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Impact of Glycation and Diabetes on sperm DNA integrity that leads to Infertility in Male

Asiya Nisa[1]*, Waqas Abdullah[2],
[1]Department of Biotechnology, Maharani Lakshmi Ammanni College for Women Autonomous, Malleswaram, Bengaluru, India
[2]Process Technologist, Gulf Pharmaceutical Industries-Julphar, RAK, UAE
Corresponding Author*- Asiya Nisa
[1]Department of Biotechnology, Maharani Lakshmi Ammanni College for Women Autonomous, Malleswaram, Bengaluru, India

ABSTRACT:-Diabetes has a consequential inflated range of sperm DNA integrity and fragment which cause the natural death of cells and increased levels of advanced glycation in the sperm, sperm motility, fertilization ability in mature sperm, and in components of seminal plasma. Diabetes and glycation intricacy in the male reproductive is very high which causes oxidative stress and cell dysfunction due to high glucose levels which damage the sperm DNA integrity. Therefore, glycation is prominent for maintaining basic cell activity as well as specific functions. Diabetes disease either Type 1 or Type 2 can have a disastrous impact on male fertility such as sperm motility, sperm DNA disintegration, and epididymis.

KEYWORDS: Glycation, AGEs, Diabetes, Sperm DNA Integrity, Male Infertility.

Introduction

Infertility is generally interpreted as the insufficiency of a partner to conceive a baby even if they had unprotected, frequent intercourse.[1] infertility is increasing by 5% to 10% per year It affects at least 186 million worldwide.[2] Male infertility is the inability of a male to make a fertile female pregnant, also for a minimum of at least one year of unprotected intercourse. The male is exclusively responsible for about 20% and is a contributory aspect in another 30% to 40% of all infertility cases.[3] It is significant that both males and females are studied for infertility and accomplished together. Overall, the malefactor significantly subsidizes about 50% of all cases of infertility. Many dissimilar medical circumstances and other factors can contribute to infertility problems, and an individual case may have a single cause, several causes like diabetes in males can cause infertility. In General, half of the infertility cases are caused by male reproductive problems, one-half by female infertility and diabetic problems, and others by both male and female problems by unknown factors.[4]

There are some reasons that might stimulate both males and females in their stage, suppositories, diabetes, medical history, a revelation of natural toxins, genotypic problems, and some illnesses. The significant persistence for estimating a male for infertility is to recognize his causative aspects, suggest medicine or cure for those that are changeable, regulate if the male is a contender for assisted reproductive techniques (ART), and suggestion to guidance for unalterable and inoperable situations.[5] In some cases, male infertility could be a very serious condition. This is an additional reason to do an inclusive assessment of the male allies of infertile couples; so that any substantial, basic health conditions can be acknowledged and preserved at an early stage with better guidance and dietary.[6] Due to a diabetic male partner that may lead to infertility. Male with diabetes and who are insulin-dependent has molecular changes and decreased sperm quality and function. Diabetic men were found to have a suggestively higher ratio of sperm with nuclear DNA integrity damage, an aspect recognized to be connected with conceded fertility and improved rates of miscarriage in females. The structure-function from diabetes and AGE-related sperm DNA integrity damage arises. Research shows that diabetes and AGE can affect fertility, especially in males. Several of the complications it can cause are Low Testosterone, DNA Damage, Reduced Semen, Reduced Sperm Quality, Sperm DNA integrity, Delayed Ejaculation, Erectile Dysfunction, and Rand retrograde Ejaculation[7,8].

Moreover, the impact of glycation on testicular function and sperm DNA integrity damage has been reported in higher studies of animal models and shows involvement with Leydig cell function and erectile, and mitochondria dysfunction that leads to infertility[9,10]. AGEs are protein products molded as a result of non-enzymatic glycosylation. PI-3K endocytotic uptake of advanced glycation endproducts by their receptor RAGE, regulating their degradation and elimination process [10]. The elimination of advanced glycation endproducts can be mediated via the insulin receptor pathway [1]). Diabetes and the formation increase free radicals activity are also associated with advanced glycation endproducts AGEs[12]. The complication in the disorder and increasing IR are facilitated by biomolecular damage

[13]. Infertility in insulin resistance and diabetes through insulin receptor-mediated pathways and free radicals, respectively, worsening the pathophysiology of the disorder which is also responsible because of Advanced glycation endproducts AGEs. Reducing glycation and the complication raised due to IR in infertility and diabetes are controlled by AGEs in the tissue by the subsequent AGEs-RAGE interaction [12]. The first step in deciphering the AGEs that have been located in the human male reproductive tract, on sperm cells, and in soluble form in the seminal plasma suggesting that they may form modifications on functionally important sperm proteins or induce DNA adducts and to understand insulin resistance at the molecular mechanism[14,15]. The formation of AGE and glycation can generate reactive oxygen species (ROS)[16,17].) Inflammation pathway leading to subsequent NADPH and Reactive Oxygen Stress production can happen through AGE-RAGE activation of the NFkB (nuclear factor kappa-light-chain-enhancer of activated B cells [18]. existence of AGE hence has the capability to reason specific DNA damage to sperm due to their high susceptibility to oxidative stress (OS). when levels of ROS overdo the antioxidant ability of the seminal plasma, leading to cell membrane damage and impaired motility and morphology is a result of the excessive level of fatty acids in the sperm membrane, which undergo lipid peroxidation [19,20]. Furthermore, detected through conventional semen analysis by elevated ROS levels cause sperm DNA fragmentation, a marker of infertility. [21,]. in the male reproductive tract, AGE, and RAGE have previously been detected suggesting that this signaling pathway may have a role in sperm damage testosterone decreased. Other studies have demonstrated a role for AGEs in diabetes-related, erectile dysfunction [22].

Glycation

The non-enzymatic interaction involving reducing sugar, proteins, lipids, and nucleic acids is known as glycation [13]. The Maillard reaction, a challenging molecular mechanism, which is associated with the glycation process, produces AGEs [12]. If glycation levels rise, the body's ability to heal the glycation is compromised, and AGEs are generated with the function and structure that permanently damages and distorts the affected tissue. Oxidation, dehydration, polymerization, and oxidative breakdown promote the synthesis of AGEs during the glycation reaction's final step [23]. Age-related diseases such as T2DM, Alzheimer's disease, and ageing are all linked to AGE accumulation because it causes physiological and pathological alterations. [24] Pentosidine, a luminous product that creates protein-protein crosslinks, carboxymethyl-lysine (CML), and glucosepane, a non-fluorescent protein adduct, are the three types of AGEs that have been classified [25]. AGEs have the ability to attach to cellular AGE. Oxidative stress (OS) levels will rise as a result of receptors and targets, further damaging the overextended tissue or cell and nearby structures and functions. Blood sugar levels that are consistently high cause glycation, AGE/RAGE interface accumulation, and oxidative stress to increase. Concluded menstruation can lay the stage for the progression of numerous disease circumstances, including heart disease, PCOS, type I and type II diabetes, and male and female infertility. The primary cause of uncontrolled glycation and AGE accumulation in the body system is an excessively high carbohydrate diet. Especially harmful and prevalent in processed foods is high-fructose corn syrup.High-fructose corn syrup, a common sweetener in processed foods is particularly damaging and causes a 1000% increase in glycation. By depressing carbohydrate consumption and taking to change these calories with superior nutritious fats and proteins, people can achieve normal blood sugar levels and prospective avoid glycation-diabetes type I type II, heart illness, PCOD in females, and infertility in males.[26] The chemical reaction between sugar and various amino acids eventually rearranges the structure of the affected protein, creating an AGE. AGEs then attach themselves and added “cross-linkage” and harm further body proteins like collagen or hemoglobin. Once advanced glycation end products are formed and destined, they target inflammation and oxidation in the impact portion.

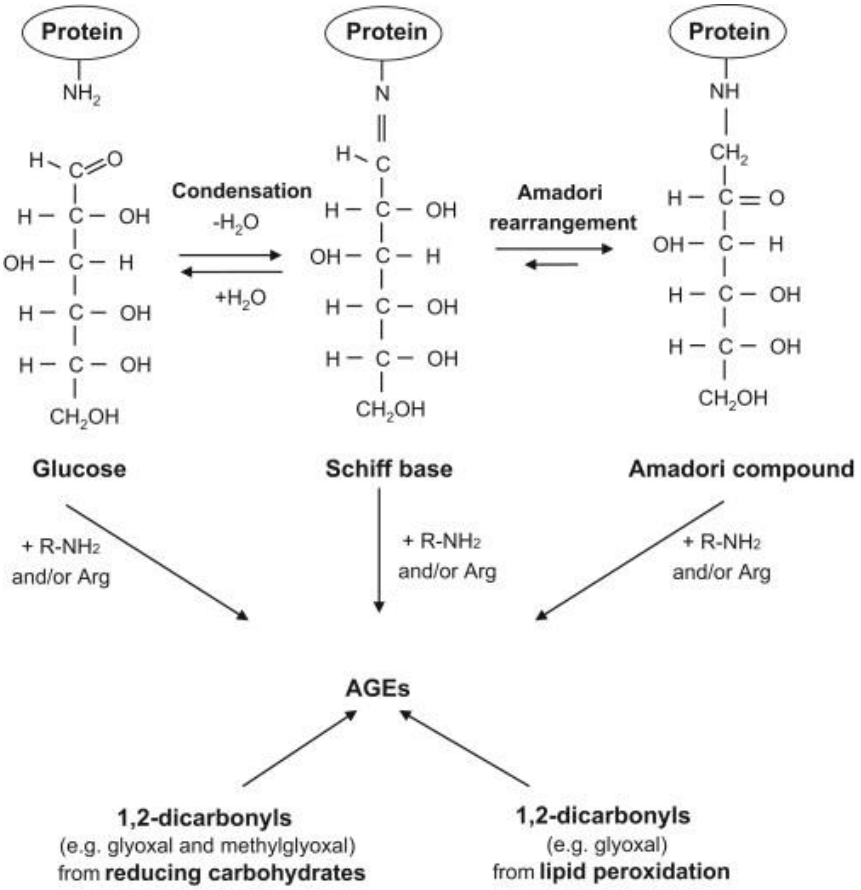

Fig:1. Glycation varies from alternative common glycating method–wherever sugars attach to proteins and fats called glycosylation.[13] Glycosylation is an enzyme-directed site-specific progressions activated in a controlled way by the body, as different to the non-enzymatic chemical reaction of glycation.[24]

According to estimates, 20–30% of infertility cases are solely attributable to male factors, while another 20% have complications that affect both men and women [29], reaching a total of 50% of cases overall [30]. Numerous studies have attempted to shed light on how molecular changes in genetic and epigenetic alterations affect male fertility [31,32]. It has been demonstrated that 10-15% of cases of infertility are caused by genetic variation, including chromosomal abnormalities and single-gene mutations [33]. Chromosomal abnormalities include differences in chromosomal numbers and structures. The most persistent karyotype anomaly in infertile males, according to reports, is numerical chromosomal variance like Klinefelter syndrome [34 However, the Y chromosome mutation is more common in oligozoospermic males due to structural alterations of the Y chromosome and translocations between the Y and autosomal chromosomes [35]. Male fertility has also been linked to differences brought on by molecular changes in the DNA sequence that result in phenotypic amendment [36,37,38]. the effects of changed proteins that were articulated either during spermiogenesis or fertilization. Large macromolecules like proteins or amino acids are involved in a variety of functional processes. [39] A protein known as testicular ceruloplasmin is produced and secreted by the Sertoli cells. The immunological role of this peptide is comparable to that of blood serum ceruloplasmin [40]. A serum protein called ceruloplasmin, which is crucial for copper transporter protein, is protease and oxidase sensitive. Additionally, it has been suggested that protein is required for germ cell viability [41,42Additionally, it has been shown that the Sertoli cells secrete a protein called testicular transferrin, which permits the transfer of iron and aids in the development of germ cells. It was stated that it was intracellularly regulated by insulin, testosterone, and vitamin A [43,44,45]. Therefore, all AQPs except for AQP6 and AQP12 are present in the male reproductive system, which includes the testes, epididymides, and efferent ducts. The most prevalent AQPs are AQP1 and AQP9 in the efferent ducts and epididymides, respectively. [46,47]. It is crucial to the dynamics of luminal fluid secretion and reabsorption during the maturation and transportation of sperm. Additionally, it has been demonstrated that AQP3, AQP7, AQP8, and AQP11 are found in sperm. They are crucial for spermatid differentiation into spermatozoa during spermiogenesis and aid in regulating osmolality during sperm transportation [48,49,50].

Additionally, estrogen controls the AQPs found in the male reproductive system (epididymides and efferent ducts). Through AQP1 and AQP9, estrogen regulates the reabsorption of water in the epididymides and efferent ducts [51,52,53,54]. While Bernardino et al. showed that the modulation of AQP9 by estrogen modifies glycerol permeability in Sertoli cells [55,56]. Infertility or subfertility may arise from changes in AQP expression or function, suggesting that they are crucial for normal male reproductive function [47]. This suggests that proteins play a role in spermatogenesis and reproductive processes in biology. Proteins are abundant in the organs and cellular pathways involved in male fertilization, hence it is important to further evaluate the effects of protein change as a result of physiological stress.male fertility[58]. Proteins go through enzymatic and non-enzymatic glycosylation in both the scenario of normalcy and problems. [59] The creation of amino acids, RNA, and DNA involves the post- and co-translational modification process known as glycosylation [60].

Enzymatic glycosylation supports the folding and physiochemical stability of glycoproteins by covalently attaching the carbonyl group of reducing sugar to them throughout proteins and lipids. But glycation happens in a non-enzymatic manner. Ahmed et al. observed in 1985 that polylysine (N-formal-N-fructosamine) and amino acids underwent a glycation process that resulted in the presence of a trace product. [13] The alleged substance was N-carboxymethyl lysine (CML), the first advanced glycation end product (AGE) to be identified [61,64]. At physiological pH and temperature, 40% CML production was found after a 15-day period in the following incubation. However, the incubation assortment's high phosphate buffer content accelerated the rate of development[63]. This suggests that AGE-forming sugars have increased sugar revelation. Numerous studies have been conducted on the involvement of AGEs in various pathologies, such as diabetes mellitus, diabetes-related disorders, chronic inflammatory diseases, Parkinson's disease, and other neurodegenerative diseases[64]. However, compared to female infertility, male infertility is less well understood. It is important to note that the majority of research that showed the effect of AGEs on male fertility also looked at the relationship between type I and type II [65,66 This is due to the fact that reducing sugars are important contributors to the development of AGEs, which have been shown to rise under hyperglycemic situations. While Agbaje et al. demonstrated increased nuclear and mitochondrial DNA damage in the spermatozoa of diabetic males[69,70], Mallidis et al. reported a significantly higher percentage of spermatozoa with nuclear DNA fragmentation and elevated levels of AGEs in the testis, epididymis, mitochondrial dysfunction, and sperm DNA integrity in diabetic individuals[67,68]. Male infertility due to sickness or diabetes is not the sole factor affecting sperm function. Reviewing their findings, Levine et al. [71,72,73] reported a considerable (50–60%) decline in sperm count over 4.6 decades in populations from North America, South America, Europe, Australasia, Asia, and Africa.[74]estrogen

Unfortunately, the root of infertility is frequently unknown, leading to its classification as unexplained [75,76]. This suggests that there are interruptions in the mechanical knowledge of spermatozoa production and function. Only the physiochemical/protein function of spermiogenesis is complex due to the cycle. Therefore, it is appropriate to think about the study fields that highlight protein modification and identification[77]. Therefore, the purpose of this study was to assess the body of knowledge already available on the effects of glycation, diabetes, and specifically AGEs on male infertility.

Diabetic and infertility

One of the most prevalent diseases nowadays that threatens the health of the global population is diabetes mellitus. Diabetes currently affects more than 346 million people globally, and without global action, this number is projected to double by 2030. Nearly 3 million persons (4.9% of the population) in Italy had diabetes in 2011 [80]. At least one in five adults over the age of 75 have diabetes, and among people under the age of 74, men are more likely than women to have the disease. However, the typical age upon diagnosis is rapidly declining, particularly for type 1 diabetes. Without a doubt, more than 90% of these patients receive their diagnoses before the age of 30. About 300,000 persons in Italy have type I diabetes frequency of this disorder is growing worldwide. The prevalence of type I diabetes in individuals under the age of 20 grew by 23% between 2001 and 2009, growing at a 3% annual rate. As a result, in addition to all the known problems of diabetes, an accurate evaluation of these patients should also consider their reproductive health [80]. We examined spermatozoa apoptosis, chromatin/DNA sperm integrity, and mitochondrial activity.

Diabetes effect on male infertility Unusual glucose homeostasis in male gametes has adverse effects on sperm DNA integrity or fertility. [80]. Both type 1 and type 2 diabetes, as well as AGEs in males, impact mitochondrial activity, sperm function, and spermatogenesis. [80,82] Molecular analysis techniques have shown that diabetic type I type II males has a dramatically increased percentage of semen with nuclear and mitochondrial DNA fragmentation and that the damage is of an oxidative nature. Ejaculate analysis suggests that the impact of diabetes on semen quality is minimal. [80,84] Damage to sperm DNA integrity is known to be associated with poorer quality embryos, reduced implantation rates, and perhaps the early beginning of several developmental illnesses. [84,85]

Diabetes and sperm DNA integrity

Men with type 1 diabetes exhibit structural flaws in their sperm cells, including fragmentation of the mitochondrial and nuclear DNA, impaired motility, and diminished zona pellucida binding. [80,81,83] According to Agbaje et alresearch, .'s increases in sperm DNA fragmentation seen in type I diabetic males were closely linked with changes in the expression of the genes involved in DNA replication and repair. It has been demonstrated that a variety of factors increase oxidative stress (OS), the formation of ROS, DNA damage in sperm, sperm motility, and sperm quality. [86,87] The polyamines (spermine, spermidine, and putrescine), which are found in semen in large amounts, exhibit antioxidant effects, are powerful antiglycation agents, and guard against structural and functional AGE changes.

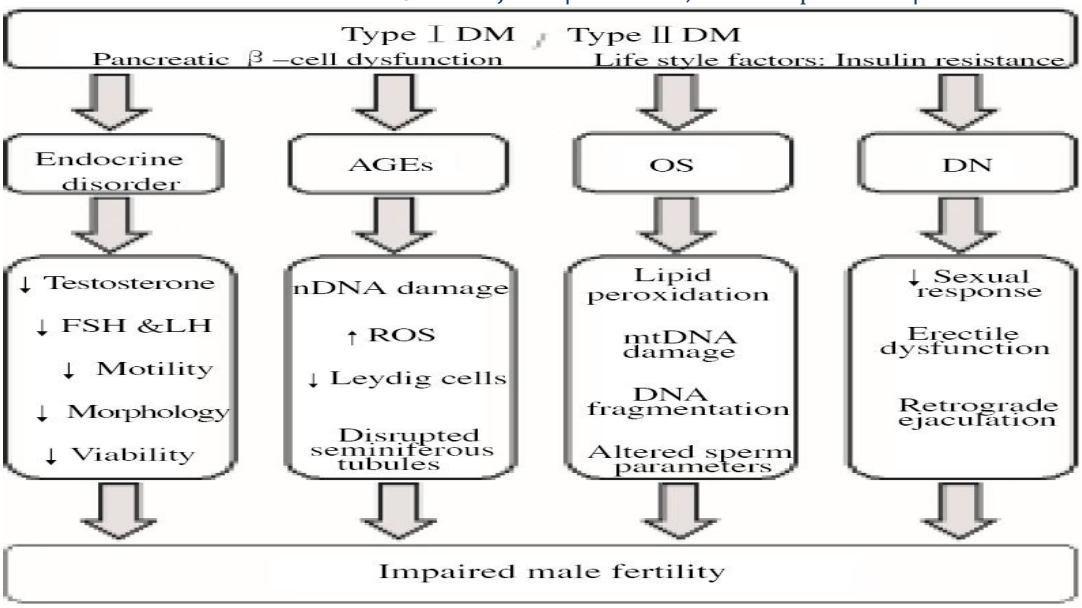

Fig:2. Type I diabetes and type II diabetes and Advance glycation endproducts impact on male infertility[80].

Accordingly, they recently showed that variations in the expression of antioxidants could be understood as reactions to a source, a situation of oxidative stress, and the quantity of spermatozoa exposing the receptor for advanced glycation end products, or RAGE, and that the inclusive protein quantity got in spermatozoa and seminal plasma was noticeably higher than from type 1 diabetic males. [86,87] Mallidis et al.86 discovered that mRNA profiles in type I diabetic men showed expression perturbations in the genes involved in stress response, DNA metabolism, and replication/repair. This was primarily because of their organization with oxidative stress, glycation, diabetes, and advanced glycation endproducts AGEs/RAGE. Many diabetic problems are significantly influenced by RAGE. High amounts of nitrate/nitrite are among the effects of ligand-RAGE interaction. High levels of nitrate/nitrite in the semen of diabetic men are suggestive of ROS-induced DNA damage that is linked with 8-OHdG levels but not sperm parameters. These are the effects of ligand-RAGE interaction. [87] This has therapeutic significance since there are no consequences on sperm motility, making it likely that these sperm can successfully fertilize an egg. Malondialdehyde, a well-known marker of OS and one of the byproducts of lipid peroxidation, was found in particularly high concentrations in the sperm of infertile men with type II diabetes. It also showed a negative correlation with sperm density, total sperm count, progressive motility, and normal forms, indicating that the increased lipid peroxidation in men with type II diabetes and poor metabolic control was linked to low sperm quality..[89,90] For diabetic men, glycemic management is a crucial component in preventing sperm destruction. [89,92] Type I diabetes, type II diabetes, and obesity are all associated with several alterations in the sperm proteome, according to research by Paasch et al. Semenogelin-1, Clusterin, and Lactotransferrin, which are all components of the Appin (epididymal proteinase inhibitor) protein complex, are thought to contribute to the pathological changes in sperm morphology and function that occur in diabetic and obese people. These changes include ejaculate sperm protection, motility regulation, and increased competence for fulfilling acrosome reactions. [93] Numerous signaling pathways involved in spermatogenesis are impacted by diabetes mellitus. All reproductive issues appear to start with elevated ROS and oxidative stress associated with diabetes, which impacts all relevant signaling pathways in spermatogenesis. [94]It seems that there was a strong interconnection between oxidative stress and all of the complicated signaling pathways in fertilization in diabetes. So, consider that diminished oxidative stress in the testis can be actual in humanizing diabetes-related male infertility complications[78].

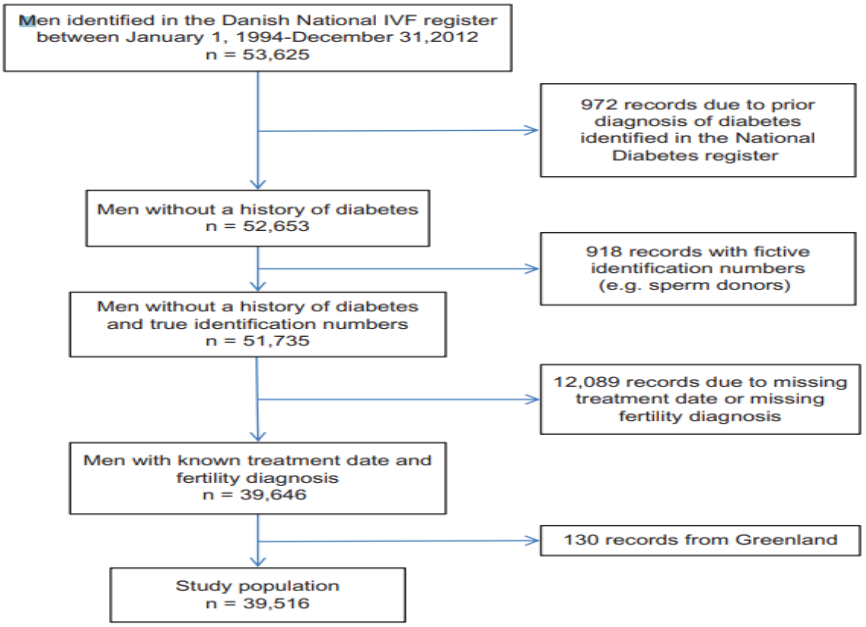

Fig:3- Flow diagram of the cohort in a study of the risk of diabetes according to male aspect to infertility [93].

Conclusion

The review discussed the significance of glycation and diabetes for sperm DNA integrity, mitochondrial function, and mitochondrial membrane potential as a critical indicator of the energetic status of the mitochondria, which is crucial for spermatozoa flagellum movement and ATP synthesis. This restriction serves as a reliable indicator of mitochondrial activity. Male fertility, specifically sperm quality such as sperm motility and DNA integrity, is negatively impacted by type I and type II diabetes with advanced glycation endproducts. AGE-RAGE communication, oxidative stress, and inflammation trigger may encourage the epigenetic conversion during sperm spermiogenesis dysregulation may be inherited through the male germ line and passed on once advanced glycation end-product accumulation is higher than the body's capacity to break them down.To improve health and get rid of diabetes and AGEs stop consuming unhealthy food and bring exercise into daily habits. Diabetes type I and an insulin-dependent person can live a normal life just have to change unhealthy habits and foods which provide more carbohydrates, then the AGE level will be decreased.

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