time, neighboring epithelial and stromal cells are affected and this situation may lead to carcinogenesis, which in turn creates an acceleration of ageing (Reuter et al., 2010).

Colotta, Allavena, Sica, Garlanda, and Mantovani (2009), indicate that recent epidemiological studies have revealed that chronic inflammation creates a strong predisposition in the body for the formation of certain cancers. Colotta et al., (2009), also explain that there always is an inflammatory agent present in the tissues of most neoplastic formations, including those that are not affected by or causally related to an inflammatory process. Important
components or agents of cancer-related inflammation (CRI) are tumor-associated macrophages (TAMs); tumor necrosis factor (TNF); interleukin-1 and 6; chemokines such as CCL2 and CXCL8; the occurrence of tissue remodeling; and angiogenesis (Colotta et al., 2009). Colotta et al. (2009), also assert that certain infections may induce the formation of cancer by creating a chronic inflammatory state in the body. Helicobacter pylori infection is directly related to gastric cancer and mucosal lymphoma (Colotta et al., 2009). Papilloma virus induces cervical cancer and hepatitis virus progress to liver cancer (Colotta et al., 2009). All these chronic inflammatory conditions damage body cells DNA, and as we have already discussed this damage induces the progression of ageing (Reuter et al., 2010). Oxidative stress (OS) is another factor together with inflammation linked in the acceleration of ageing, when either MetS or AGEs are present.

**What is Oxidative Stress?**

Oxidative stress (OS) can be understood as an imbalance in the production of free radicals, and reactive metabolites also called oxidants or reactive oxygen species ROS, and the production of antioxidants created by our body’s protective mechanisms (Reuter et al, 2010). Most of ROS products are formed from normal metabolic body functions, such as the mitochondrial cell respiratory chain, that produces metabolic by-products that include superoxide anion O2, hydrogen peroxide H2O2, hydroxyl radical OH, and organic peroxides, that stem from the biological reduction of molecular oxygen (Reuter et al., 2010). ROS or oxidative stress (OS) can damage our cells with long exposure to its damaging effects creating bodily cell imbalances that generate in illnesses such as cancer, diabetes, cardiovascular disease, Alzheimer, acute respiratory distress syndrome, aging, inflammatory joint disease, neurological disease, and inflammation (Reuter et al., 2010). It is important now to investigate the relationship between OS and AGEs, and how OS induces the formation of most of the same illnesses that the metabolic
syndrome creates and the acceleration of ageing. This interrelation is crucial in understanding the mechanism that OS develops in the onset of several metabolic diseases.

**Oxidative Stress and AGEs**

Advanced glycation end products or AGEs, also known as glycotoxins are substances formed after the heating process of foods in modern diets (Uribarri et al., 2010). AGEs are known to induce the formation of increased oxidant stress or OS and inflammation (Uribarri et al., 2010). Glycotoxins are a group of highly oxidant compounds with pathogenic activity and are thought to be active in the aging process and the onset of several diseases including diabetes, cardiovascular disease, Alzheimer’s disease, and stroke (Uribarri et al., 2010). The formation of AGEs is characterized by a nonenzymatic reaction between reducing sugars, which are carbohydrates that are oxidized by a weak oxidizing agent and free amino groups of proteins, lipids, or nucleic acids. This reaction is also known as the Maillard or browning reaction (Uribarri et al., 2010). The pathologic effects of AGEs are connected to their ability to promote oxidative stress (OS) and inflammation, which occurs when they bind with cell surface receptors or cross linking with body proteins, altering their function and structure (Uribarri et al., 2010). AGEs can affect nearly all types of cells and molecules in the body (Uribarri et al., 2010). AGEs are formed both outside and inside the body, and they stem from a glycation reaction which is the addition of a carbohydrate, like glucose (a reducing sugar) to proteins, lipids, or nuclei acids without the involvement of an enzyme, this process is called a non-enzymatic reaction (Gkogkolou & Bhom, 2012). Enzymatic reactions are different from glycation and are called glycosylation. They involve reactions of polysaccharide carbohydrates or glycans when they attach to proteins, lipids and other molecules (Gkogkolou & Bhom, 2012). When glucose binds with proteins in the glycation process this makes cells stiffer, less pliable
and more subject to damage and leads to premature aging (Uribarri et al., 2010). One of the leading metabolic illnesses in which AGEs has been found to be a major cause is diabetes.

**AGEs and Diabetes**

Even though there has been major advances in drug therapies, insulin resistance or IR, type 2 diabetes mellitus T2DM, and its complications remain as big medical challenges (Vlassara & Uribarri, 2014). It is a fact that IR which is related to over nutrition and obesity results from oxidant stress and chronic inflammation (Vlassara & Uribarri, 2014). However it is less known that a major cause for the inflammation is produced by the consumption of advanced glycation endproducts AGEs derived mainly from the standard western diet (Vlassara & Uribarri, 2014). Vlassara and Uribarri (2014), assert that recent strong epidemiological findings suggest that high concentration of AGEs in the body can be a significant risk factor for the formation of type 1 diabetes; and also for beta cell injury and insulin resistance (IR). High AGEs levels in T2DM patients had been considered to be from endogenous sources such as OS and hyperglycemia until it was discovered that non-diabetic people also could have increased levels of serum AGEs and OS if they consumed a diet high in AGEs (Vlassara & Uribarri, 2014). Vlassara and Uribarri (2014), also indicate that AGEs catabolism is dependent on tissue antioxidant reserves, macromolecular turnover, and receptor mediated AGE degradation, prior to being eliminated by the kidneys.

Two types of AGEs cellular receptors are known: RAGE, and AGER1 (Vlassara & Uribarri, 2014). RAGE is considered to maintain and promote cell activation and tissue injury in the presence of elevated OS (Vlassara & Uribarri, 2014). AGER1 binds and degrades AGEs, and protects against OS injury. Studies of AGER1 on transduce cells and transgenic mice have shown AGER1 to contain many anti-inflammatory and antioxidant properties (Vlassara &
Uribarri, 2014). AGEs induce AGER1, however a constant production of external AGEs reduces or depletes it. This creates a surplus of oxidative stress which in turn increases inflammation via RAGE, TLR4, EGFR, and other receptors (Vlassara & Uribarri, 2014). Thus we can say that AGER1 is an anti-AGE receptor and is involved in the removal of AGEs and is characterized also by the maintenance of host defenses controlling AGEs pro-inflammatory effects (Vlassara & Uribarri, 2014). The balance between these two receptors is critical for OS homeostasis or the advancement to diabetes accelerating ageing (Vlassara & Uribarri, 2014).

Recent well-controlled cellular and animal studies suggest that a chronic exogenous overload of oxidant AGEs can create B- cell injury and thus the onset of type1 diabetes and T2DM and the undesirable health consequences they bring (Vlassara & Uribarri, 2014). Lifestyle in food preparation changes are suggested by Vlassara and Uribarri (2014), in order to reduce the ingestion of AGEs in food thus reducing their levels in blood serum. For instance they recommend to use low-heat and high humidity when cooking such as instead of frying, grilling, or roasting, we should do steaming, stewing and poaching, etc. Also we should avoid the use of highly processed pre-packaged and fast foods (Vlassara & Uribarri, 2014). Vlassara and Uribarri (2014), also mention that several investigators have suggested the use of antioxidants as anti-AGEs including, vitamin E, N-acetyl cysteine, taurine, alpha lipoic acid, penicillamine, nicanartine, and others. In a new study an agent named sevelamer carbonate has been introduced and has reported excellent results (Vlassara & Uribarri, 2014). This is a non-absorbable negatively charged polymer that is known for its phosphate-binding capacity. This agent in addition to binding phosphates can also bind AGEs in a Ph-dependent manner, and possibly trap AGEs in the gut (Vlassara & Uribarri, 2014). After two months of trials sevelamer carbonate showed a reduction of circulating AGEs and also the markers of OS and inflammation in diabetic
patients with chronic kidney disease. Furthermore it also restored AGER1 to normal levels (Vlassara & Uribarri, 2014). If high levels of AGEs can be controlled with certain type of treatment, be it via antioxidant therapy or by other means then the progression or acceleration of ageing can be slowed. The authors suggest that more studies are necessary to prove the efficacy of this treatment.

In another study Nowotny et al. (2015) explain that the formation of ROS, reactive oxygen species, is an inevitable result of metabolism and the main source of ROS in mammalian cells is the dripping of electrons from the mitochondrial respiratory chain and their transfer to molecular oxygen which results in the formation of the superoxide anion O2- that together with hydrogen peroxide H2O2, and nitric oxide NO is considered to be one of the main primary ROS. These ROS are the leading substances in the formation of oxidative stress (Nowotny et al., 2015). Therefore the body needs and creates antioxidant defenses in order to counterattack the constant production of ROS (Nowotny et al., 2015). Nowotny et al. (2015) explains that the antioxidant cell repair machinery presents three possible lines of defenses which entail a first line composed of low molecular ROS scavenger antioxidants that include, vitamin C, E, carotenoids, flavonoids, etc. A second line of defense is comprised of antioxidative enzymes that include, catalase, glutathione peroxidase, ferritin, transferrin, etc (Nowotny et al., 2015). And the third line of defense includes “restoring enzymes” that are capable of restoring oxidatively modified amino acids, such as methionine sulfoxide reductase, proteasome, DNA/ases, RNA/ases, etc (Nowotny et al., 2015). If both the cell’s antioxidative machinery is overwhelmed and the cellular redox-signaling is disturbed by the ROS concentrations, then the cell enter the stage called “oxidative stress”. This condition induced by the concentration of high amounts of ROS in the body is the main cause of several pathologies including diabetes which in turn promotes
cellular ageing causing DNA damages (Nowotny et al., 2015). Another illness in the group of pathologies affected by AGEs stimulation is cardiovascular disease or CVD.

**AGES and Cardiovascular Disease**

Experimental data suggests that AGEs may play a role in the formation of cardiovascular disease or CVD, particularly in type 2 diabetes patients. Although some other data give inconclusive reports about this correlation (Hanssen et al., 2015). In a cohort study conducted by Hanssen et al. (2015), it was found that there is relation between high levels of AGEs and the incidence of cardiovascular events in individuals without prior cardiovascular problems. It was also found that there was an incidence of cardiovascular events in individuals with prior cardiovascular problems (Hanssen et al., 2015). Hanssen et al. (2015) explain that one of the suspected culprits in vascular stiffening formation is pentosidine, which is an AGES adduct. It also has been discovered in human studies that AGEs accumulate in atherosclerotic plaques (Hanssen et al., 2015). Hanssen et al. (2015) also assert that AGEs were found to be more common in rupture-prone plaques than in more stable ones. Which suggest an association between inflammation and the development of a necrotic corpus in advanced atherosclerosis (Hanssen et al., 2015). This relation of AGES formation and the development of inflammation in atherosclerosis may strongly indicate that AGES play an important role in the onset of cardiovascular disease CVD (Hanssen et al., 2015). Hanssen et al. (2015) cohort study concluded that high plasma AGES are closely associated with incident cardiovascular events in individuals with T2DM and that these results underline the potential importance of AGES in CVD (Hanssen et al., 2015). Since diabetes has been linked to be an important factor in ageing progression a relation between CVD formation in T2DM and ageing is reasonable.
In another study it was found that AGEs may be implicated in the development of coronary artery calcification, CAC. Van Eupen Et al., (2013) studied the relationship between plasma AGEs in association with type 1 diabetes mellitus T1DM and CAC. During the study it was shown that individuals with T1DM had higher plasma levels of pentosidine, Ne-(carboxymethyl) lysine or CML, and Ne-(carboxymethyl) lysine or CEL (Van Eupen et al., 2013). Pentosidine is probably one of the most important AGEs in the body (Van Eupen et al., 2013). It is a unique substance that can be formed by the reaction of lysine and arginine, forming a type of fluorescence crosslink with several carbohydrates precursors such as glucose, ribose, ascorbic acid, etc. (Van Eupen et al., 2013). It is thought that AGEs such as pentosidine are active intermediates in the cross-linking of proteins and the formation of reactive oxygen species ROS (Van Eupen et al., 2013). The study concluded that there was a positive association between pentosidine and CAC in T1DM and that these results may indicate that AGEs are possibly related in the development of CAC in individuals with T1DM (Van Eupen et al., 2013). This conclusion in the study suggests definitively a link between AGEs and CVD in an illness such as coronary artery calcification CAC. The connection of CVD and ageing is then found to be very obvious because of the relation of AGEs in the stimulation of ageing already discussed.

AGEs has also been implicated in several other conditions. Some of these conditions are independent risk factors in the development of diseases such as heart disease, diabetes and others which we have already discussed.

**AGEs and other Diseases**

AGEs has been also implicated in the onset of several other diseases. In *Atherosclerosis*, Den Dekker et al., (2013), contend that AGEs may be involved in the development of atherosclerosis beyond diabetes and renal disease. In a study conducted by Den Dekker et al.,
(2013), it was found that skin autofluorescence or skin AF is associated with subclinical and clinical atherosclerosis. Skin AF is a non-invasive marker for AGEs. This study found a close relationship between AGEs and atherosclerosis due to the high presence of skin AF in atherosclerotic patients independently of diabetes and renal function (Den Dekker et al., 2013). The study presented some conclusions. It indicated that skin AF was found to be increased in documented sub-clinical and clinical atherosclerosis, independent of known risk factors such as diabetes and renal disease and this data suggests that AGEs may be a factor in the onset of atherosclerosis (Den Dekker, et al., 2013). Atherosclerosis as we have already discussed is also implicated in the acceleration of ageing. Another risk factor thought to be affected by the progression of AGEs in the body is **hypertension**.

Bauman (2012), made a review of several studies that investigated the relationship between AGEs and **hypertension** and cardiovascular disease and found that the clinical data suggests that the AGE-RAGE axis does not support evidence for the role of AGEs in hypertension but instead it does provide evidence for a role of AGEs in **vascular disease**, which includes macrocirculation and microcirculation. The author of the study suggests that better conducted trials are necessary to elucidate the correlation between AGEs and the circulatory system and its potential role in hypertension (Bauman, 2012). **Chronic renal disease** is also considered an illness affected by AGEs and its accumulation in the body.

Diabetic nephropathy is the leading cause of **chronic renal disease** and also of cardiovascular mortality, and evidence suggests that chronic hyperglycemia is the main cause of its progression, which in turn is the consequence of the production and accumulation of AGEs (Gallo et al., 2014). Gallo et al. (2014), conducted a study in order to prove the use of Lysozyme, which is a human enzyme to reduce the incidence of AGEs in diabetic nephropathy. The study
concluded that the protective action of lysozyme on the nephrotoxic effects of AGEs may depend in part on its ability to prevent the production and release of inflammatory mediators such as IL-6 and to reduce macrophage concentrations in the inflammatory sites (Gallo et al., 2014). Since this illness is related to diabetes and we already know that diabetes is a factor in the stimulation of aging, this fact then suggests that chronic renal disease is also involved in the acceleration of ageing. One illness that is thought to be caused by the ageing process is **age related macular degeneration or AMD**, one of the leading causes of blindness in western societies (Lin et al., 2013). AGEs has also been implicated in the stimulation and early development of this degenerative eye disease (Lin et al., 2013).

In a study by Lin et al. (2013), the relationship of AGEs and **age related macular degeneration or AMD** was investigated. The study investigated the effects of AGEs stimulation on pro- and anti-inflammatory pathways in primary culture of human retinal pigment epithelial cells or RPE. The investigation found that the pathways and novel genes identified in the study demonstrated inflammation as a key response to AGEs stimulation in primary culture of human RPE, and identified chemokine CXCL11 as a possible AGEs agent associated with the pathogenesis of AMD (Lin et al., 2013). There is a possible incidence of AGEs in AMD based on these strong findings. However the authors of this study still consider that the etiology of AMD is still not very clear and because it may well be a multifactorial disease it is necessary to conduct more studies in order to explain all the relationships of AGEs and AMD other pathological factors (Lin et al., 2013).

Finally it is very important to discuss how food is transformed into AGEs and the different preventive measures we can initiate using food as antioxidant agents to reduce AGEs accumulation in the body.
Food and AGEs

AGEs is the byproduct of the heating process of foods. This is accomplished by Maillard-reactions after the initial binding of aldehydes with amines or amides in heated foods or living organisms (Poulsen et al., 2013). A Maillard-reaction is a chemical process that involves amino acids and reducing sugars that gives browned foods its desirable flavor i.e. steaks, breads, etc. and it is obtained using heat at temperatures above 140 grades Centigrade or approximately 285 grades Fahrenheit (Poulsen et al., 2013). The mechanism of formation may include ionic as well as oxidative and radical pathways and the reactions start within proteins to form high molecular weight AGEs or HMW-AGEs or with small molecules to form low-molecular weight AGEs or LMW-AGEs (Poulsen et al., 2014). It is known that all free amino acids form AGEs but we must consider lysine or arginine side chains to dominate AGEs formation within proteins (Poulsen et al., 2013). Only LMW AGEs including peptide-bound forms, and carbonyls may be absorbed from the gut and are contributors to the formation of AGEs and some AGEs interact with specific pro-or anti-inflammatory receptors (Poulsen et al., 2013).

Many foods which contain high antioxidant levels are recommended to eat to counterattack the ill effects of AGEs. Harris et al., (2014), studied the benefits of wild berries in the management of chronic diseases such as cardio- and cerebrovascular disease, diabetes, and Alzheimer’s disease which are affected by the formation of AGEs. Harris et al., (2014), found that two related pathophysiological features common to many of these conditions are oxidative stress and the accumulation of advanced glycation endproducts AGEs. In their study Harris et al., (2014) encountered a reduction of AGEs formation in all the different samplings of wild berries extracts they used including those with phenolic and anthocyanin content and the reduction was a concentration-dependent manner of both extracts, being the phenols the more positive ones than
the anthocyanin group. These findings suggest that a diet rich in phenolic metabolites from wild berries and other different foods may help reduce the concentration of the formation of AGEs and their incidence in chronic diseases and the aging process (Harris et al., 2014).

**DISCUSSION**

It appears that there is a close relation between the metabolic syndrome, inflammation, AGEs, and oxidative stress according to all the studies presented in the result section. Furthermore it seems that MetS, inflammation and AGEs are the result of some of the diseases that they are purported to be the cause of or etiology (Vlassara & Uribarri, 2014). Both the metabolic syndrome and AGEs mediate their action through the creation of an inflammatory condition prior to the development of a disorder such as cardiovascular disease, diabetes or cancer (Western Washington University, 2014). However many of the studies presented also consider, for instance, inflammation as the result, of disorders such as diabetes or cancer induced by an infection or overnutrition (Esposito & Giugliano, 2004). There is also present in the studies the notion that genetics is involved in the formation of many of the diseases thought to be caused by either MetS or AGEs (Western Washington University, 2014). For a diabetic for instance, there is the inability to properly metabolize sugar. But is this the result of the metabolic syndrome, AGEs or a genetic disorder? (Nowotny, 2015). Apparently in a case like diabetes mellitus type 1, one could think that a genetic problem is the main cause of this disorder because most of the symptoms appear at an early age and in order to be the result of MetS or AGEs it is necessary that the diabetic patient had been under the inflammatory condition for a long period of time for the condition to develop according to the different investigations researched (Nowotny et al, 2015). But in diabetes mellitus type 2 one could think that it is possible that its genesis may be due to a metabolic imbalance produced by overnutrition or an insulin dysfunction.
rather than a genetic disorder (Nowotny, 2015). However a genetic disorder can be expressed later in life and the diabetic condition may be the result of this genetic disorder and not from any of the known causes such as MetS or AGEs (Pizzorno & Murray, 2013). Some of the studies researched consider that more research is needed in order to clarify this situation. The author believes that even though there is a clear incidence of MetS and AGEs in the onset of many of the so called metabolic diseases it is necessary to draw a line between those disorders that are generated by metabolic problems due to lifestyles that include environmental, social, feeding habits, and other aspects that may influence the onset of some of these pathologies, and the development of the same illnesses due to DNA disorders or organ malformations produced from external factors or genetics.

But considering the overwhelming amount of studies that indicate that there is a close link between many diseases and MetS or AGEs it is necessary to analyze closely why these relationships are formed. Let’s begin by saying that most of the metabolic diseases that stem from either MetS or AGEs can be resolved with changes that involve personal or individual resolutions (Western Washington University, 2014). The western diet is considered by many researchers as the main culprit in the onset of MetS or AGEs, and as such they can be stopped by doing the necessary changes to these lifestyles (Western Washington University, 2014). The researches presented agree that with changes to western lifestyles in all aspects it is possible to reduce and even eliminate the onset of the so called metabolic disorders (Esposito & Giugliano, 2004). Hence a personal decision to change needs to be put into action in order to reverse the ill conditions created by the western lifestyles. This decision entails great will power and discipline. It is not an easy task to change feeding habits and life conditions overnight and therefore it conveys a hard and long process of adjustment (Western Washington University, 2014). It can be
assumed that habits are more like addictions in which only constant and strong desire to make the chances necessary to attain the results will lead us to success.

Ageing is definitely affected by MetS and AGEs. An increasing number of studies confirm that both disorders have a strong incidence in the acceleration of ageing (Bonomini et al., 2015). All of the data presented suggest a clear incidence of MetS and AGEs in the damage of tissue and cells generating a cascade of biological malfunctions in the human body thus ensuing the development of many chronic diseases which affect humans in different stages of life (Bonomini et al., 2015).

Diabetes appears to be one of the diseases in which MetS and AGEs have a higher implication (Western Washington University, 2014). Extensive research has been conducted to explain the pathological mechanism that can lead to the onset and progression of T1DM and T2DM and a great amount of these investigations center their focus on MetS and AGEs formation and accumulation in patients with T1DM and T2DM (Nowotny et al., 2015). Increasing concentrations of different types of MetS and AGEs in serum and tissue of diabetic patients and the association of MetS and AGEs with diabetic complications in several studies make MetS and AGEs as the biomarkers and even predictors for diabetes complications (Vlassara & Uribarri, 2014).

An increasing number of the research findings establish a close relationship between food and MetS and AGEs formation and hence the onset of several diseases. The western diet has a big impact in the formation of both MetS and AGEs (Western Washington University, 2014). Processed and fast food intake is a daily occurrence in western societies especially the US. The high intake of AGEs concentrated foods such as fried chicken, hotdogs, French fries, well-cooked steaks, etc. has resulted in a big incidence of AGEs and MetS related diseases, especially
CVD as the leading cause of death in the US and the western world (Harris et al., 2014). The low ingestion of fresh fruits and fresh vegetables with their antioxidant content in the western diet is another culprit of MetS and AGEs formation (Harris et al., 2014). Recent studies have shown the positive action of antioxidants in restraining the formation of MetS and AGEs (Nowotny et al., 2015). One of the studies of this research includes antioxidants as the first line of defense exerted by the body in three ways using vitamins i.e. vitamin C, E, etc., against AGEs formation followed by antioxidant enzymes such as catalase, ferritin, glutathione, etc., and restoring antioxidant enzymes to counterattack the effects of AGEs (Nowotny et al., 2015). And they can be applied to MetS as well. Lifestyle changes should be put into practice in order to establish a healthy eating pattern that includes low heated foods, high moisture cooking, ingestion of fresh fruits and vegetables and the avoidance of packaged foods, fast foods, and preserved and fried foods (Vlassara & Uribarri, 2014).

**CONCLUSIONS AND RECOMMENDATIONS.**

One of the most important aspects the author has found during the preceding research is that after reading many investigations about the metabolic syndrome (MetS) and advanced glycation end-products (AGEs), the majority of them agree that both conditions lead to the formation of illnesses such as diabetes, cardiovascular disease, and others no less important like cancer or obesity, which in turn induce the acceleration of ageing. However the mechanisms through which either MetS or AGEs carry out the onset of these diseases are not clear to some researchers.

Inflammation is the main culprit according to researchers and is considered the leading cause of the majority of the above mentioned diseases. Both MetS and AGEs create inflammatory conditions in the body that induce metabolic illnesses (Uribarri et al., 2010).
Western Washington University (2014) explains that inflammation is closely linked to MetS. And is also considered an independent risk factor in the development of diseases such as heart disease, stroke, diabetes, and obesity. If we develop a condition called low-grade inflammation or chronic inflammation it is usually the result of our bad lifestyles (although genetics and the environment may also play a role) (Western Washington University, 2014). This include poor eating habits that contain refined foods, lots of dense carbohydrates, which elevate blood sugar levels (Western Washington University, 2014). This diet is also made up of large amounts of processed foods, and the ingestion of sugar in different forms used in food processing is one of the main factors in the formation of low-grade inflammation (Western Washington University, 2014). Also low or no consumption of fresh fruits and vegetables together with little or no physical activity are hallmarks of people with either MetS or AGEs or both. All these elements constitute the so called western diet and lifestyle that is prevalent in the majority of western societies, especially in the United States.

It is important to note that inflammation is a necessary process in our body. It is a reaction of our immune system to a stimuli, such as when we are injured or an infection develops in our body (Harvard Medical School, 2007). But when inflammation becomes a chronic disorder in our body it creates the feeding ground for the onset of many metabolic diseases (Harvard Medical School, 2007). Thus the importance of preventing the generation of this chronic state of inflammation should be of paramount importance to attain permanent health. As was discussed previously the formation of chronic inflammation can be prevented with personal interventions, that include changes in our lifestyles involving many aspects. Our feeding habits are at the top of the factors that should be changed radically in order to begin the healing process.
The western diet is comprised mostly of processed refined foods, with high sugar content in different forms, low ingestion of fresh produce, including vegetables and fruits, well-cooked or overcooked foods, a practice that involves overheating our food causing Advanced Glycation End-products (AGEs), lack of exercise, and stressful social conditions (Western Washington University, 2014). All these factors should be addressed once we start the changing process. It is also recommended to supplement with antioxidants such as vitamin C, E, and B complex, which exert an action in metabolism and cognitive functions especially in the elderly (Nowotny et al., 2015). One of the B vitamins important in reducing the risk of cardiovascular disease is vitamin B6 (pyridoxine) which together with B12 (cobalamin) and folic acid lower the concentrations of a protein metabolic by-product called homocysteine (Stengler 2010). This metabolite is known to cause heart disease and is thought to be involved in approximately 10% of all heart attacks (Stengler, 2010). Vitamins B are also known to be involved in treating anemia, diabetes, Alzheimer’s, and other health problems where MetS or AGEs are considered the culprits (Stengler, 2010).

The study of the metabolic syndrome (MetS) and Advanced Glycation End-products (AGEs), should be recognized as an important advancement in the discovery of the etiology of devastating and prevalent diseases such as diabetes, cancer, cardiovascular disease, and obesity among others emanating from metabolic disorders that lead to an acceleration in ageing. The link between these above mentioned diseases and MetS, AGEs and the stimulation of ageing has already been established. But there are still intrinsic aspects of this connection that need better discerning so we can build strong evidences that will eventually help scientist develop suitable protocols of prevention and treatment. The incidence of genetics and the environment in the development of these disorders are factors that play a role in their genesis but where is the fine
line that divides when MetS or AGEs are the result of genetics, environment, diet, lifestyles or other possible agent? Meanwhile we should urge Federal Agencies such as the FDA (Food and Drug Administration); the USDA (United States Department of Agriculture) or the CDC (Center for Disease Control), that it is important to initiate campaigns to make the general population aware of the dangers involved in current lifestyles and the western diet. One campaign should be labeling (like in cigarrete) all processed foods advising of all the dangers involved in consuming these type of food. Informing the public of the effects of additives such as sodium, dextrose, corn syrup, etc. in human health.

The food industry needs to change the way food is produced today. In order to help reduce the incidence of the illnesses created by the western diet as it has been proven by many researchers. Public awareness is the strongest weapon we can have in this struggle. Because the more aware people are about these dangers in their present health the better the final outcome. Sooner or later public concern will determine the change from processed foods to healthier products that the food industry engineering will have to develop to satisfy the growing demand. Also on the personal level the government should initiate campaigns starting at schools to inform teachers, students, and parents of the need for healthier eating habits; the importance of keeping daily physical activity; improve the social environment where people live with activities that involve sports, or socio-cultural gatherings that will help in the management of stress and the hardships of daily life. The betterment of all these aspects in our daily routine will help us live, happier, healthier, more productive, and longer lives.
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