Chemistry & Biology Interface, 2021, 11, 6, 182-196

REVIEW PAPER ISSN: 2249 –4820

CHEMISTRY & BIOLOGY INTERFACE

An official Journal of ISCB, Journal homepage; www.cbijournal.com

OXIDATIVE STRESS AND DIABETIC COMPLICATION: A systematic review

Kaneez Fatima[A] ,Zakir Hussain[B], Dr. Rabia Hamid*[A]

[A]*Department of Biochemistry, University of Kashmir, India -190006.*
Fatima47kaneez@gmail.com
[B]*Department of Chemistry, University of Kashmir, India -190006*
Received; 16 June 2021, Accepted; 15 November 2021

Abstract: Various indicators, such as protein modification biomarkers and lipid peroxidation products, have been used in research to show a relationship between diabetes and oxidative stress. Due to their capacity to damage lipids, proteins, and DNA, free radicals are thought to play a key role in the initiation and progression of late diabetes complications. Oxidative stress causes a number of clinical illnesses, including rheumatoid arthritis, diabetes, and cancer. Coronary artery disease, neuropathy, nephropathy, retinopathy, and stroke are all consequences of DM caused by free radicals and oxidative stress. In-vivo studies back up the theory that hyperglycemia causes oxidative stress, which leads to endothelial dysfunction in diabetes patients' blood vessels. Increased glucose and insulin levels, as well as dyslipidemia, produce macroangiopathies, which lead to oxidative stress and atherosclerosis in diabetic patients.

Objective- Exogenously and endogenously produced reactive oxygen and nitrogen species promote oxidation of cellular molecules by transferring electrons to them. Exogenous antioxidants can be obtained, and the body's antioxidant defence system comprises vitamins A, C, and E, glutathione (GSH), and the enzymes superoxide dismutase (SOD), catalase, and others. Hyperglycemia causes the creation of free radicals, which causes an imbalance between free radical formation and the antioxidant defence system, resulting in oxidative stress. Increasing data suggests that oxidative stress plays a key role in diabetes mellitus development (DM). Increased formation of advanced glycation end-products (AGEs), polyol pathway, increased expression of the receptor for AGEs and its activating ligands, activation of protein kinase C (PKC) isoforms, and overactivity of the hexamine pathway are the main pathways involved in diabetic pathogenic complications

Data source- Pubmed, Google scholar, google, Researchgate

Keywords: Piperine, chemical constituents, bioenhancer, formulations, and pharmacological activity.

1. Introduction

More than 180 million individuals in industrialised and developing countries have diabetes, and the number is expected to quadruple by 2030. (1). Diabetes mellitus is characterised by an increase in blood glucose levels and a decrease in insulin production or sensitivity to its goals (2). Diabetic problems damage the eyes, kidneys, nerves, and blood vessels as a result of long-term hyperglycemia and oxidative stress (3). Sulphonylureas and arginine, in addition to glucose, stimulate beta cells to release insulin, and glucose is a major determinant of insulin secretion (4). Type 1 diabetes is an autoimmune illness caused by the death of pancreatic cells. It accounts for around 80% to 90% of diabetes in children and adolescents (5, 6). T-cells and B-cell responses both have a role in autoimmune type 1 diabetes (7). The major symptoms of type 1 diabetes include polydipsia, polyuria, polyphagia, abrupt weight loss, and blurred eyesight (7). Type 2 diabetes mellitus accounts for approximately 90% of all diabetes cases. The majority of these patients are adults, and obesity is the leading cause. Adult diabetes is a term used to describe diabetes that develops beyond the age of 40. The release of plasma free fatty acids (FFA) and tumour necrosis factor alpha (TNFα) by "full" adipocytes is one of the key causes of type 2 diabetes and obesity. [8,9,10]

OxidativestressandDiabetes

Oxidative stress is a type of physiological stress that occurs when the antioxidant defence system and free radical production in the body are out of balance (11, 12). Vitamins A, C, and Glutathione, as well as superoxide dismutase, catalase, and other antioxidant defencesystems(13), and free radical production comprises ROS and RNS in the body. When reactive oxygen and nitrogen species are present in low or normal amounts, they are helpful. However, at high concentrations, they cause oxidative stress, which is the root of many diseases such as Diabetes, Kidney disease, Lung cancer, etc (14). The creation of ATP by cells when they use oxygen, as well as the generation of free radicals by mitochondria, are all probable sources of Reactive Oxygen Species (ROS). Reactive Nitrogen Species (RNS) and other biological redox products are common. Superoxide, hydrogen peroxide, hydroxyl radical, singlet oxygen, and RNS nitrous oxide, peroxynitrate, nitric oxide, and peroxynitrite (15,16) are examples of ROS.ROS and RNS have favourable effects on cellular response and immunological function at low or moderate levels. They cause oxidative stress at high doses, which is a harmful process that can harm all cell structures. (17, 18, and 19). Beta cells have lesser levels of antioxidant enzymes, making them more vulnerable to oxidative and cytotoxic stress (20). Hyperglycemia-induced oxidative stress and inflammation increased apoptosis and disrupted insulin secretion by causing a shift in gene expression regulation (21).

Oxidative Stress-Induced Cellular Damage AProteins

In vitro ROS react with protein amino acid residues, resulting in nonfunctional proteins. Because proteins have distinct primary, secondary, and tertiary protein structures, ROS can react with any biomolecule, including proteins, altering their structure and making them more vulnerable to proteolysis (23).

In vivo studies in diabetic rats revealed a decrease in serum proteins, which could be due to the following factors: a) decreased amino acid uptake (24) b) a significantly lower concentration of a variety of essential amino acids (25) c) an increased conversion rate of glycogenic amino acids to CO2 and H2O, and

d) a reduction in protein synthesis secondary to a decreased amount and availability of mRNA (26).

In vivo studies in diabetes-induced rats revealed a decrease in serum proteins, which could be due to the following factors: a) decreased amino acid uptake (24) b) a significantly lower concentration of a variety of essential amino acids (25) c) an increased conversion rate of glycogenic amino acids to CO2 and H2O, and d) a reduction in protein synthesis secondary to a decreased amount and availability of mRNA (26).

B Lipids

Since plasma membrane is made up of polyunsaturated fatty acids (PUFA), which are an easy target for ROS due to their numerous double bonds, a shift in membrane receptors occurs. (27). Peroxynitrite (ONOO) oxidises LDL but does not attach to LDL receptors, allowing scavenger receptors in macrophages to pick up LDL and generate foam cells, resulting in atherosclerotic plaques (28,29).Sato et al. (30) published the first evidence of lipid peroxidation in DM, noting that the levels of lipid peroxides in plasma of DM patients were substantially higher than that of normal persons

Lipid peroxidation, which is the most researched field of research when it comes to ROS, is a significant biomarker of oxidative stress (31). After reacting it with thiobarbituric

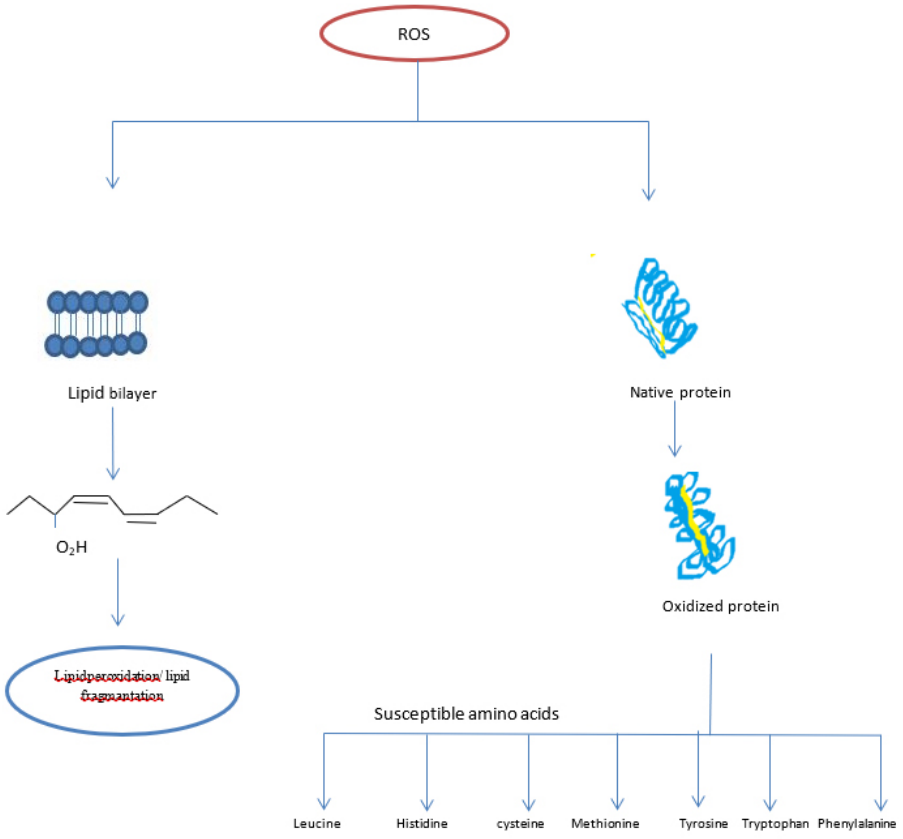


Figure 1. Shows ROS react with susceptible amino acids of proteins and polyunsaturated lipid-schange the structure of lipids and proteins.

acid, malondialdehyde (MDA) is generated as a result o1f lipid peroxidation, and it can be used to assess lipid peroxides (32).

ROLES OF ORGANELLES IN OXIDATIVE STRESS

Mitochondria

As electrons transfer through the electron transport system, proton move into intermembrane space, generating a proton gradient that drives ATP synthase, but some electrons leak out of complex 1 or 3 and interact with molecular oxygen to form superoxide anion, mitochondria is rightly called the powerhouse of the cell. Hyperglycemia causes more oxygen to be released, which leads to an increase in the generation of reactive oxygen species (ROS) (33-35).

Furthermore, enzymes such as acyl-CoA dehydrogenase and glycerol phosphate dehydrogenase can produce ROS (36). By increasing mitochondrial superoxide buildup in the retina, inactivation of complex 3 activities worsens diabetic retinopathy outcomes (37).

Hyperglycemia caused superoxide to develop in the mitochondrial electron transport chain by raising the inner mitochondrial membrane potential through the Krebs's cycle (37).

Hyperpolarization of the mitochondrial membrane potential and an increase in the ATP/ADP ratio occurred as a result of this scenario, followed by inhibition of complex-III and electron buildup at coenzyme Q. As a result of the partial reduction of O2, free radical production is accelerated, and ATP synthesis is reduced (38,39).

Endoplasmic reticulum stress and insulin resistance

Beta pancreatic cells have a well-developed endoplasmic reticulum (ER), which is the organelle responsible for protein folding and exporting. Because they must produce and secrete significant amounts of insulin, they

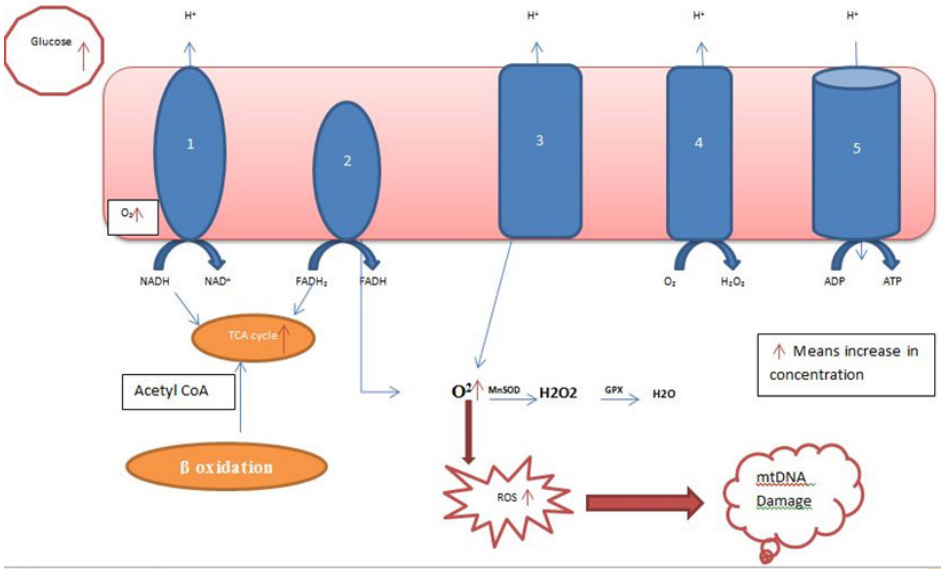


Figure 2. Shows hyperglycemia produces more and more superoxides which end up with mitochondrial DNA damage leads to Apoptosis of beta-pancreatic cells.

have a well-developed ER (40-42)

Protein disulfide isomerases (PDI), endoplasmic reticulum oxidoreductase 1 (ERO1), and glutathione (GSH) combine as a chaperone-like effect in ROS production, which in turn inhibits disulfide bond formation, causing endoplasmic reticulum ER stress by increasing the amount of misfolded proteins in the ER lumen.

Hyperglycemia or an increase in misfolded proteins triggers the unfolded protein response (UPR). In normal physiological settings, the three transmembrane proteins Inositol-required kinase 1 (IRE1), protein kinase-like ER kinase (PERK), and activating transcription factor 6 (ATF6) are all inactive. When the UPR coping mechanisms fail to restore ER stability or homeostasis, the ER stress response ensues. The separation of Bip from ER transmembrane proteins causes ER stress to activate them. (43,44). NO generates ER stress and the production of unfolded proteins by depleting ER Ca2+. The cell responds to unfolded proteins in three ways: upregulation of chaperon proteins, upregulation of chaperon proteins, and upregulation of chaperon proteins.(45,46)

Mechanisms of Hyperglycemia-Induced Damage

Five main major mechanisms are underlying hyperglycemia-induceddiabetic vascular damage which leads to diabetic complication,microvascularandmacrovascular damage. ROS responsible for the activation of these five mechanisms which is produced due to mitochondria over activation- polyol pathway, increased intracellular formation of advanced glycation end-products (AGEs), increased expression of the receptor for advanced glycation end products and its activating ligands(RAGE), activation of protein kinase C (PKC) isoforms, and overactivity of the hexamine pathway. . However, the results of clinical studies in which only one of these pathways is blocked have been disappointing (47,48)

Increase polyol pathway

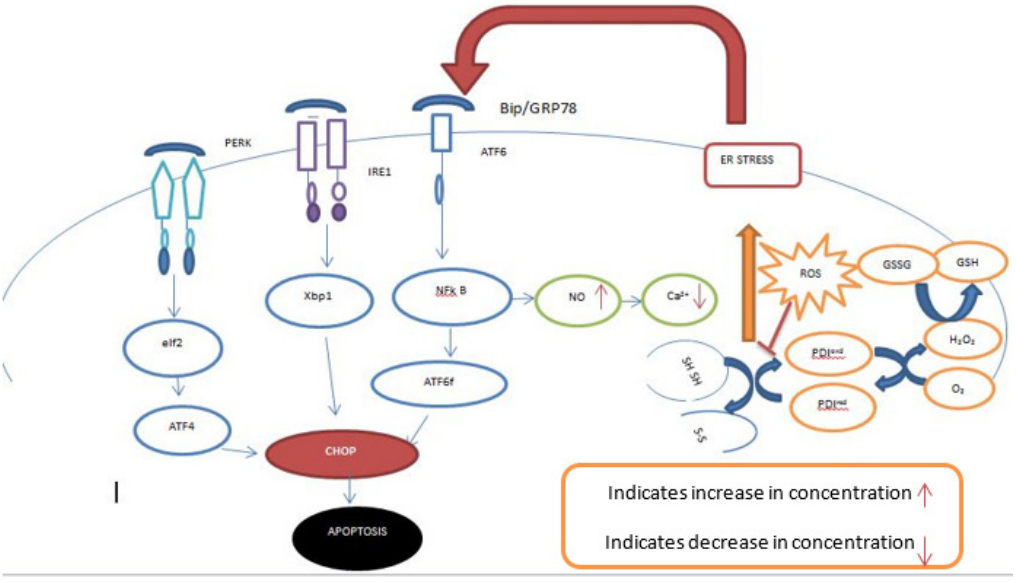


Figure 3. ROS inhibits proper disulfide formation in protein folding cause dissociation of Bip from ER transmembrane proteins like PERK, IRE1, ATF6 cause ER stress. Activation of these proteins causes apoptosis of cells by expression of CHOP gene.

Nerve, retina, lens, glomerulus, and vascular cells rich in Aldose reductase(49).When the body experiences hyperglycemia, the enzymes aldose reductase and sorbitol dehydrogenase are active, converting glucose to sorbitol and sorbitol to fructose, respectively (50). As a result of these reactions, NADPH is oxidised and NAD+ is reduced, which is employed as a cofactor by aldose reductase and sorbitol dehydrogenase, respectively, causing the following:-

1, Because NADPH is utilised as a cofactor to replenish reduced glutathione (GSH), oxidation of NADPH causes a drop in NADPH content in the cell, which lowers the activity of the reducing enzyme Glutathione, resulting in more superoxides being produced (49-50).

Sorbitol does not permeate through the cell membrane and accumulates intracellularly because it is hydrophilic. Furthermore, sorbitol is tough to digest (51,52,53).

2, Sorbitol produced by aldose reductase is oxidised to fructose by sorbitol dehydrogenase, which uses NAD+ as a cofactor to make NADH, which serves as a substrate for NADH oxidase, which produces reactive oxygen species (ROS) (54,55).

The synthesis of diacylglycerol, a key activating cofactor for protein kinase-C, is increased by hyperglycemia inside the cell(56,57) PKC changes gene expression and protein function when it is activated by intracellular hyperglycemia (57).

Increased Intracellular AGE Formation

Advanced glycation end-products form non-enzymatically as a result of the reaction of reducing sugars with free amino groups, which occurs not only in proteins but also in lipids and nucleic acids and is known as Maillard's reaction (58). The first reaction produces an unstable product (Schiff base), which undergoes rearrangement to produce a more stable product (amadori product), which then undergoes oxidation, dehydration, and cyclization processes to produce a glycated molecule (59). AGEs cross-link proteins, resulting in proteinase-resistant aggregates. (60).

IgG accounts for 75% of the total immunoglobulin in serum (61) It has the longest half-life of all the immunoglobulins, which makes it a prime target for ROS because the longer the half-life, the more vulnerable to ROS (62)Glycation of IgG causes a change in its structure and function, which is linked to

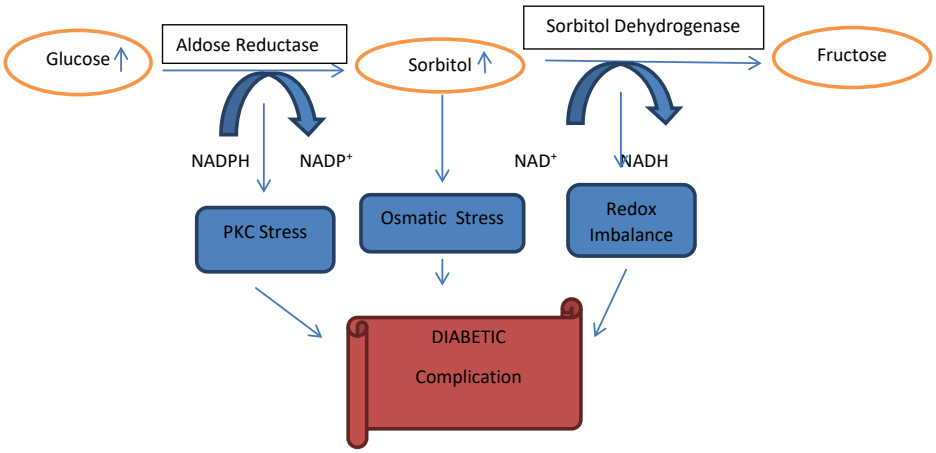


Figure 4: Polyl pathway involved in diabetic complication by osmatic stress,PKC stress and Redox imbalance

inflammation and a target for autoantibodies in individuals with rheumatoid arthritis (63)

Glycation of collagen and elastin can cause skeletal fragility and osteoblast differentiation by modifying characteristics such as the triple helix, solubility, and flexibility, which reduce toughness and stiffness. (64-69)Glycated collagen affects endothelial cell function, which contributes to the formation of atherosclerotic plaques. (69)

Several in vitro investigations have established the critical role of glycated albumin in platelet activation and aggregation (70) and glycated albumin can impact glucose metabolism in both skeletal muscle and adipocyte. (71) Glycated fibrinogen hinders fibrinolysis and increases fibrin gel permeability, resulting in a thrombogenicfibre network. (72,73) The interaction of AGEs with RAGE on macrophages activates p21ras and the mitogen-activated protein (MAP) kinase signalling pathway, which leads to nuclear factor-B (NF-B) activation (74). Which, in turn, modify gene transcription for a variety of reasons, including the production of pro-inflammatory cytokines like interleukin-1 (IL-1), tumour necrosis factor- α(TNF-α), and adhesion molecules like collagen.In order to modulate immune surveillance and inflammation, VCAM-1 works in conjunction with other adhesion molecules. Excessive levels of ROS, oxidised low density lipoprotein (oxLDL), 25-hydroxycholesterol, turbulent shear stress, high hyperglycemia, and microbial stimulation of endothelial cell TLRs all increase VCAM-1 expression. The transcription factors nuclear factor kappa B (NFB), SP-1, Ap-1, and interferon regulatory factor-1 influence the activation of VCAM-1 gene expression. (75-79)

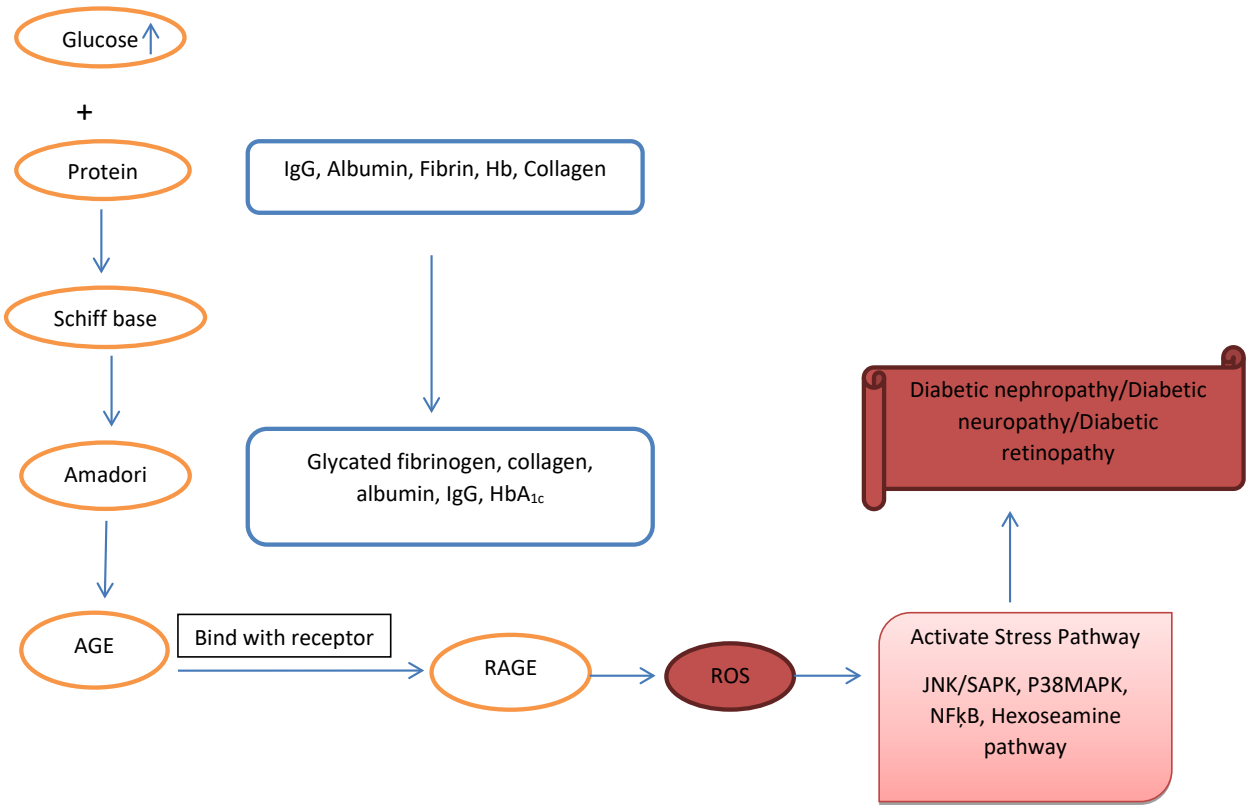


Figure 5: AGE role in diabetic complication by interacting with RAGE , produce ROS activate stress pathway result in diabetic complication.

Following the interaction of AGEs with RAGE in endothelial cells, NF-B and hemeoxygenase mRNA, both indicators of oxidative stress, are activated .(80) Following the interaction of AGEs with RAGE in endothelial cells, NF-B and hemeoxygenase mRNA, both indicators of oxidative stress, are activated, according to a study (81)

The aetiology of diabetic problems is complicated by the interaction of AGEs with their cellular receptors .(75)

PKC pathway :

Hyperglycemia causes a rise in glycolysis, intermediate dihydroxyacetone phosphate, and glycerol-3-phosphate, all of which boost de novo DAG synthesis. (82) There are two forms of PKC conventional PKC (cPKC) isoforms (PKC-α, -β1, -β2, and -γ) are activated by phosphatidylserine (PS), calcium, and DAG or phorbol esters, whereas novel PKCs (nPKC; PKC-δ, -ε, -θ and -η) by other than calcium. The atypical PKCs (aPKC; PKC-ζ and -ι/λ) are not activated by calcium, DAG, or PMA(83).

Diabetes sequelae indicated a rise in total DAG content in both vascular and nonvascular tissues from diabetic animal models and patients, including renal glomeruli,(84-86), heart, aorta,(87), and retin(88), liver (89)), skeletal muscles,(90). Tight junction between endothelial cells provide a vascular barrier, although PKC enhances the permeability of EC albumin and other macromolecules in diabetic circumstances. (91,92) PKC influences the expression and activity of vascular endothelial growth factor (VEGF) and increases the synthesis of thromboxane endothelin-1 (ET-1) through modifying the bioavailability of NO (93,94,95)Endothelial dysfunction occurs as a result. Different forms of PKC activated by Hyperglycemia among which PKC-α, -β-δ, and –ε involved in retina dysfunction. PKC-α, -β-δ, and –ε altering enzymes NO, ET-1, VEGF, PDGF, etc involved EC and pericytes. (96-99) Many in vitro investigations have shown that different versions of PKC perform diverse roles in the proximal tubules of the kidney and the glomerulus. By changing NADPH and boosting renal serum and urinary VEGF, PKC- α causes superoxide to develop. (100,101)The deletion

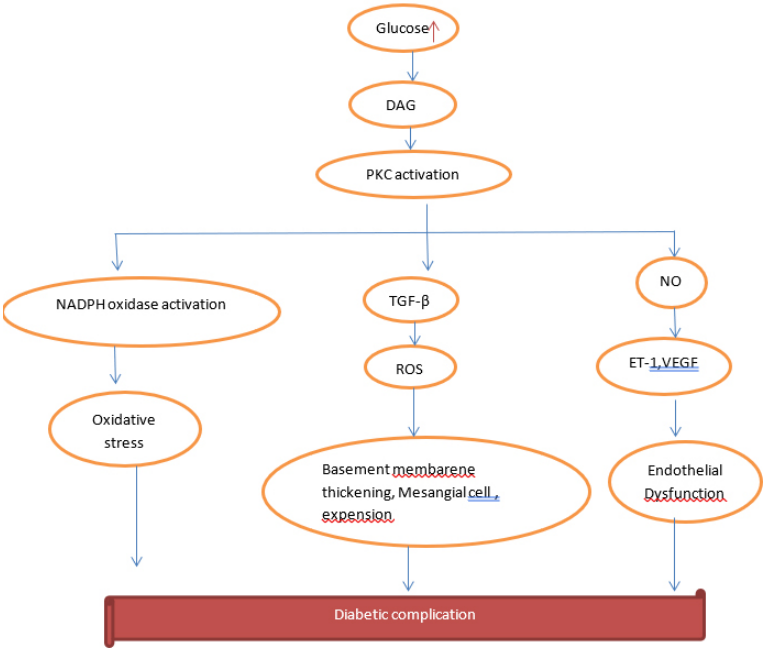


Figure 6: Denovo synthesis of DHA in hyperglycemia activate PKC pathway, result in activation of different factors lead to produce ROS , complicate diabetes.

of the TGF gene protects diabetic kidney disease in animals. TGF- causes the development of reactive oxygen species (ROS), which impairs glomerular filtration.(102)

Hexosamines Pathway

Excess glucose is provided by hyperglycemia, and the rate-limiting enzyme glutamine: fructose-6-phosphate (F-6-P) amidotransferase (GFAT) allows additional fructose 6 phosphate to enter HSP, forming the primary end product UDP-N-acetylglucosamine (UDP-GlcNAc). Which modulates glucose entrance into the HSP pathway by acting as an allosteric feedback inhibitor of GFAT (103) UDP-N-acetylglucosaminetransferase (O-Glc NAC transferase) is an enzyme that uses UDP-N-acetylglucosamine (UDP-GlcNAc). Many proteins/transcription factors are acylated by transferring N-acetyl glucosamine to Olinkage of serine or threonine residues in certain proteins55 IRS-1 and 2, Glut 4, glycogen synthase (104,105)and RNA polymerase II (106)

Sp1 protein with an O-GlcNAc modification that binds to Sp1 binding sites of plasminogen activator inhibitor 1, (PAI-1) triggered by hyperglycemia. In vascular smooth muscle cells (107), aortic endothelial cells (108) and mesangial cells (109), Sp1 regulates hyperglycemia-induced activation of the PAI-1 promoter, which is regarded to be an important element in the development of vascular disease in diabetes.

The promoter sequence of TGF-β homologs glucose response elements of genes of glucose metabolic proteins involved in glycolysis, such as pyruvate kinase. As a result of their association with the stimulatory factors USF-1 and 2, GREs produce TGF-β1 overexpression in hyperglycemic conditions. TGF-β synthesis has been shown to be a distinct impact of high glucose levels (110,111).

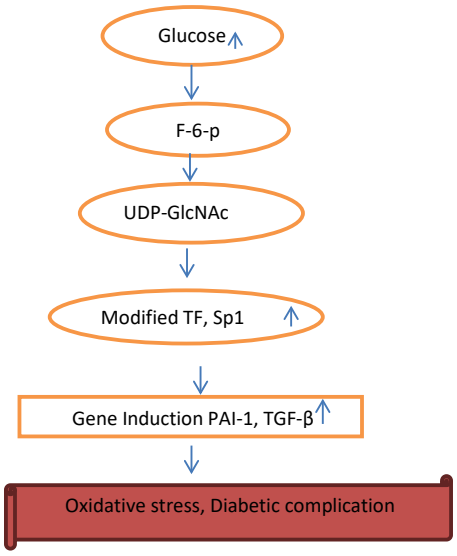


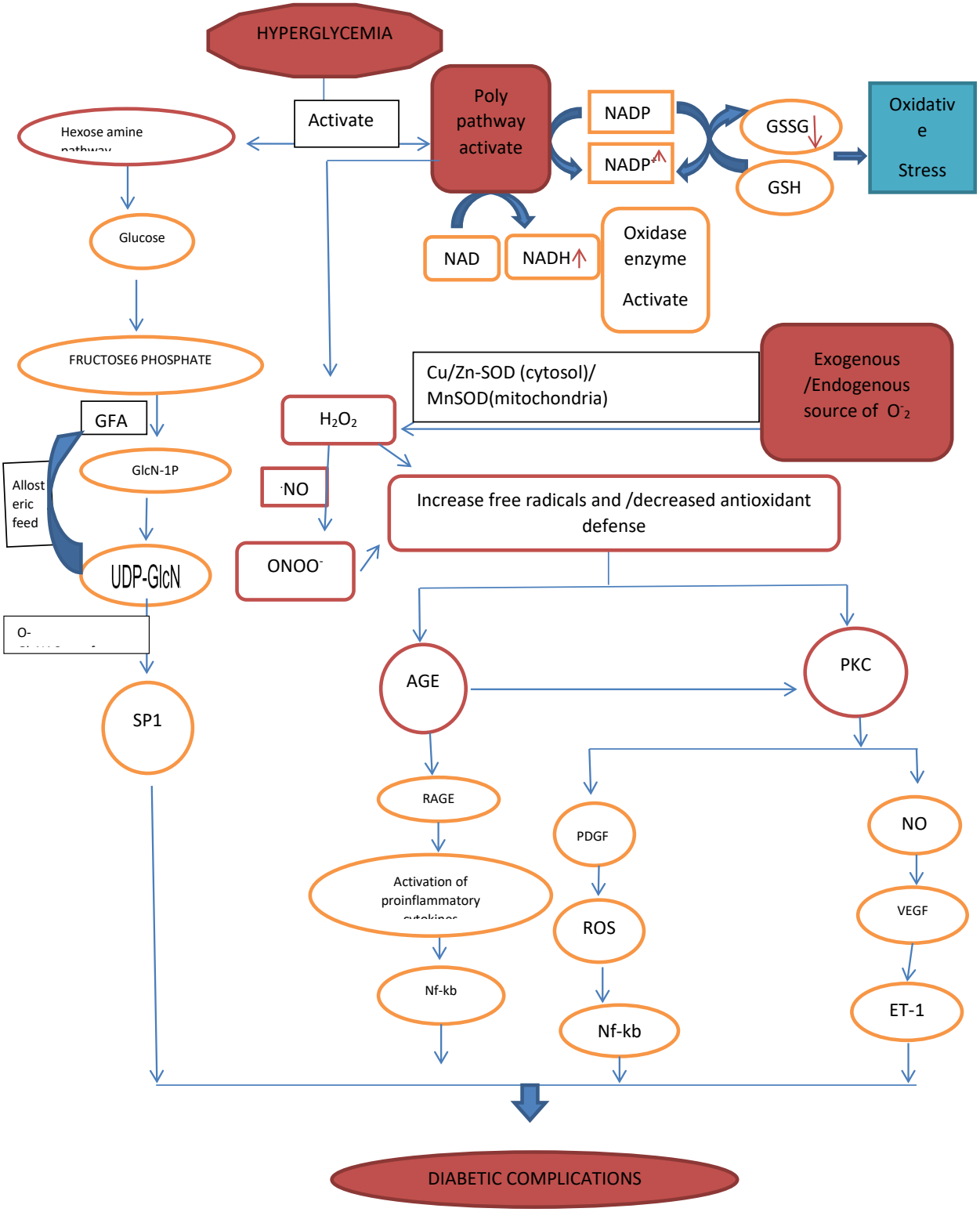
Figure 7:Hyperglycemia supplies extra glucose, and the rate-limiting enzymes enables more fructose 6 phosphate into HSP, resulting in the major end product UDP-N-acetylglucosamine (UDP-GlcNAc).

CONCLUSION-

Several research investigations have indicated that oxidative stress is a crucial factor in the occurrence and consequences of diabetes, as mentioned in this review.

As discussed above, there is substantial evidence from in vitro and in vivo studies that hyperglycemia and perhaps raised FFA levels cause the formation of ROS and RNS, resulting in enhanced oxidative stress in a number of organs. The mechanism becomes overwhelmed in the absence of a suitable compensating response from the cell's natural antioxidant network, resulting in redox imbalance and aggravating the problem. The reactive species not only cause direct cell damage by oxidising DNA, protein, and lipids, but they also cause indirect cell damage by activating stress-sensitive intracellular signalling pathways such NF-B, p38 MAPK, JNK/SAPK, hexosamine,

UDP-N-acetylglucosaminetransferase use (UDP-GlcNAc) to acylate .proteins55 IRS-1 and 2, Glut 4, glycogen synthase,Sp1 proteindevelopment of vascular disease in diabetes.



PKC, AGE/RAGE, sorbitol, and others. Activation of these pathways leads to increased production of a variety of gene products that induce cellular damage and play a key role in the development of diabetes' late consequences. Furthermore, recent evidence from in vitro and in vivo studies suggests that activation of the same or similar stress pathways leads to insulin resistance and decreased insulin production. As a result, we propose that hyperglycemia and FFA-induced increases in ROS and oxidative stress, activation of stress-sensitive pathways, and the development of not just late complications of diabetes, but also insulin resistance and -cell dysfunction, are all linked.

Acknowledgments

The work was supported by the council of scientific and industrial research New Delhi India and the department of biochemistry, University of Kashmir, India. The funding agencies had no role in the Design of the study; in the collection, analysis, or interpretation of data; in the writing of the manuscript; and in the decision to publish the results.

Declarations

I KANEEZ FATIMA, declare that the Submitted Research Paper is my original work and no part of it has been published anywhere else in the past. I take full responsibility, that if in future, the paper is found invalid according to basic rules, the last decision will be of the Authorities concerned. Any form of plagiarism will lead to the disqualification of the paper.

Funding

Not applicable

Competing interests

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

1. KANEEZ FATIMA SIGN. --- --------- 2020-21

2. ZAKIR HUSSAIN SIGN. ---------- 2020-21

3. Dr. RABIA HAMID …… ..2020-21

Ethics approval

Not applicable

Consent for publication

Not applicable

Author contribution

The authors confirm contribution to the paper as follows: study conception and Design, data collection, analysis andinterpretation of results: Kaneez Fatima; draft manuscriptpreparation:, Zakir Hussain and Dr Rabia Hamid. All authors reviewed the results and approvedthe final version of the manuscript.

Availability of data and material

The data and material is available online and can view by using the reference address.

REFRENCE

1. 1.Torben H , Genetics of Type 2 diabetes. CurrSci, 2002; 83:1477–1482
2. Imam K, "Clinical features, diagnostic criteria and pathogenesis of diabetes mellitus," Journal of Advances in ExperimentalMedicine and Biology,2012; 771: 340–355.
3. Elosta .A, Ghous. T, andAhmed. N, "Natural products asAntiglycation agents: possible therapeutic potential for diabetic complications," Current Diabetes Reviews,2012; 8, : 92– 108.
4. Joshi, S.R., Parikh, R.M., Das, A.K., 2007. Insulin-history, biochemistry, physiology and pharmacology. J. Assoc. Phys. India 2007;55:19-23.
5. Craig ME, Hattersley A, Donaghue KC. Definition, epidemiology and classification of diabetes in children and adolescents. PediatrDiabetes 2009; 10: 3-12
6. Devendra D, Liu E, Eisenbarth GS. Type 1 diabetes: recent developments. BMJ 2004; 328: 750-754.
7. Dabelea D, Mayer-Davis EJ, Saydah S, Imperatore G, Linder B, Divers J, Bell R, Badaru A, Talton JW, Crume T, Liese AD, Merchant AT, Lawrence JM, Reynolds K, Dolan L, Liu LL, Hamman RF. Prevalence of type 1 and type 2 diabetes among children and adolescents 2014; 311: 1778-1786 .
8. Hotamisligil GS, Arner P, Caro JF, Atkinson RL, Spiegelman BM. Increased adipose tissue expression of tumor necrosis factor-alpha in human obesity and insulin resistance. J Clin Invest 1995; 95:2409-15.
9. Jatla Jyothi Swaroop, Duggirala Rajarajeswari, and J.N. Naidu Association of TNF-α with insulin resistance in type 2 diabetes mellitus IndianJ Med Res. 2012 ; 135: 127–130.
10. Devendra D, Liu E, Eisenbarth GS. Type 1 diabetes: recent developments. BMJ 2004; 328: 750-754.
11. Kraemer FB, Ginsberg HN. Gerald M. Reaven, MD: Demonstration of the central role of insulin resistance in type 2 diabetes and cardiovascular disease. Diabetes Care 2014; 37: 1178-1181 .
12. Weseler, A.R., Bast, A. Oxidative stress and vascular function: implications for pharmacologic treatments. Curr.Hypertension Rep2010;12:154–161.
13. Joseph LE, Ira DG, Betty AM, Gerold MG. Are oxidative stress activated signaling pathways mediators of insulin resistance and cell dysfunction? Diabetes 2003; 52:1-8.
14. Savita Khanna, .Thiol Antioxidants, Ph.D. Dissertation. Department of Physiology University of Kuopio, Kuopio, Finland; 2000
15. El Faramawy SM, Rizk RA. Spectrophotometric studies on antioxidants-doped liposomes. J Am Sci 2011; 7:363-9.
16. Maiese K, Morhan SD, Chong ZZ. Oxidative stress biology and cell injury during type 1 and type 2 diabetes mellitus. Curr Neurovasc Res 2007;4:63–71.
17. Kenneth M, Zhao ZC, Yan CS. Mechanistic insights into diabetes mellitus and oxidative stress. Curr Med Chem 2007;14:1729–38.
18. Halliwell B, Gutteridge JMC. Free radicals in biology and medicine.4th ed. Oxford, UK. Clarendon Press, 2007.
19. Young IS, Woodside JV. Antioxidants in health and disease. J. Clin. Pathol 2001; 54: 176-
20. 186.Droge W. Free radicals in the physiological control of cell function. Physiol. Rev 2002; 82: 47-95.
21. Gilbert,E.R., 2012).Epi- genetics:themissinglinktounderstanding beta-celldysfunction in the pathogenesis of type 2 diabetes. Epi- genetics 2012; 7:841–852.
22. M. Tiedge, S. Lortz, J. Drinkgern, and S. Lenzen, "Relation between antioxidant enzyme gene expression and antioxidative defense status of insulin-producing cells," Diabetes, 1997; 46:1733–1742.
23. Oxidative stress. From: http://www.plantstress.com/Articles. Accessed: Dec 1996.
24. Butterfield DA, Howard B, Subramaniam R, Hall N, Hensley K, Yatin S, et al. Structural and functional changes in proteins induced by free radicalmediated oxidative stress and protective action ofthe antioxidants N-tert-butyl-alpha-phenylnitrone and vitamin E. Ann N Y Acad Sci 1998;854:448–62.
25. Brosnan JT, Man KC, Hall HE, Clobourne SA, Brosnan ME. Inter organ metabolism of amino acidsin streptozotocin-diabetic rats. Am J Physiol 1984; 244:E151-8.
26. Peavy DE, Taylor JM, Jefferson LS. Time course of changes in albumin synthesis and mRNA in diabeticand insulin treated diabetic rats. Am J Physiol 1985; 248:E656-63.
27. Leeuwen C, Rasmussen JE, Hsu FF, Mueller DM,Pennathur S, Heinecke JW. Mass spectrometricquantification of markers for protein oxidation by tyrocyle radicals, copper, and hydrocyle radicals inLDL isolated from human athersosclerotic plaques. J Biol Chem 1997; 227:3520-6.
28. Esterbauer H, Schaur RJ, Zollner H. Chemistry and biochemistry of 4-hydroxynonenal malonaldehydeand related aldehydes. Free Radic Biol Med 1991; 11:81-128.
29. Aronson D, Rayfield EJ (2002) How hyperglycemia promotes atherosclerosis: molecular mechanisms. Cardiovasc Diabetol 2002; 1: 1.
30. Boullier A, Bird DA, Chang MK, Dennis EA, Friedman P, et al. Scavenger receptors, oxidized LDL, and atherosclerosis. Ann N Y AcadSci2001; 947: 214-222.
31. Hatice, P. Lipid peroxidation and resistance to oxidation in patients with type 2 diabetes mellitus. Tohuku J. Exp. Med.2004; 203: 211–218.
32. Esterbauer, H., Schaur, R.J.r., Zollner, H.,. Chemistry and

biochemistry of 4-hydroxynonenal, malonaldehyde and related aldehydes. Free Rad. Biol. Med;1991: 11 , 81–128.
33. Sato Y, Hotta N, Sakamoto N, Matsuoka S, Ohishi N, et al. Lipid peroxide level in plasma of diabetic patients. Biochem Med 1997;21: 104-107.
34. Murphy . M.P, How mitochondria produce reactive oxygen species, Biochem. J. 2009;417:1–13.
35. Kowaltowski A.J. , de Souza-Pinto N.C., Castilho R.F., Vercesi A.E., Mitochondria and reactive oxygen species, Free Radic. Biol. Med. 2009;47: 333–343.
36. Hogg .N . Inhibition of low-density lipoprotein oxidation by nitric oxide potential role in atherogenesis. FEBS Lett. 1993;334:170–4.
37. Korshunov SS, Skulachev VP, Starkov AA. High protonic potential actuates a mechanism of production of reactive oxygen species in mitochondria. FEBS Lett. 1997;416:15–8.
38. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001;414:813–20.
39. Nishikawa T, Edelstein D, Brownlee M. The missing link: a single unifying mechanism for diabetic complications. Kidney Int. 2000;58:6–30.
40. Trumpower B.L. , The protonmotive Q cycle. Energy transduction by coupling of proton translocation to electron transfer by the cytochrome bc1 complex, J. Biol. Chem. 1990;265:11409–11412.
41. Schroder M, Kaufman RJ , ER stress and the unfolded protein response. Mutat Res 2005; 569:29–63
42. Shi Y, Taylor SI, Seng-Lai T, Sonenberg N When translation meets metabolism: multiple links to diabetes. Endocr Rev 2003; 24:91–101
43. Murphy, M.P. Mitochondrial dysfunction indirectly elevates ROS production by the endoplasmic reticulum. Cell Metab. 2013;18:145–146.
44. Malhotra, J.D.; Kaufman, R.J. Endoplasmic reticulum stress and oxidative stress: A vicious cycle or a doubleedged sword? Antioxid.Redox Signal.2007; 9: 227–2293.
45. Ignarro, L. J. in Nitric Oxide Biology and Pathobiology, ed. Ignarro, L. J. (Academic, San Diego), 2000; 3–19.
46. Kaufman, R. J. (1999) Genes Dev. 13, 1211–1233.40 Mori, K. (2000) Cell 101, 451–454.
47. Pober J. S and Sessa W. C., Evolving functions of endothelial cells in inflammation, Nature Reviews Immunology, vol. 2007;7:803–815.
48. D. N. Sang and P. A. D'Amore,Is blockade of vascular endothelial growth factor beneficial for all types of diabetic retinopathy? Diabetologia, 2008; 51: 1570–1573.
49. Ramasamy R, Goldberg IJ. Aldose reductase and cardiovascular diseases, creating human-like diabetic complications in an experimental model. Circ Res. 2010;106:1449 –1458
50. Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circ Res. 2010;107:1058–1070
51. Aldebasi Y, El-Gendy SM, Kamel A, Mohieldein A. Aldo-ketoreductase and sorbitol dehydrogenase enzymes in Egyptian diabetic patients with and without proliferative diabetic retinopathy. ClinExpOptom. 2013;96:303–309.
52. Hotta N. New concepts and insights on pathogenesis and treatment of diabetic complications: polyol pathway and its inhibition. Nagoya J Med Sci. 1997;60:89–100
53. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001;414:813–820.
54. Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circ Res. 2010;107:1058–1070.
55. Yan LJ. Pathogenesis of chronic hyperglycemia: from reductive stress to oxidative stress. J Diabetes Res. 2014;2014:137-919.
56. Baynes JW. Role of oxidative stress in development of complications in diabetes.Diabetes. 1991;40:405–412.
57. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. Nature. 2001;414:813–820.
58. Helou C, Marier D, Jacolot P, Abdennebi-Najar L, Niquet- Léridon C, Tessier FJ, Gadonna-Widehem P. Microorganisms and Maillard reaction products: a review of the literature and recent findings. Amino Acids. 2013.
59. Monnier VM, Nagaraj RH, Portero-Otin M, Glomb M, Elgawish AH, Sell DR, Friedlander MA. Structure of advanced Maillard reaction products and their pathological role.Nephrol Dial Transplant. 1996;11:20-26.
60. Kikuchi S, Shinpo K, Takeuchi M, Yamagishi S, Makita Z, Sasaki N, Tashiro K. Glycation--a sweet tempter for neuronal death. Brain Res Brain Res Rev. 2003;41:306-323.
61. Lapolla A, Fedele D, Garbeglio M, Martano L, Tonani R, Seraglia R, Favretto D, Fedrigo MA, Traldi P. Matrix-assistedlaser desorption/ionization mass spectrometry, enzymatic digestion, and molecular modeling in the study of nonenzymatic glycation of IgG. J Am Soc Mass Spectrom. 2000; 11:153-159.
62. Bork P, Holm L, Sander C. The immunoglobulin fold. Structural classification, sequence patterns and common core. JMol Biol. 1994;242:309-320
63. Ahmad S, Moinuddin, Khan RH, Ali A. Physicochemical studies on glycation-induced structural changes in human IgG. IUBMB Life.2012;64:151-156
64. Said G, Guilbert M, Millerot-Serrurot E, Van Gulick L, Terryn C, Garnotel R, Jeannesson P. Impact of carbamylation and glycation of collagen type I on migration of HT1080 human fibrosarcoma cells. Int J Oncol. 2012;40:1797-1804.
65. Avery NC, Bailey AJ. The effects of the Maillard reaction on the physical properties and cell interactions of collagen. Pathol Biol (Paris). 2006;54:387-395.
66. Sanguineti R, Storace D, Monacelli F, Federici A, Odetti P. Pentosidine effects on human osteoblasts in vitro. Ann N YAcad Sci. 2008;1126:166-172.
67. Wang X, Shen X, Li X, Agrawal CM. Age-related changes

in the collagen network and toughness of bone. Bone.2002; 31:1-7.
68. Alikhani M, Alikhani Z, Boyd C, MacLellan CM, Raptis M, Liu R, Pischon N, Trackman PC, Gerstenfeld L, Graves DT. Advanced glycation end products stimulate osteoblast apoptosis via the MAP kinase and cytosolic apoptotic pathways. Bone. 2007;40:345-353.
69. Kemeny SF, Figueroa DS, Andrews AM, Barbee KA, Clyne AM. Glycated collagen alters endothelial cell actin alignmentand nitric oxide release in response to fluid shear stress. J Biomech. 2011;44:1927-1935.
70. Yuen A, Laschinger C, Talior I, Lee W, Chan M, Birek J, Young EW, Sivagurunathan K, Won E, Simmons CA, McCulloch CA. Methylglyoxal-modified collagen promotes myofibroblast differentiation. Matrix Biol. 2010;29:537-548.
71. Rubenstein DA, Yin W. Glycated albumin modulates platelet susceptibility to flow induced activation and aggregation Platelets. 2009;20:206-215.
72. Unoki H, Bujo H, Yamagishi S, Takeuchi M, Imaizumi T, Saito Y. Advanced glycation end products attenuate cellular insulin sensitivity by increasing the generation of intracellular reactive oxygen species in adipocytes. Diabetes Res Clin Pract. 2007;76:236-244.
73. Dunn EJ, Philippou H, Ariëns RA, Grant PJ. Molecular mechanisms involved in the resistance of fibrin to clot lysis by plasmin in subjects with type 2 diabetes mellitus. Diabetologia. 2006;49:1071-1080.
74. Jörneskog G, Hansson LO, Wallen NH, Yngen M, Blombäck M. Increased plasma fibrin gel porosity in patients with Type I diabetes during continuous subcutaneous insulin infusion. J Thromb Haemost. 2003;1:1195-1201.
75. Hortelano S. Lopez-Fontal R. Traves PG. Villa N. Grashoff C. Bosca L. Luque A. ILK mediates LPS-induced vascular adhesion receptor expression and subsequent leucocyte trans-endothelial migration. Cardiovasc Res. 2010;86:283–292.
76. Iademarco MF. McQuillan JJ. Rosen GD. Dean DC. Characterization of the promoter for vascular cell adhesion molecule-1 (VCAM-1) J Biol Chem. 1992;267:16323–16329.
77. Lee YW. Kuhn H. Hennig B. Neish AS. Toborek M. IL-4-induced oxidative stress upregulates VCAM-1 gene expression in human endothelial cells. J Mol Cell Cardiol. 2001;33:83–94.
78. Luo SF. Fang RY. Hsieh HL.Chi PL. Lin CC. Hsiao LD. Wu CC. Wang JS.Yang CM. Involvement of MAPKs and NF-kappaB in tumor necrosis factor alpha-induced vascular cell adhesion molecule 1 expression in human rheumatoid arthritis synovial fibroblasts.Arthritis Rheum. 62:105–116.
79. Mackay F. Loetscher H. Stueber D. Gehr G. Lesslauer W. Tumor necrosis factor alpha (TNF-alpha)-induced cell adhesion to human endothelial cells is under dominant control of one TNF receptor type, TNF-R55. J Exp Med. 1993;177:1277–1286.
80. Li YM, Mitsuhashi T, Wojciechowicz D, Shimizu N, Li J, Stitt A, He C, Banerjee D, Vlassara H. Molecular identity and cellular distribution of advanced glycation endproduct receptors: relationship of p60 to OST-48 and p90 to 80K-H membrane proteins. Proc Natl Acad Sci U S A. 1996;93:11047-11052.
81. Jung HA, Jung YJ, Yoon NY, Jeong da M, Bae HJ, Kim DW, Na DH, Choi JS. Inhibitory effects of Nelumbo nucifera leaves on rat lens aldose reductase, advanced glycation endproducts formation, and oxidative stress. Food Chem Toxicol. 2008;46:3818-3826.
82. Xia P, Inoguchi T, Kern TS, Engerman RL, Oates PJ, King GL. Characterization of the mechanism for the chronic activation of diacylglycerol-protein kinase C pathway in diabetes and hypergalactosemia. Diabetes 1994;43:1122–1129.
83. Steinberg SF. Structural basis of protein kinase C isoform function. Physiol Rev 2008;88:1341–1378.
84. Derubertis FR, Craven PA. Activation of protein kinase C in glomerular cells in diabetes. Mechanisms and potential links to the pathogenesis of diabetic glomerulopathy. Diabetes 1994; 43: 1–8.
85. Ishii H, Jirousek MR, Koya D et al. Amelioration of vascular dysfunctions in diabetic rats by an oral PKC b inhibitor. Science 1996; 272: 728– 731.
86. Craven PA, Davidson CM, DeRubertis FR. Increase in diacylglycerol mass in isolated glomeruli by glucose from de novo synthesis of glycerolipids. Diabetes 1990; 39: 667–674.
87. Inoguchi T, Battan R, Handler E et al. Preferential elevation of protein kinase C isoform {beta}II and diacylglycerol levels in the aorta and heartof diabetic rats: differential reversibility to glycemic control by islet cell transplantation. Proc Natl Acad Sci USA 1992; 89: 11059–11063.
88. Shiba T, Inoguchi T, Sportsman JR et al. Correlation of diacylglycerol level and protein kinase C activity in rat retina to retinal circulation. Am J. Physiol Endocrinol Metab 1993; 265: E783–E793.
89. Considine RV, Nyce MR, Allen LE et al. Protein kinase C is increased in the liver of humans and rats with non-insulin-dependent diabetes mellitus: an alteration not due to hyperglycemia. J Clin Invest 1995; 95: 2938–2944.
90. Saha AK, Kurowski TG, Colca JR et al. Lipid abnormalities in tissues of the KKAy mouse: effects of pioglitazone on malonyl-CoA and diacylglycerol. Am J Physiol Endocrinol Metab 1994; 267: E95–E101.
91. Lynch JJ, Ferro TJ, Blumenstock FA, Brockenauer AM, Malik AB. Increased endothelial albuminpermeability mediated by protein kinase C activation. J Clin Invest 1990;85:1991–1998.
92. Wolf BA, Williamson JR, Easom RA, Chang K,

Sherman WR, Turk J. Diacylglycerol accumulation and microvascular abnormalities induced by elevated glucose levels. J Clin Invest 1991;87:31–38.

93. Hink U, Li H, Mollnau H, Oelze M, Matheis E, Hartmann M, Skatchkov M, Thaiss F, Stahl RA,Warnholtz A, Meinertz T, Griendling K, Harrison DG, Forstermann U, Munzel T. Mechanisms underlying endothelial dysfunction in diabetes mellitus. Circ Res 2001;88:E14–22.
94. Cardillo C, Campia U, Bryant MB, Panza JA. Increased activity of endogenous endothelin in patients with type 2diabetes mellitus. Circulation 2002;106:1783–1787.
95. Cosentino F, Eto M, De Paolis P, van der Loo B, Bachschmid M, Ullrich V, Kouroedov A, Delli Gatti C, Joch H, Volpe M, Luscher TF. High glucose causesupregulation of cyclooxygenase-2 and alters prostanoid profile in human endothelial cells: Role of protein kinase C and reactive oxygen species. Circulation 2003;107:1017–1023.
96. Way KJ, Katai N, King GL. Protein kinase C and the development of diabetic vascular complications. Diabet Med 2001;18:945–959.
97. Giacco F, Brownlee M. Oxidative stress and diabetic complications. Circulation Research. 2010;107:1058–1070.
98. Bursell SE, Clermont AC, Kinsley BT, Simonson DC, Aiello LM, Wolpert HA. Retinal blood flow changes in patients with insulin-dependent diabetes mellitus and no diabeticretinopathy. InvestOphthalmol Vis Sci 1996;37:886–897.
99. Koya D, King GL. Protein kinase C activation and the development of diabetic complications. Diabetes. 1998;47:859–866.
100. Menne J, Park JK, Boehne M, Elger M, Lindschau C, Kirsch T, Meier M, Gueler F, Fiebeler A,Bahlmann FH, Leitges M, Haller H. Diminished loss of proteoglycans and lack of albuminuria in protein kinase C-alpha-deficient diabetic mice. Diabetes 2004;53:2101–2109.
101. Thallas-Bonke V, Thorpe SR, Coughlan MT, Fukami K, Yap FY, Sourris KC, Penfold SA, BachLA, Cooper ME, Forbes JM. Inhibition of NADPH oxidase prevents advanced glycation end product-mediated damage in diabetic nephropathy through a protein kinase C-alpha-dependent pathway. Diabetes 2008;57:460–469.
102. Kelly DJ, Edgley AJ, Zhang Y, Thai K, Tan SM, Cox AJ, Advani A, Connelly KA, Whiteside CI, Gilbert RE. Protein kinase C-beta inhibition attenuates the progression of nephropathy in nondiabetic kidney disease. Nephrol Dial Transplant 2009;24:1782–1790.
103. Kelly DJ, Edgley AJ, Zhang Y, Thai K, Tan SM, Cox AJ, Advani A, Connelly KA, Whiteside CI, Gilbert RE. Protein kinase C-beta inhibition attenuates the progression of nephropathy in nondiabetickidney disease. Nephrol Dial Transplant 2009;24:1782–1790.
104. Marshall S, Bacote V, Traxinger RR. Discovery of a metabolic pathway mediating glucose-induced desensitization of the glucose transport system. Role of hexosamine biosynthesis in the induction of insulin resistance. J Biol Chem 1991;266:4706–4712.
105. Parker G, Taylor R, Jones D, McClain D. Hyperglycemia and inhibition of glycogen synthase in streptozotocin-treated mice: role of O-linked N-acetylglucosamine. J Biol Chem 2004;279:20636–20642.
106. Parker GJ, Lund KC, Taylor RP, McClain DA.Insulin resistance of glycogen synthase mediated by o-linked N-acetylglucosamine. J Biol Chem 2003;278:10022–10027.
107. Chen YQ, Su M, Walia RR, Hao Q, Covington JW, Vaughan DE. Sp1 sites mediate activation of theplasminogen activator inhibitor-1 promoter by glucose in vascular smooth muscle cells. J Biol Chem 1998;273:8225–8231.
108. Comer FI, Hart GW. Reciprocity between O-GlcNAc and O-phosphate on the carboxyl terminaldomain of RNA polymerase II. Biochemistry 2001;40:7845–7852.
109. Du XL, Edelstein D, Rossetti L, Fantus IG, Goldberg H, Ziyadeh F, Wu J, Brownlee M.Hyperglycemia-induced mitochondrial superoxide overproduction activates the hexosaminepathway and induces plasminogen activator inhibitor-1 expression by increasing Sp1 glycosylation. Proc Natl Acad Sci U S A 2000;97:12222–12226.
110. James LR, Fantus IG, Goldberg H, Ly H, Scholey JW. Overexpression of GFAT activates PAI-1promoter in mesangial cells. Am J Physiol Renal Physiol 2000;279:F718–727.
111. Pouwels MJ, Tack CJ, Span PN, Olthaar AJ, Sweep CG, Huvers FC, Lutterman JA, Hermus AR. Role of hexosamines in insulin resistance and nutrient sensing in human adipose and muscle tissue J Clin Endocrinol Metab 2004;89:5132–5137.