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Review

The effects of inflammation, aging and oxidative stress on the pathogenesis of diabetes mellitus (type 2 diabetes)

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ABSTRACT

Diabetes mellitus is seen to be prevalent among the different epidemics. The prevalence rate of the diabetes mellitus is seen to be increasing in different regions of the world. Type 2 diabetes mellitus is the most common form of the disease that causes the defect in the production of insulin. It is associated with the disruption in the metabolism of fat, proteins and carbohydrates. Different complications that are associated with T2DM includes the retinopathy, neuropathy, nephropathy and weakness and other issues. Due to the loss of the function of the insulin, the metabolism is disturbed. . It is needed to consider the effects of inflammation aging and the oxidative stress on the diabetes mellitus. Therefore this review has dealt with this particular issue in great detail. The predominant aim of this review was to evaluate the effects of inflammation aging and oxidative stress on the T2DM. It was achieved through correlating and comparing the studies of different researchers. This review article has reviewed this topic in great detail considering the different researches related to the inflammation aging, oxidative stress and their impact on the diabetes mellitus.

1. Introduction

A group of chronic diseases being characterized by hyperglycemia is referred to as diabetes. Hyperglycemia can render direct as well as indirect effects on the human vascular tree; thus, the importance of controlling the body from hyperglycemia cannot be neglected. The predominant source of mortality and morbidity intype 1 and type2diabetesis the impact created by hyperglycemia on the human vascular tree. It is regarded as the medical condition which potentially results in high rates of mortality and illness [5]. Conventionally, the injurious effects of hyperglycemia are categorized into two parts namely macrovascular complications and microvascular complications. The microvascular complications include retinopathy, diabetic nephropathy, and neuropathy, whereas, the macrovascular complications include stroke, coronary artery disease and peripheral arterial disease [2]. However, some of the other complications evident in the individuals with diabetes include depression and erectile dysfunction (ED). Depression is associated with poorer glycemic control, health complications, decreased the quality of life and increased healthcare costs, and whereas, erectile dysfunction (ED) is the complication which is conventionally exhibited by diabetic men. Risk factors include increasing age, duration of diabetes, poor glycemic control, cigarette smoking, hypertension, dyslipidemia and cardiovascular disease. Protein glycation plays an important role in the development of the pathogenesis of different complications of the diabetes such as nephropathy, retinopathy, aging and others. The enzyme aldose reductase is involved in the canalization of the reduction of the glucose into sorbitol in the polyol pathway and its role in the development of the complications of diabetic nephropathy are considered in detailed. There are different signaling pathways in the cells that are responsible for the transmission of the information in the cell. There are two types of cell signaling; most of them respond to the external stimuli that are initiated at the cellular surface in the form of different chemical signals like the neurotransmitter, growth factors or the hormones. These are received through receptors at the side line of the different cells that play their role just like an antennae that are submerged into the plasma membraneAMPK is a conserved protein a serine/therionine kinase that causes the activation of the insulin −sensitization effects thus making it as an effective target for T2D. Basically this enzyme is an energy-sensing enzyme which is activated in the condition of low energy levels and the different signals cause the stimulation of the glucose

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uptake in the different skeletal muscles, adipose tissues and the fatty acids oxidation (see Tables 1 and 2, Figs. 1 and 2).

2. Different complications of diabetes

The acute (metabolic) and chronic (systematic) complications of diabetes mellitus are major growing causes of hospital admissions, disability, and premature death.

2.1. Metabolic acute complications

The metabolic acute complications are relatively short-term complications and include ketoacidosis and hyperosmolar non-ketonic coma. It is being further postulated that the acute complications include diabetic keto acidoses (DKA) and non-ketotic hyper-osmolar state (NKHS). The latter is prevalent in the people withT2DM, whereas, the former is mainly associated with the individuals with type 1 diabetes mellitus. However, both of the disorders are correlated with the changing mental state, deficiency of insulin and depletion of volume. Non-ketotic hyper-osmolar state is predominantly exhibited by the elderly people with T2DM. The neurological symptoms of the state are seizure, lethargy, changing mental state and obtundation, whereas, the prominent characteristics of the state include orthostatic hypotension and polyuria. Normally, the underlying sources of NKHS include the inadequate fluid intake and deficiency of insulin. The insulin deficiency also significantly contributes to hyperglycemia. The osmotic dieresis induction by the hyperglycemia leads to intense depletion of the intravascular volume. Additionally, a study suggests that the adolescents with type2 diabetes are more likely to exhibit several acute complications such as hyperglycaemic hyperosmolar state and diabetic ketoacidoses [6]. These complications contribute towards short-term risks associated with mortality and morbidity.

2.2. Systemic late complications

These complications are often referred to as chronic complications of diabetes mellitus. These complications hold the potential to create an extensive impact on the organ systems of the body. Moreover, they are responsible for the high rate of mortality and morbidity [3]. The chronic complications are conventionally categorized into two complications namely vascular complications and non-vascular complications. The vascular complications are further subcategorized into microvascular and macrovascular complications. The microvascular complications include neuropathy, nephropathy, and retinopathy, whereas, the macrovascular complications include cerebrovascular disease (CVA), coronary artery disease (CAD) and peripheral vascular disease (PVD). Similarly [4], agrees that numerous studies acknowledge the association of diabetes with coronary heart disease. Additionally, the researcher also postulated that the chances that an individual will develop cardiovascular diseases inevitably increases with the presence of diabetes. The sexual dysfunction, skin diseases, and gastroporesis are also included in the nonvascular complications. The examples of the other macrovascular complications also include peripheral vascular disease, ischemic cardiomyopathy and cerebrovascular disease [5]. These complications might even possibly lead to death in adverse circumstances. The microvascular complications namely neuropathy, nephropathy and retinopathy are associated with neurological lesions, kidney diseases and damage to vision respectively. These complications are the common causes of the prevalence of chronic kidney diseases, irreversible blindness, and non-traumatic leg amputations.

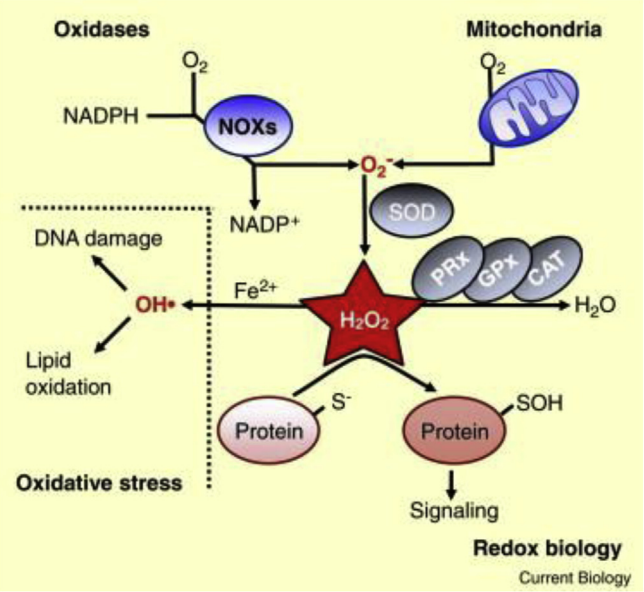

Fig. 1. The mechanism of redox signaling.

Table 1
Diabetes mellitus and age as risk factors for oxidative stress.

	OR	CI	P Value
Diabetes mellitus	2.1	1.2–3.8	0.015
Age (≥60 years)	1.6	1.1–3.3	0.020
Interaction (diabetes mellitus by age)	3.1	1.3–7.5	0.014

(Source: Mendoza-Núñez et al., 2011)

3. Pathophysiology of Type2 diabetes mellitus

The chronic hyperglycemic condition leading to the group of metabolic disorders is referred to as diabetes. The chronic hyperglycemic condition is the outcome of defects in the levels of insulin. Similarly [8], agrees by stating that the abnormal insulin secretion and insulin action is exhibited by the individuals with T2DM. The combination of genetic factors associated with the impaired insulin

Table 2
Selected pro-inflammatory cytokine gene polymorphisms.

Condition	SNP
BMI	IL-6 -174C > G, IL6 CA rep., TNFα −308G > A
IGT	IL-6 -174C > G
Insulin resistance	IL-6 -174C > G, TNFα −308G > A
Obesity	IL-6 -174C > G, IL6R 394T > G, TNFα −308G > A
T2DM	IL-6 -174C > G, IL6R 48867A > G, TNFα −308G > A, TNFα −863C > A
Diabetic nephropathy	IL-6 -634C > G, IL1β −511C > T

(Source: Badwi et al., 2010)

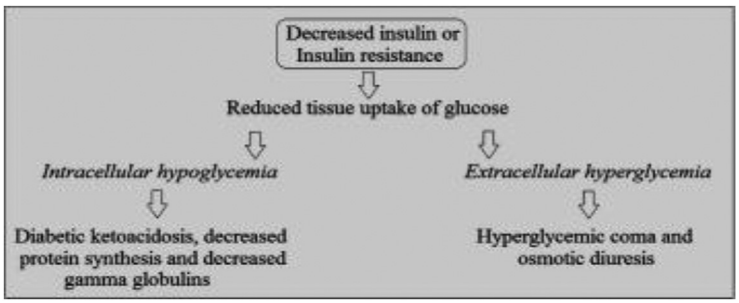

Fig. 2. Insulin resistance (Source: Asmat, Abad, & Ismail, 2016).

secretion, environmental factors and insulin resistance typically accounts for the Type2 (Non-insulin dependent) diabetes. The environmental factors include overeating, aging, obesity, and lack of exercise [7]. The predominant characteristic of type2 diabetes includes lack of need for the insulin which is required for the prevention of ketoacidosis. On the other hand, the type2 diabetes is the most common form of idiopathic diabetes. This type of diabetes is not considered as an autoimmune disorder. Moreover, the genes susceptible to predispose to the type2 diabetes are not yet found in many of the patients of T2DM.

According to the pathophysiology of the T2DM, the characteristics of the T2DM are peripheral insulin resistance, insulin insensitivity, decreasing beta-cell function, and impaired regulation of hepatic glucose production which ultimately leads to pancreatic beta-cell failure. During the fasting conditions which are also referred to as the normal physiological conditions, there are extensive fluctuations in the supply and demand of the concentrations of the plasma glucose. Despite such fluctuations, the concentrations are typically kept in the narrow range through regulating the dynamic interaction between the insulin secretion and tissue sensitivity [7]. Under fasting conditions, the blood used by the brain is being rendered by the liver of an individual which clearly exhibit the independency on the insulin. However, when a person is undergoing through T2DM, the glucose transport to the muscle cells, liver and fat cells is reduced. Hyperglycemia leads to the increase in the rate of the breakdown of the fats [9]. Moreover, the glucagon and hepatic glucose levels are likely to rise under the fasting condition. However, the dysfunction which is caused due to hyperglycemia does not allow the suppression of risen glucagon and hepatic glucose levels through the meal. The hyperglycemia is likely to result from the increased as well as decreased levels of insulin resistance. In the process of insulin release, the incretins are the important mediators. In agreement with the pre-determined pathophysiology of T2DM, the researcherstates that when an individual consumes a meal slightly above the average amount then, defects occur in the glucose homeostasis system [10]. These defects occur to impair the glucose responsiveness of the beta-cell to the meals. The impairment of glucose responsiveness occurs by impairment of insulin response which encourages the rise in the blood glucose level. This glucose level rises into the range of the impaired glucose tolerance (IGT). The insulin resistance and obesity are typically characterized by the excess fatty acids. The rise in the blood glucose levels harmonizes with these excess fatty acids. It further causes an increase in the deterioration of insulin resistance and beta-cell function. Eventually, the blood glucose levels get increased to full-blown diabetes.

The insufficient energy consumption, aging, alcohol drinking, smoking, and obesity are considered as the independent environmental risk factors involved in the pathogenesis of type 2 diabetes. The lack of exercise normally accounts for obesity which is further accompanied by reduced muscle mass and induced insulin resistance. Obesity is also rapidly exhibited by the increasing number of high aged and middle-aged patients. There are some factors which contribute to the obesity and deteriorate the level of glucose tolerance. These factors include a decrease in the dietary fiber intake, increase in fat intake, and increase in simple sugar consumption and a decrease in starch intake.

3.1. Relationship between inflammation and diabetes mellitus

Inflammation is widely inferred as an essential aetiological factor which plays a vital role in the development of insulin resistance which significantly leads to T2DM. It also contributes to the foreseen diabetes complications. This notion has been proposed on the basis of the conclusions being drawn from the different studies which were focused on the association between the development of type2 diabetes, increased levels of circulating acute phase inflammatory markers and the levels of insulin resistance [12]. The major characteristics of the T2DM are various levels of insulin resistance and the relative deficiency in the insulin secretion. The various levels in the development of T2DM are extensively dependent upon different environmental and genetic factors. Obesity is considered as one of the major factors as it is quite directly associated with the development of resistance in inflammatory state and peripheral tissues. The inflammatory responses can either establish a causal relationship in the emergence of T2DM which further contributes to insulin resistance or it may augment through the hyperglycemic state which leads to T2DM complications [13]. Another research directly indicates the involvement of immune system activation and chronic low-grade inflammation in the pathogenesis of T2DM and insulin resistance with accordance to obesity [14]. The development of type2 diabetes and its macrovascular complications involve the risk factors which are systematic inflammatory markers. Some examples of the inflammatory markers include ESR, SLE and ulcerative colitis. Similarly [15], identified the specific role of inflammatory markers by stating that many evidences confirmed the intermediary role of inflammatory markers in the occurrence of Type2 diabetes and its eventual long-term complications. It correlates the occurrence of diabetes with the conditions originating due to inflammatory mechanisms. As far as the positive role of inflammation is concerned, several studies potentially entailed that the inflammatory markers can be utilized to refine the prediction of the risks associated with diabetes. It could further improvise the lifestyle interventions of the people. The outcomes of the study suggested that the inflammation is likely to cause a direct impact on the insulin resistance or blood glucose levels by increasing it significantly.

Numerous studies being conducted in the last few years suggest that risk involved in the development of T2DM is positively linked with the low levels of inflammation [28]. Majority of the studies

mutually agree that the inflammatory responses contribute towards the development of T2DM through the insulin resistance. In turn, due to the presence of hyperglycemia, the insulin resistance might potentially augment and contribute to long-term complications. Some of the epidemiologic studies have explored the relationship of the inflammatory biomarkers with the development of T2DM and its consequent complications. After the synthesis of fatty acids is carried out by adipose tissues, they release tumor necrosis factor-alpha and pro-inflammatory cytokines. The inflammatory markers are quite closely related to the body fats. However, the triggering role of the inflammation in the prevalence of T2DM and its complications are still left unexplored by the researchers [27].

4. Relationship between ROS and inflammation

The regulation of the reactive oxygen species levels can create a significant impact on the disease and health. The examples of reactive oxygen species include free radicals (superoxide/O_2^- and hydroxyl radicals), peroxides (hydrogen peroxide/H_2O_2) and oxygen ions/O_2. The usually occurring metabolic processes in the body give rise to the ROS. When the ROS are maintained at the proper cellular concentrations, they tend to play important cell signing roles. ROS are small molecules but, high in reactivity. The ROS levels are likely to increase with the increase in the cell stress. The relatively high reactive nature of ROS enables its role of modifying the other proteins, lipids or oxygen species. This scenario of modification is referred to as oxidative stress. In order to ensure the proper physiologic functioning of the cell types throughout the body, it is important to maintain the normal cellular ROS concentrations. The pathogenesis of the diverse diseases, for instance, cancer, atherosclerosis, neurodegeneration, and diabetes implicates the decrease scavenging or excess production of the reactive oxygen species [16]. On the other hand, inflammation is regarded as the defensive immune response of the host against the foreign pathogens. This survival strategy property has been evolved by the immune system of the vertebrates. The purpose of this survival strategy is to facilitate the repairing of damaged tissues. Moreover, the inflammation cycle is often accelerated through the lack of proper ROS scavenging. The relationship between the inflammation and ROS is being defined as follows in the several studies: The lack of proper ROS scavenging contributes to the reduction in bioavailable NO which further leads to unchecked exocytosis [45]. The ROS can decrease the NO bioactivity through modifying the protein sites where there are chances of reactions. Moreover, it can even directly interact or inactivate the NO. It helps to reduce the physiologic influence of the NO. The loss of antioxidant activity might lead to decrease in bioavailable NO and increase in endothelial exocytosis. The increase in vascular inflammation and WBC localization is the consequence of increased endothelial exocytosis [16]. The reactive oxygen species (ROS) are referred to as the key signaling molecules which contribute importantly to the progression of the inflammatory disorders. The increase in the production of ROS through polymorphonuclear neutrophils (PMNs) at the inflammation site leads to tissue injury and endothelial dysfunction.

The Reactive oxygen species (ROS) play a vital role in the progression of the inflammatory disorders. The enhanced production of the ROS at the site of inflammation by the polymorphonuclear neutrophils (PMNs) is the key contributors towards tissue injury and endothelial dysfunction. In the passage of inflammatory cells (those cells participating in inflammation) different and macromolecules travelling from the blood to tissue, an important role is being played by the vascular endothelium. The oxidative stress is being produced by the PMNs under the inflammatory conditions. This oxidative stress contributes to opening the inter-endothelial junction. The role of oxidative stress is not just limited to that, it also encourages the inflammatory cells migration around the endothelial barrier [33]. As far as the inflammatory reactions are concerned, the inflammatory reactions also instigate the production of reactive oxygen species (ROS) [34]. Moreover, the researcher also suggest that the reverse process is also possible in which the ROS induce the production of inflammatory reactions. The interactions expressed by the components of these reactions exhibit the synergistic effect. The characteristics of the inflammatory reactions include cellular and vascular events, whereas, the endogenous and exogenous aggressions are the major triggers of the inflammatory reactions. In the inflammatory reactions, the activated leucocytes tend to leave the circulating blood and instead move to the site of aggression. At the aggression site, they release the granules content as well as large supplies of reactive oxygen species. When the effects of the inflammatory reactions are just restricted to the pathogens, they are advantageous for the human beings. If a component of the inflammatory reaction is inadequate, it might possibly lead to adverse bacterial infections. However, in the reverse sequence of the events, the production of ROS during the drug metabolism and irradiation tends to instigate the inflammatory reaction. The inflammatory reactions are induced along with the production of secondary ROS. The chronic ROS production leads to chronic inflammatory reaction between atherosclerosis and endothelium, whereas, the acute ROS production leads to thrombosis. Furthermore, the ROS also holds the potential to control the activity of the inflammatory molecules either negatively or positively [34].

5. Relationship between aging and diabetes mellitus

The rising age encourages the increase in the prevalence level of T2DM and impaired fasting glycemia (IFG). Moreover, the glucose intolerance level also tends to increase with the increase in the age. Some factors are particularly involved in the pathophysiology of impaired glucose intolerance in the elderly people. The predominant factor is that aging instigates the alteration, decrease the insulin sensitivity and insufficiently compensate the beta-cell functional in the course of increasing the insulin resistance. The states which are particularly associated with the aging include increased sensitivity to the apoptosis and reduction in the proliferation capacity of beta-cell.

According to a study conducted by Szoke et al. (2008), the second and first phase of the insulin secretion tends to reduce by around 0.7% annually with the increase in the age. The rate of deterioration of beta-cell function is double in the individuals with impaired glucose tolerance level. However, the insulin sensitivity which is independent of the changes in body composition is not affected by the aging process. The major factors contributing to the insulin resistance are decrease in the lean body mass and increase in the body fat particularly “visceral adipocytes”. Lean body mass is defined as the amount of weight irrespective of the fat. According to the recently proposed studies, the decline in the mitochondrial function associated with the age tends to contribute to insulin resistance in the elderly people. The increase in the intramyocellular and intrahepatocellular lipid content and decrease in the insulin-stimulated glucose uptake was associated with the 40% reduction in the mitochondrial oxidative and phosphorylation function. The research also suggests the existence of relationship between pathophysiological basis of sarcopenia with insulin resistant state, reduced neuronal stimulation, oxidative stress and subclinical inflammation. Sarcopenia is related to the reduction in the muscle and the quality of the mass with the age. It causes the decrease in the bone density, glucose intolerance and the decrease in the tolerance of warm and cold temperatures among the elderly people. It could be said that sarcopenia is most important factor in

aging. These conditions make a significant contribution to the development of the Type2 diabetes as well as the glucose intolerance occurrence [17]. Similarly, the diabetes mellitus in the old age people of 60–65 years or more is gradually becoming a prevalent and alarming public health problem in the developing as well as developed countries. For some of the authors, one old person out of the two old persons is either diabetic or pre-diabetic. On the other hand, some authors proposed that 8 out of 10 people are suffering through dysglycemia [19].

Sarcopenia that promotes the aging is considered to be an importantfactor for the metabolic disorders. These metabolic disorders include type2 diabetes, impaired glucose tolerance level and obesity. Furthermore, according to the reports, the prevalence of the type2 diabetes tends to inflate with the increase in the age and the peak age is suggested to be 60-74. The diabetes itself increases the risk and leads to the multiple age-related diseases for example nonalcoholic fatty liver disease (NAFLD), atherosclerosis, cardiovascular disease (CVD, Parkinson's disease, stroke, Alzheimer disease (AD) and cancer. However, the evidence such as by researchers suggests thatType 3 diabetes particularly accounts for the Alzheimer's disease [42]. The pathogenesis of Type2 diabetes in the aging process exhibit two major characteristics namely impaired insulin secretion from beta-cells and peripheral insulin resistance [18]. Another study also states that the prevalence and incidences of impaired glucose tolerance (IGT) and Type2 diabetes are more common in the older people as compared to younger people. However, the mechanism associated with the age-related glucose intolerance level is still not completely clear. The interaction of various factors associated with the aging process is likely to contribute to the changing levels of glucose tolerance in the people. These factors include decreased physical activity, increased adiposity, insulin secretory defects which are associated with the aging process, coexisting illnesses and medications. With the advancing age, reduced hepatic sensitivity to insulin's action during suppressing the glucose output, increased insensitivity to the insulin actions are likely to occur [20].

6. Relationship between ROS and aging

An intricate process which features the increase in mortality and continuous decline in the physiological functions of an individual are regarded as aging [46]. Similarly, it is a complex process which usually occurs in the muscles and is characterized by the reduction in the velocity of concentration, mass and strength [29]. The major impact of aging on the muscle is called sacropenia. It is a biological process which features the progressive decline in the biochemical and physiological functions of the major systems. The intricate process of aging is often followed by the advent of pathological diseases. Despite the fact that the process of aging is conserved universally, the molecular mechanisms which underlie the aging process are still vague. Many theories have been previously proposed by different scholars and researchers such as mitochondrial theories of aging and free radical theory of aging. Both of these mentioned theories hypothesize that one of the major causes of aging is the cumulative damage caused by the reactive oxygen species (ROS) on the mitochondrial DNA (mtDNA) and mitochondria. However, it is also being postulated by the research that the succinct relationship between the mitochondrial dysfunction, aging and damaged associated with ROS is still not clarified by the several studies [23]. A conventional view in the free radical biology field suggest that the accumulated damage posed by the reactive oxygen species creates a partly effect on the process of aging. However, still many of the recent researchers of this field are striving to explore the beneficial effects of ROS and superoxide radical. Therefore, these reactive oxygen species are considered as being involved in the cellular regulation by playing the role of redox signals [24]. Furthermore, the high levels of Reactive Nitrosative Species (RNS) and/or Reactive Oxygen Species (ROS) are also extensively correlated with the aging rate.

The specific increases in the levels of reactive oxygen species are potentially important for the maintenance and induction of cell senescence process. Many of the studies intensely studied the causal relationship between cell senescence, aging, ROS and pathologies related to aging. The development of human aging is the result of the accumulation of social, physical and environmental factors. Some of the theories tend to associate various factors with the rate of aging, such as high production of ROS and changes of metabolic control. The low levels of reactive oxygen species are also associated with the elongation of the life span of the organism [25]. The current biological programmed theories on ageing include Endocrine theory and immunological theory; however, neither of them proves to be satisfactory [48]. The immunological theory suggests that the immune system is being programmed in such a way that it would inevitably be prone to infectious diseases and eventually death. On the other hand, Endocrine theory states that the pace of aging is generally controlled by the hormones. Another particular theory named as the free radical theory was proposed by Denham Harman. The theory postulated that aging is the outcome of the accumulation of adverse effects generated by the free radicals. Moreover, the induced ability to cope with the cellular damage by the ROS also plays a vital role in determining the lifespan of the organism. The outcomes of the study were in agreement with the suggested free radical theory. The results showed the increased ROS production by the mitochondria in the aged tissues. The results suggested that the production of ROS is relatively high in the elderly people. It also suggested that the aging process is being often contributed by the progressive accumulation of oxidative DNA damage. Many of the studies collectively suggest that the interplay between the protective antioxidant responses and ROS helps to determine the lifespan and aging.

The reactive oxygen species play an important role in the stem cell aging. The stem cells named as adult stem cells have the ability of differentiation and self-renewal. Throughout the lifetime of an organism, these cells play a vital role in the regenerative repair and normal homeostatic maintenance of the tissues. The self-renewal ability of the adult stem cells tends to reduce to reduce with the increase in the age. It suggested that the decline in the function of stem cells play a vital part in the process of aging. The evidence gathered from new studies suggests that the deregulated formation of the reactive oxygen species moves the progenitor and stem cells into the premature senescence. It potentially hinders the homeostasis of the normal tissues. Generally, the relationship between the aging and the reactive oxygen species is defined as follows: The imbalance between antioxidant defenses and the increased production of the reactive oxygen species (ROS) significantly contributes to the aging process. Historically, the mitochondrial ROS production and oxidative damage have been associated with the aging and age-related diseases for quite a long time. The two major theories of aging namely intrinsic (programmed) and extrinsic (error) theories have been the topic of controversial discussion for a long time. The intrinsic theory states that the aging is partly under the control of the genetics [30]. The intrinsic aging theory suggests that the effects of the intrinsic aging are predominantly caused due to the internal factors. The intrinsic aging is often referred to as the chronological aging, whereas, the extrinsic aging is referred as the photoaging. According to the intrinsic theory, the declines in the tissue function associated with the progressive age are the result of the homeostatic changes in the biological processes. These conventionally occur in the absence of the disease. On the other hand, the extrinsic model suggests that the aging is the result of the

environmental insults. This environmental insult tends to gradually decline the tissue functioning [31].

7. Oxidative stress and ROS

The first definition of oxidative stress was proposed by Sies (1985) which stated that oxidative stress is the disturbance being created in the pro-oxidant to antioxidant which leads to damage [43]. The disturbance is in the favor of pro-oxidant. Another definition of oxidative stress states that oxidative stress is an excessive amount of the reactive oxygen species. This excessive amount is the net result of the variance in the production and destruction of ROS. The increase in the production of the free radicals and/or the decrease in the physiological acidity of the antioxidant defenses potentially contribute to the oxidative stress. These antioxidant defenses are conducted against the free radicals. As far as the relationship between the oxidative stress and ROS is concerned, the level of oxidative stress being experienced by the cell is the function of the activity carried out by the reaction generating system of ROS as well as the scavenging system of the ROS. Basically, oxidative stress can be defined as the state which characterizes the production of ROS. The formation of excessive ROS can lead to oxidative stress which further damages the cells. The cell damage can culminate the death of the cells [21]. Hence, the cells usually have the antioxidant networks which enable the scavenging of excessive produced ROS. Similarly, another study postulates the same mechanism that the overproduction of ROS cellular affects the intrinsic antioxidant capacity. It further contributes to the oxidative stress which may cause the damage to tissue or biomolecules of the normal cells. Other than the excessive production of ROS, the factors contributing to the oxidative stress are impaired antioxidant system and mitochondrial dysfunction [22].

The oxidative stress is often associated with the increase in the intracellular levels of reactive oxygen species (ROS) which can cause potential damage to lipids, DNA and proteins. It is a phenomenon that arises due to the disparity in the elimination and production of the ROS. Moreover, this phenomenon contributes towards the development of T2DM. Oxidative stress is also quite related to the insulin resistance. Some studies also suggest that oxidative stress also holds the responsibility to alter the intracellular signaling pathways which further induces insulin resistance [26].

Various enzymes potentially contribute to the cellular protection against the unwanted oxidation and these enzymes include glutathione peroxidase, catalase and superoxide dismutase (SOD). The elevated antioxidant defense also helps to eliminate the damaging effects of ROS and it includes catalase, superoxide dismutase, and glutathione peroxidase.

7.1. Glutathione

Glutathione (GSH) is often referred to as the “the mother of all antioxidants” [44]. It is an important antioxidant which is conventionally found in bacteria, animals, fungi, and plants. It is highly abundant in all of the compartments of organism's cells. Moreover, it is the major soluble antioxidant and its ratio helps to determine the oxidative stress. The Glutathione detoxifies the lipid peroxides and hydrogen peroxide through the action of GSH-Px. Glutathione (GSH) is also regarded as an intracellular thiol which eradicates the free radicals and causes reduction in the levels of hydrogen peroxide. In the erythrocyte of diabetics, the impairment in GSH metabolism and reduction in the GSH levels is being reported. The hyperglycemia leads to an increase in the reactive oxygen metabolites. Since glutathione is an important antioxidant, the deficiency of GSH led to an increase in the oxidative stress. The blood glucose regulation is also associated with the levels of GSH [35]. The deficiency of glutathione in the body is common in the patients who have uncontrolled Type2 diabetes.

7.2. Catalase

Some of the early studies in Drosophila postulated that the increase in the catalase activity and Superoxides dismutases (SOD). Catalase is a very common enzyme which is found in nearly all the living organisms which are exposed to the oxygen for example it is found in animals, bacteria, and plants. The enzyme catalyzes the decomposition of hydrogen peroxide into oxygen and water. Moreover, it plays a vital role in protecting the cell from the oxidative damage which is caused by the reactive oxygen species (ROS). Erythrocyte catalase is the major regulator of the hydrogen peroxide metabolism. The hydrogen peroxide concentrations can be increased through the acquired deficiencies in the levels of the enzyme. It can create both physiological and toxic effect. However, the increased concentrations of hydrogen peroxide are a risk factor for the patients with Type2 diabetes [36].

7.3. Superoxide dismutase (SOD)

The superoxide anion ($O_2^{\bullet -}$) plays an imperative role in the pathogenesis of the cardiovascular diseases. These diseases include atherosclerosis and hypertension. The super dismutases (SODs) enzymes are the major antioxidant defense systems against the O_2. In mammals, the enzyme consists of three isoforms of SOD. The recent evidences postulated that the SODs catalyze the conversion of $O_2^{\bullet -}$ H_2O_2 which further participates in the signaling of the cell. Additionally, the superoxide dismutase also plays a vital role in the inhibiting the oxidative inactivation of nitric oxide. Through this process, peroxynitrite formation and endothelial and mitochondrial dysfunction are being prevented. The SODs play an important role in the cardiovascular diseases; thus, it is becoming the topic of substantial interest. However, the clinical evidence related to the SOD is controversial [32].

8. Relationship between diabetes mellitus, obesity and cardiovascular diseases

The mechanism of oxidation stress is unclear to the people and is famous for contributing its part in resistance to insulin. The resistance of insulin arises by the insulin inability to perform normally in the regulation of the metabolism of nutrients in peripheral tissue. Evidence increases by the study of human population. Causative and correlative links were established by the research of animals between the insulin resistance and chronic inflammation. Moreover, the molecular pathways which were underlying are unknown. The type 2 diabetes and obesity are the biggest danger for the growth of atherosclerosis and CAD (coronary artery disease) [37]. These two medical conditions are related to the insulin resistance, inflammation, and oxidative stress.

In past few years, many studies of the human population have come up and associated the resistance of insulin to systemic inflammation. For instance, in one of the current report, Caucasian subjects with the T2DM studies the response of the acute-phase [41]. Serum Sialic acid significantly increased the grades. According to the study which was based on the large area CRP (C-reactive proteins) white cell and fibrinogen helps to count the parts of the insulin resistance syndrome and it was found in the population of known diabetic people. According to the reporter of the cardiovascular event, CRP was dealing the insensitivity of insulin individually.

Patients of diabetes are at the greater risk of dying from the

different complicated issues of the cardiovascular disease. Women and men both are seen to be at a higher risk. The vascular thrombosis and the problems like atherosclerosis are considered to be the main issues. Different investigations have shown that in the thromboxane is seen to be released in excess in the diabetes patients with the CVD disease. Aspirin causes the blockage of the thromboxane as it causes the acetylation of the platelet cyclooxegenase and therefore is used to overcome the CVD problems in the different diabetic and non-diabetic individuals. Patients with T2DM are usually affected by CVD. Usually adults are at the higher risks as compared to the middle-aged and old people than those who are not diabetic but are affected by CVD. Aspirin that causes the inhibition of the platelets could reduce the risk but it might increase the risk of gastrointestinal bleeding.

In addition, Aspirin and sodium salicylate both were used to deal with the conditions of inflammation, for instance, rheumatoid arthritis and rheumatic fever. The high doses of the salicylates can lower the concentration of the blood glucose. TZD's are used to normalize the glucose in blood and it also increases the risk of atherosclerosis for the long-term which might be dangerous for the patient.

Obesity is a problem of every person in the world, especially in adults. This is a problem of only one home in the United States of America [40] as its quite extensively spread. One-third of the adults are suffering from obesity. Obesity is associated with the type 2 diabetes. And it is predicted that it will rise to 366 million at the end of 2030. It is linked to the insulin resistance but it is observed that hyperglycemia is not developed by those people who are the patients of insulin resistance and obesity. The sensitivity of the insulin fluctuates in the normal lifecycle. The resistance of the insulin is mostly observed with the aging, in pregnancy days and in puberty also.

The changes in the style of living especially the use of carbohydrate and physical activity during a day were increased to improve the insulin resistance. If the person will take the excessive amount of the carbohydrate then, the excessive amount of NADH will produce by the citric acid cycle. For the prevention of ROS, it is necessary to get rid of all those compounds which have the high level of energy (fats and fatty acids) and the insulin stimulating nutrients [39].

By the release of Glycerol and NEFAs hormones, adipose tissues change the metabolism of obesity. Furthermore, proinflammatory cytokines, lepiten and adiponectin were released by the human placenta and adipose tissue. When NEFA releases it becomes the most important cause of modification of insulin sensitivity [38]. If the level of NEFA increased the both obesity and type 2 diabetes will be observed. And it is also observed that these both are linked to the insulin resistance. It takes few hours to develop the acute swell in plasma.

Further, according to the recent study by the regulation of the pentose-phosphate pathway the cells of cancer can counter the oxidative stress. Whereas, another research told us that the cells of tumor have produce pathway of strong antioxidants against the oxidative stress. Diabetes has made some effects which are just like the insulin resistance. Additionally, some of the clinics have suggested glutathione, Vitamin C, and Vitamin E for the improvement of insulin resistance from the person who has suffered from insulin resistance.

One of the research was done on the 144 number of people by admitting them to a hospital for 8–10 day and the officials of the hospital were giving all those patients a food which was full of nutrients and in that research the people were of 18–50 years of age and their plasma was stored in the fridge [40]. These people were examined by the doctors and went through a different physical test. This study was conducted in India by the approval of the government and under their protocol. After the report of 10 days, it was found that those people who have the diabetic problem are more obese as compared to the healthy and lean people. Therefore, it can be concluded that the obesity is correlated with the diabetes.

9. Conclusion

The purpose of this review article was to determine the potential effects of inflammation, aging and oxidative stress on theT2DM. To achieve the purpose of the research, the research discussed the diabetes mellitus and its complications, Pathophysiology of diabetes mellitus, Relationship of diabetes mellitus, aging, inflammation, reactive oxygen species (ROS) and oxidative stress with one another. Generally, it is concluded that all of the above-mentioned factors positively relate and create a significant impact on each other.

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