Pathomechanisms of non-coding RNAs and hub genes related to the oxidative stress in diabetic complications [version 1; peer review: awaiting peer review]

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Abstract
Cytokine storms, oxidative stress, and hyperglycemia can enhance the risk of type 2 diabetes (T2D). Moreover, T2D may change the functional and structural heart. However, some signaling pathways, such as insulin resistance, dyslipidemia, and hyperglycemia, can play in T2D, and various pathomechanics and pathophysiology involved in T2D are not understood. Moreover, it is well documented that the non-coding RNAs are potentially pivotal molecules in oxidative stress, inflammation, and cell death signaling pathways. Hence, long non-coding RNAs (lncRNAs) and microRNAs may have vital roles in oxidative stress, inflammation, metabolism, T2D, and cardiovascular systems. Non-coding RNAs can target hub gene networks and suppress or trigger various cascades. Furthermore, lifestyle is the other factor that may affect the prevalence of T2D. A sedentary lifestyle and excessive sitting can enhance inflammation, oxidative stress, and hyperglycemia. Here, we attempt to comprehend the role of hub genes, non-coding RNAs, and unhealthy lifestyles on the pathomechanics and pathophysiology of diabetic vascular complications.

Keywords
Diabetes, Cardiovascular diseases, Oxidative stress, Inflammation, Non-coding RNAs, Lifestyle

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Introduction

Type 2 diabetes (T2D) has been classified as one of the four primary non-communicable diseases (NCDs), and it demands immediate medical attention to manage its prevalence and related problems. Growing evidence indicates that T2D could be a severe metabolic condition affecting more than 400 million individuals globally, and predicts that this number might surpass 600 million by 2040.\textsuperscript{2,3} Statistical evidence has demonstrated that T2D is a top 10 cause of death globally, killing over 1.5 million people worldwide.\textsuperscript{4} Moreover, T2D is the third most significant risk factor for worldwide premature mortality due to inflammation, hyperglycemia, and oxidative stress.\textsuperscript{5} Vascular complications, macrovascular and microvascular, are the leading causes of morbidity and mortality in people with diabetes, placing a significant economic burden on developed and developing nations due to disparities in healthcare spending and the inaccessibility of effective medicines.\textsuperscript{5,6} There is a well-established clinical connection between diabetes and atherosclerotic lesions.\textsuperscript{7} Foam cell production, fatty streak development, and plaque rupture are all proven to occur during atherosclerotic damage. In atherosclerotic lesions, vulnerable plaque development generates systemic inflammation that ultimately results in myocardial infarction.\textsuperscript{8}
T2D is recognized by β-cell dysfunction and hyperglycemia, which result in defective or inadequate insulin receptor activity, impaired function, and early destruction of insulin during its synthesis. Immense studies have indicated that T2D leads to severe chronic complications such as cardiovascular disease, peripheral nerve damage, neuropathy, retinopathy, and nephropathy. Impaired glucose tolerance in T2D is associated with insulin resistance, and insulin shortage impacts glucose consumption in the liver, adipose tissues, and skeletal muscle. Recent studies have revealed oxidative stress as a critical player in developing diabetes complications. Hyperglycemia causes increased oxidative stress, pro-inflammatory proteins, and infiltrating macrophages secreting inflammatory cytokines that impair the body’s function. Moreover, It has been discovered that insulin resistance is associated with increased inflammation molecules such as tumor necrosis factor-alpha (TNF-α) production.

The release of bioactive metabolites from adipocytes, such as lipids, free fatty acids, monocyte chemoattractant protein-1, and pro-inflammatory cytokines, have been associated with insulin resistance in obese people. On the other hand, evidence has indicated that the human body has an antioxidant defense mechanism that drastically lowers the rate at which oxidizing chemicals are oxidized. There are both enzymatic and non-enzymatic antioxidants in the human body. Glutathione peroxidase (GPX), catalase (CAT), and superoxide dismutase (SODs) are examples of enzymes that neutralize free radicals (Figure 1).

Figure 1. Oxidative stress process-related protein–protein interactions in the genetics network according to the network’s visualization parameters.
Even though many pathophysiological changes are produced by metabolic disorders such as insulin resistance, hyperglycemia, and dyslipidemia, oxidative stress may have a vital role in the physiological and pathological mechanisms of T2D.20 However, immense evidence has indicated that the vital role of oxidative stress in T2D, the molecular mechanism of oxidative stress is not elucidated. By generating ceramides, diacylglycerol, and reactive oxygen species (ROS), free fatty acids can accelerate oxidation and accumulate in the cytosol, resulting in lipotoxicity. Along with the development of cardiac glucotoxicity, hyperglycemia produces a rise in the concentration of ROS and the production of advanced glycation end products (AGEs). In addition, cell death is induced by ROS, which can have significant consequences that modulate pathogenic reactions in the rest of the cells, resulting in dysfunction and remodeling.21,22

Besides, oxidative stress can trigger inflammation, cytokine storm, nitric oxide (NO) accumulation, mitochondrial dysfunction, and reduced mitochondrial biogenesis.10 Furthermore, epidemiology studies demonstrated that a sedentary lifestyle and excessive sitting caused dysmetabolic conditions.23 Furthermore, a lifestyle change, including being physically active, avoiding smoking and drinking, and eating healthy, could prevent many occurrences of T2D.24,25

Based on the data mining, oxidative stress plays a key role in T2D, but the precise mechanism and essential factors related to oxidative stress are not comprehended. Hence, The main goal of this review article attempt to find out:

1. The cellular mechanisms relating oxidative stress and cell death in T2D.
2. The role of the non-coding RNAs and oxidative stress in managing T2D.
3. Finally, we will discuss how lifestyle can enhance oxidative stress in the body.

**Cellular mechanisms relating oxidative stress and cell death in T2D**

Free radicals and other non-radical reactive derivatives are referred to as oxidants and are collectively referred to as ROS and reactive nitrogen species (RNS).26 Highly reactive molecules created during normal cellular metabolism react with a wide range of organic substrates, including lipids, deoxyribonucleic acid (DNA), and proteins.27 Oxidative radicals, including superoxide (O2 \(^{−}\)), hydroxyl radical (-OH), and hydrogen peroxide (H2O2), are produced at high concentrations in response to oxidative stress, leading to damaged cells and even cell death.28 Oxidative stress and cell death are hallmarks of diabetes and cardiovascular diseases, although managing these hallmarks may help postpone the development of diabetes and diabetic vascular complication.14

*In silico* and bioinformatics analysis have revealed that the hub genes involved in cell death, cytokine production, and oxidative stress pathways could be related to T2D (Figures 1–3). As a significant target in cardiac apoptosis, the cytochrome C (Cycs), sirtuin 3 (Sirt3), B-cell lymphoma 2 (Bcl-2), and Fas cell surface death receptor (Fas) network may be essential for preventing heart failure.29 BCl-2 protein may inhibit the cell death apoptosis pathway and can reduce cytochrome C activity in mitochondria, whereas apoptosis activators such as BAX (BCL2 Associated X) can increase cytochrome C secretion.30 Under certain pathological situations, the interaction between FAS and FAS ligands may also mediate the apoptotic death of cardiac cells. Thereby, hyperglycemia prompts the increased ROS, releasing cytochrome C, mitochondrial malfunction, and damage to heart tissue.31–33

Based on the evidence, Sirt3 is identified as a coding gene that encodes class III histone deacetylases of the sirtuin family and is exclusively found in the mitochondrial matrix membrane. Consequently, this gene may function as a master regulator under various circumstances and induce apoptosis.29,34 In addition, Sirt3 has been discovered as a gene with far-reaching effects on energy metabolism, aging, apoptosis, diabetes, cardiovascular diseases, and neurological illnesses.35,36 Enhancement of ROS production causes oxidative stress, which triggers several cellular alterations.37 Increased ROS generation and apoptotic activation in β-cells are hallmarks of diabetes, whether the condition is acute or chronic.38 Tissue damage in the retina, heart, nervous system, and kidneys may lead to apoptosis and necroptosis, all of which play critical roles in developing diabetes complications.39,40 Growing evidence has indicated that apoptosis, autophagy, necroptosis, and ferroptosis are the categories of cellular death41–47 (Figure 3).

It should be noted that cell death mechanisms have a diversity of functions. The nomenclature committee on cell death (NCCD) has developed criteria for the morphological, biochemical, and functional classifications and descriptions of cell death.47 Type 1 cell death (apoptosis) occurs following cytoplasmic shrinkage, chromatin condensation (pyknosis), nuclear fragmentation (karyorrhexis), apoptotic bodies formation, phagocytic activity, and degradation within lysosomes by neighboring cells.48 Immense evidence has indicated that triggered Caspase is a crucial mechanism for inducing cell death.37 Multiple triggers operate on different cellular components in the intrinsic process of apoptosis, also called the
mitochondrial pathway.  As well as, after environmental damage, natural killer cells and macrophages release death molecules that, upon binding with death receptors (DRs) on the target extracellular membrane, trigger the extrinsic cascade of apoptosis by activating procaspase 8 to caspase 8. The DRs are a class of proteins that belong to the TNF (tumor necrosis factor) superfamily.

On the other hand, saturated fatty acid lipid peroxidation is dramatically accelerated in the presence of iron, especially divalent iron. Cells generate ROS in addition to ATP during iron-dependent oxidative phosphorylation in the mitochondria. An oxidative stress response is triggered when the amounts of ROS in a cell are higher than its ability to neutralize them, and this can cause harm or death to the cell by directly or indirectly damaging significant molecular components, including proteins, nucleic acids, and lipids. Hence, increased levels of iron-dependent lipid peroxide cause ferroptosis cell death. Initiating ferroptosis requires reactive oxygen species production and iron availability.

Moreover, According to recent investigations, autophagy has emerged as a critical position in preventing insulin resistance and death generated by oxidative stress in pancreatic islet beta cells. Antioxidant-rich proteins and organelles are degraded and recycled by autophagy to preserve cellular homeostasis. ER stress, starvation, and growth factor deficiency can all trigger this process. Reducing aberrant protein build up, eliminating intracellular infections, and eliminating aberrant proteins can all be achieved by autophagy. This vital process directly influences cellular homeostasis.
and cell survival. According to growing research, autophagic dysfunction has been linked to numerous disorders, including tumors, neurodegenerative diseases, and inflammatory diseases. Autophagy may have a role in the pathophysiology of metabolic diseases like diabetes by redistributing resources away from inefficient activities and toward crucial ones essential for life.

Necroptosis is the best-understood format of programmed necrosis death, exhibiting necrosis and apoptosis characteristics. TNF-1 (TNFR1) and Fas receptor ligands are involved in the cascade of necroptosis activation in response to high glucose stimulation. As well as necroptosis, damage-associated molecular patterns (DAMPs), nucleotide binding and oligomerization domain (NLRs), ripoptosome, and protein kinases R (PKR) complex are also involved. Apoptosis, necroptosis, or cell survival are all potential outcomes of TNFR1 binding to TNFs. Cell survival, apoptosis, or necroptosis are three distinct obligations that various signaling complexes can mediate following TNFR1 activation by TNFs binding. Based on the evidence, complex-I promotes survival, while complex IIa promotes apoptosis. Necroptosis occurs as a result of the development of complex IIb. Moreover, necroptosis is regulated by the receptor-interacting protein 3 (RIP3). In diabetes, RIP3 controls necroptosis by regulating RIP1 in a RIP-dependent way. RIP3 is triggered by self-phosphorylation to enhance MLKL phosphorylation after being recruited by RIP1 during high glucose exposure. This results in the cell membrane being permeable when MLKL oligomers translocate to the cell membrane, interacting with PI(3,4,5)P3 lipids and cardiolipin. It has been discovered that CaMKII, a recently discovered RIP3 substrate, induces necroptosis. The myocardium contains a lot of CaMKII, which is usually inactive. RIP1 phosphorylation or Ca2+ phosphorylation of CaMKII is a necroptosis-inducing factor. High glucose raises ROS, oxidizing CaMKII and activating it.

![Figure 3. Protein–protein interactions in the genetics network are associated with apoptosis.](image-url)
To sum up, these pathogenic alterations lead to necroptosis by activating the mitochondrial permeability transition (mPTP). Some evidence suggested that knocking down CypD, which increased the likelihood of mPTPs opening, could protect against RIP3-induced cardiomyocyte necrosis. Finally, the opening of the mPTP is brought about by the up-regulation of RIP3, which increases CypD phosphorylation and boosts PGAM5 expression. As the death signal was amplified, necroptosis occurred in the endothelial cells due to excessive mPTP opening.

On the other hand, toll-like receptor 4 (TLR4) activation is another critical mechanism of ROS and hyperglycemia that can trigger apoptosis. A literature review revealed that the expression of the TLR4 is up-regulated in diabetic conditions, and TLR4 gene silencing may be able to regulate cardiac apoptosis in diabetes. Evidence has demonstrated an association between TLR4 and oxidative stress. As a result, the reduction of TLR4 leads to the dampening of stress responses, and caspase 3 in cardiomyocytes may be inhibited.

Notably, the inflammatory mediators of diabetes, such as lipoprotein-associated phospholipase A2, adiponectin, tumor necrosis factor-a (TNF-a), high mobility group box-1 (HMGB-1), advanced glycation end products (AGEs), and chemokines, interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8), and interleukin-18 (IL-18). Upregulation of these inflammatory mediators might activate nuclear factor xB (NF-xB), which induces cytokine storm and angiogenic mediators. Hence, accumulation of the ROS molecule and inflammation agents leads to cell death and impairs the function of the cell.

Nitric oxide (NO), a free radical component with pathophysiological effects, could induce inflammation. Overly, NO is an inflammatory and damaging component due to interactions with the intermediate factors of reactive oxygen species generally available in cells. Several diseases, including lung squamous cell carcinoma, colon cancer, depression, and diabetes, have been coupled to the NO/inflammation signaling cascade pathway. One category of nitric oxide synthase factors, endothelial nitric oxide synthase (eNOS), plays a significant role in managing NO function by stimulating NO synthesis.

Ischemia/reperfusion-induced acute kidney injury, ischemia/reperfusion-induced liver injury, hypertension, and steatohepatitis have been highlighted as associated disorders with the PPAR/eNOS axis. Even though the PPAR/eNOS axis mediates the inflammatory status involved in T2DM pathogenesis, the mechanism and vital molecules remain controversial.

Overall, based on the mentioned evidence, we could conclude that enhanced ROS molecules mediated the other pathomechanisms such as inflammation, apoptosis, autophagy, necroptosis, and ferroptosis. Furthermore, we found that oxidative stress correlated with inflammation and cell death based on the in silico analysis (Figure 2).

**Non-coding RNAs and oxidative stress in the management of type 2 diabetes**

The pathogenetic state is established by interactions between genetic and epigenetic elements and may be affected by several regulatory elements. The length of non-coding RNAs is utilized for the recognition category of short non-coding RNAs and long non-coding RNAs (LncRNAs). MicroRNAs (miRNAs), one type of short non-coding RNA consisting of around 20–25 nucleotides, have a role in the biological processes by modifying the post-translational events of mRNAs. miRNAs regulate gene expression through binding to specific seed sequences in the 3′ untranslated region (3′UTR) of target genes. Moreover, miRNAs are considered significant biomolecules involved in the beginning, development, prognosis, diagnosis, and therapy of different pathophysiological indications due to their role as fine tuners of gene expression, control of signaling, and molecular-cellular processes. Typically a nucleotide sequence of over 200 bp displaying as long noncoding RNAs (lncRNAs) influences gene expression by many mechanisms. Both the linear and the circular forms of lncRNAs are found in cells and the extracellular space. The lncRNAs that exist in a circular structure are referred to as circular RNAs (circRNAs). Furthermore, the annotated lncRNAs have been used to classify lncRNAs as the signal, decoy, guide, and scaffold molecules. Hence, non-coding RNAs are also interesting and attractive therapeutic targets since of their potential impact on various disease-related cellular processes.

Growing evidence highlighted that lncRNAs have been recognized as significant transcripts involved in oxidative stress, inflammation, cell damage, apoptosis cell death, beta-cell function, insulin resistance/insulin secretion, metabolism, etc., and are now considered potential diagnostic biomarkers. Hence, lncRNAs are potentially pivotal molecules in oxidative stress, inflammation, and cell death studies. Only a significant portion of annotated lncRNAs have been shown to play critical roles in diseases associated with oxidative stress, such as those affecting the nervous, respiratory, metabolism, and cardiovascular systems. Based on the evidence, lncRNAs could be targeting ARE/Nrf2/Keap1 network and, through genetic interactions, are associated with the oxidation and antioxidation balance system. As major effective lncRNAs...
related to oxidative stress conditions could be pointed to the MALAT1, H19, SCAL1, NEAT1, gadd7, MACC1-AS1, ODRUL, LINC01619, LINCO0963, FOXD3-AS1, and BDNF-AS. The previous review study briefly discussed IncRNAs Meg3, SNHG16, MALAT1, GAS5, HOTAIR, and CASC2's role in diabetic cardiovascular vascular damage through the oxidative stress response. Pei-Ming Chu et al. revealed that MEG3 targets miR-145/PDCD4 and HOTAIR by inhibiting miR-34a/SIRT1, miR-126/SIRT1, and P13K/Akt could be regulated oxidative stress in diabetic cardiomyopathy complication status. Moreover, H19/miR-675 axis has been shown to modulate apoptosis cell death of cardiomyocytes by influencing voltage-dependent anion channel 1 (VDAC1), which is one of the several pathways involved in the progression of diabetic cardiomyopathy. Based on a systematic review and in-silico analysis, Cristine Dieter and colleagues revealed that IncRNAs Amril, Hotair, Malat1, Miat, and Kcnq1ot1 are up-regulated in diabetes Mellitus patients compared with control subjects, and MEG3 is down-regulated, consistently.

**Lifestyle and oxidative stress**

Epidemiological evidence has indicated that environmental risk factors such as alcohol, smoking, high-fat diet, and physical inactivity could contribute to oxidative stress. In addition, environmental factors may play a crucial role in the pathogenesis of heart failure and non-communicable diseases. Some studies have demonstrated that ROS might regulate the activity and mechanism of tissues, including muscle, liver, bone, intestinal, and brain. Most tissues, especially muscle and adipose tissue, continuously produce ROS at low-level exercise intensity. ROS production indirectly or directly influences muscle activity by several mechanisms (metabolism, calcium homeostasis, contractility, and excitability), which causes skeletal muscle exhaustion during intense exercise.

Moreover, long exercise training, overtraining syndrome, and exhausting exercises trigger oxidative stress pathways. In contrast, prolonged and low/moderate-intensity training ameliorates endogenous antioxidant status. Based on the evidence, physical activity could up-regulate mitogen-activated protein kinase (MAPK), and NF-κB induces several hub genes and proteins involved in the homeostasis, inflammation, and antioxidant/oxidative intracellular.

Physical activity and dietary modifications are two of the most effective nonpharmacological strategies for many chronic conditions, especially cardiovascular conditions. In addition, ample evidence has revealed that exercise training and physical activity positively affect the cardiovascular system by improving oxidative stress, apoptosis, mitochondrial biogenesis, metabolism, and autophagy. Endurance training could up-regulate the expression level of the PPARγ/Pgc-1α/Fndc5 pathway in the heart and muscle mice. Evidence indicated that FND5C (fibronectin type III domain containing 5) and its cleavage type, irisin, might have an essential role to play in energy regulation and metabolism. Several studies demonstrated that PPARγ/Pgc-1α/Fndc5 could trigger by physical activity and exercise training, which induced the white adipose tissue's browning, and enhanced weight and energy expenditure.

Moreover, Abedpoor and colleagues revealed that the consumption of the branched-chain amino acids (BCAAs) and endurance training significantly regulated the expression of the PPARγ/Pgc-1α/Fndc5 and mitochondrial biogenesis genes such as Tfam, Cox4i1, ATP5a1, ATP5b, and Sirt1. Interestingly, Bahadorani et al. demonstrated that BCAAs and physical activity modified the percentage of sperm lipid peroxidation and sperm parameters. On the other hand, ample evidence indicated that a High-fat diet and diet enriched in advanced glycation end products (AGEs) could dysregulate the detoxification status and increase the oxidative stress in the cells. Besides, endurance exercise and leucine consumption modified the hub genes and IncRNAs involved in the brain-gut axis in mice with depression-like behaviors. In the current study, the authors found common genes, including Kdr/Vegf/Pten/Bdnf, between the hippocampus region and ileum tissue. Moreover, some mediators such as IncRNAs such as MEG3 (maternally expressed 3), GAS5 (growth arrest-specific 5), TUG1 (taurine up-regulated 1), and HOTAIR (HOX transcript antisense RNA) could target the Kdr/Vegf/Pten/Bdnf hub genes and modified by endurance exercise and leucine consumption.

In addition, several evidence indicated that lifestyles such as physical activity and unhealthy diets could impact fertility and sperm function. High-fat diet and diet enriched advanced glycation end products dysregulated the function, parameters, and intracellular reactive oxygen species of sperm. Furthermore, the high-fat diet enriched AGEs enhanced the inflammation and apoptotic signaling pathway in the intestinal of the mice. Based on these data, consuming the high-fat diet enriched significantly increased the IL-6, AGER (advanced glycation end products receptor), ZO-1, P53, and NF-κB. In this study, the relative expression of the Sirt-1 and Ddost were decreased by consumption of the high-fat diet enriched. In the other study, a high-fat diet enriched with AGEs significantly increased the relative expression of the IL-1B, which induced inflammatory bowel disease (IBD). Based on these data, we could conclude that physical inactivity and unhealthy food enhanced the inflammation and oxidative stress in the whole body.

Epidemiology studies revealed that a sedentary lifestyle and ultra-processed foods such as AGEs-rich meals and high carbohydrates distributed the defense mechanisms against oxidative stress, including the Nrf2-Keap1 signaling pathway.
and downstream genes such as HO1, Nqo1, Txn, and Gpx1. These hub genes could regulate antioxidant response elements. AGEs rich meals and physical activity significantly dysregulated the expression level of the Nrf2 HO1, Nqo1, Txn, Gpx1, and antioxidant capacity of the liver in diabetic mice. Notably, physical activity and herbal medicine reversed these hub genes and improved the antioxidant capacity, insulin and glucose concentration, and liver damage in diabetic mice. Impaired muscle mitochondrial function and biogenesis could be the other side effect of the sedentary lifestyle and ultra-processed foods. Hence, the mitochondrial markers were significantly decreased in response to a high-fat diet and ultra-processed foods. These results show that the relative expressions of the Cpt2, Tfam, Pgc-1α, mt-Nd1, mt-Nd5, Ndufa2, Cox8b, Cox5a, mt-Co2, and mt-Co1 were dysregulated. Notably, exercise training and dietary phytochemicals modified and improved the relative expression of genes related to the muscle mitochondrial markers (function and biogenesis) and β-oxidation.

Conclusion
Overall, based on these studies, we could conclude that environmental and exogenous factors have a substantial role in regulating oxidative stress of the cell. Moreover, environmental risk factors could raise ROS production due to oxidative stress, which induces several signaling pathways, including apoptosis, inflammation, autophagy, necroptosis, and ferroptosis.

Data availability
There are no underlying data associated with this article.

Declarations

Ethics approval and consent to participate
N/A

Authors’ contributions
Fatemeh Hajibabaie and Navid Abedpoor conducted the study design. The data mining was evaluated by Fatemeh Hajibabaie, Navid Abedpoor, and Faranak Aali. The manuscript was written by Fatemeh Hajibabaie, Navid Abedpoor, and Faranak Aali and was approved by Navid Abedpoor. The authors declare that all data were generated in-house and that no paper mill was used.

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References

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