

epidemiological factors predisposing to T2D is obesity [9, 14]. Autophagy is a common term for the destruction of the cytoplasmic component within lysosomes [15]. Autophagy machinery has also been implicated in the pathophysiology of T2D, regulating the physiology of pancreatic β -cells [16].

From the standpoint of therapy and to understand all aspects of the disease, we need to know the causative mechanisms. Therefore, it is essential to recognize the factors that are implicated in the pathogenesis of T2D. In this paper, the main factors that cause T2D by collecting practical information are discussed.

Table 1. Effects and consequences of factors that involved in β -cell dysfunction and the pathogenesis of type 2 diabetes.

Mechanism	Effect(s)	Result(s)
Oxidative Stress	Produce reactive oxygen species	Develop insulin resistance, β -cell dysfunction, impaired glucose tolerance and type 2 diabetes
Mitochondrial dysfunction	ATP level that regulates by mitochondria is impaired	The release of insulin that regulates by mitochondrial ATP level is impaired
ER stress	Secretory proteins at significant levels in the ER begin to accumulate in incompletely modified and unfolded forms	The presence of unfolded proteins stimulates unfolded protein response (UPR). The UPR changes its physiological outputs from promoting adaptation to promoting self-destruction if ER stress remains at irretrievably high levels
Autophagy	Protect ER against stress and facilitate mitochondrial turnover	Altered autophagy might lead to the loss of the functional mass of β cells
Inflammation	Changes in levels of specific cytokines and chemokines, changes in the number and activation state of different populations of leukocyte and increased apoptosis and tissue fibrosis	The increased concentration of circulatory cytokines as a result of inflammation is observed in T2D. inflammation participates in the pathogenesis of T2D

DISCUSSION

1. Role of reactive oxygen and nitrogen species in protein oxidation and the pathogenesis of type 2 diabetes

Oxidative stress plays a key role in the beginning and development of T2D [17]. Oxidative stress can be defined as a large amount of ROS, can cause oxidative stress and damage the body's cells and resulting in their death [1]. Oxidative stress has been extensively identified as a significant contributing factor in the development of diabetes, as well as its advancement and tolls [18] (Table 1). The mitochondrial respiratory chain is the main source of ROS in pancreatic β cells. By oxidizing NAD(P)H ROS are produced directly through the reduction of molecular oxygen. cytosolic and plasma membrane oxidoreductases do this [19]. It has previously been reported that the development of insulin resistance and metabolic syndrome can be predicted by markers of oxidative stress and inflammation [20]. Insulin resistance and β cells dysfunction are often present in prediabetes, a condition in which plasma sugar is elevated but not to the extent that diabetes is considered, which can lead to T2D and cardiovascular disease. Hyperglycemia in pre-diabetes can itself cause oxidative stress. On the other hand, oxidative stress impairs the absorption of glucose from fat and muscle cells and reduces insulin secretion from β cells. Using a nicotinamide adenine dinucleotide phosphate (NADPH) oxidase inhibitor can reduce systemic oxidative stress and improve glucose metabolism in a mouse model [21]. The interesting point is that in addition to the constant rise in blood sugar, fluctuations in circulating glucose can also increase oxidative stress (6). Some lactic acid bacteria have antioxidant activity, such as *Lactobacillus rhamnosus*, *Lactobacillus lactics*, and *Lactobacillus plantarum* [22-24]. The lack of homeostasis in diabetes is a result of the endogenous antioxidants and enzymes being downregulated, generating ROS and reactive nitrogen species (RNS), resulting in the loss of cellular adaptation activity [25]. An imbalance in the redox state caused by hyperglycemia can also cause damage to biomolecules, such as lipids, peptides including DNA. The body's various antioxidant production mechanisms protect cells from free radicals damage and help prevent disease. In addition, enzymes such as superoxide dismutase, catalase and glutathione peroxidase, decreased glutathione levels, and vitamins C and E act as antioxidants in the body by optimizing the physiological usage of oxygen via mitochondria. However, if the capacity of the defence system is undermined by damage and the formation of oxidative products, it can lead to cardiovascular disease, cancer, diabetes, neurological, immune and eye diseases, atherosclerosis, and premature death [25-30]. Elevated levels of lipid peroxidation [31, 32], oxidative damage to DNA [28, 33], and protein oxidation [34] have been documented in T2D caused by hyperglycemia, which leads to the production of ROS. Different mechanisms involved in the formation of

ROS, namely glucose autoxidation, stimulation proteins glycation and formation of advanced glycation end products [28, 35]. Hyperinsulinemia and impaired insulin action also lead to elevated ROS [28, 36]. High levels of protein oxidation can lead to diabetes, cardiovascular diseases, and cancer [37]. Nitrotyrosine, produced by the oxidation of tyrosine amino acids, is an essential biomarker for RNS that can be used to estimate oxidative damage to proteins [38]. Nitrotyrosine is not found in healthy subjects but has been found in T2D patients [39]. Myeloperoxidase is also a convenient biomarker for protein oxidation [27].

2. Role of DNA oxidation and diagnostic biomarkers in oxidative stress and pathogenesis of type 2 diabetes

ROS and RNS are major sources of DNA damage because they either modify DNA directly or cause damage indirectly, both of which affect cell viability (Figure 1). The major targets of oxidative stress are mitochondrion and the nucleus. They contain a variety of enzymes to repair DNA changes induced by oxidants. Hydroxyl radicals cause a change in the deoxyribose sugar by reacting with and cross-linking DNA. Thymine glycol and 8-hydroxy guanosine (8-OHdG) are metabolites resulting from oxidative damage to DNA. ROS easily attacks guanine bases in DNA and forms 8-OHdG, which can bind to thymidine instead of cytosine, which is the most common product of oxidative DNA damage. 8-OHdG has also been documented as an important source of oxidative damage in diabetes. Several different ROSs, including hydroxyl radicals, singlet oxygen, peroxy radicals, and peroxyxynitrite, are also responsible for DNA damage. Removal of damaged proteins and organelles by autophagy is one of the protective mechanisms against oxidative stress. Autophagy is a catabolic mechanism that is caused by oxidative stress through lysosomal vesicle formation to protect cells from various stress factors and regular degradation. Several studies have shown that autophagy can postpone apoptotic cell death by supplying the energy required to support DNA repair [28, 30, 40-44].

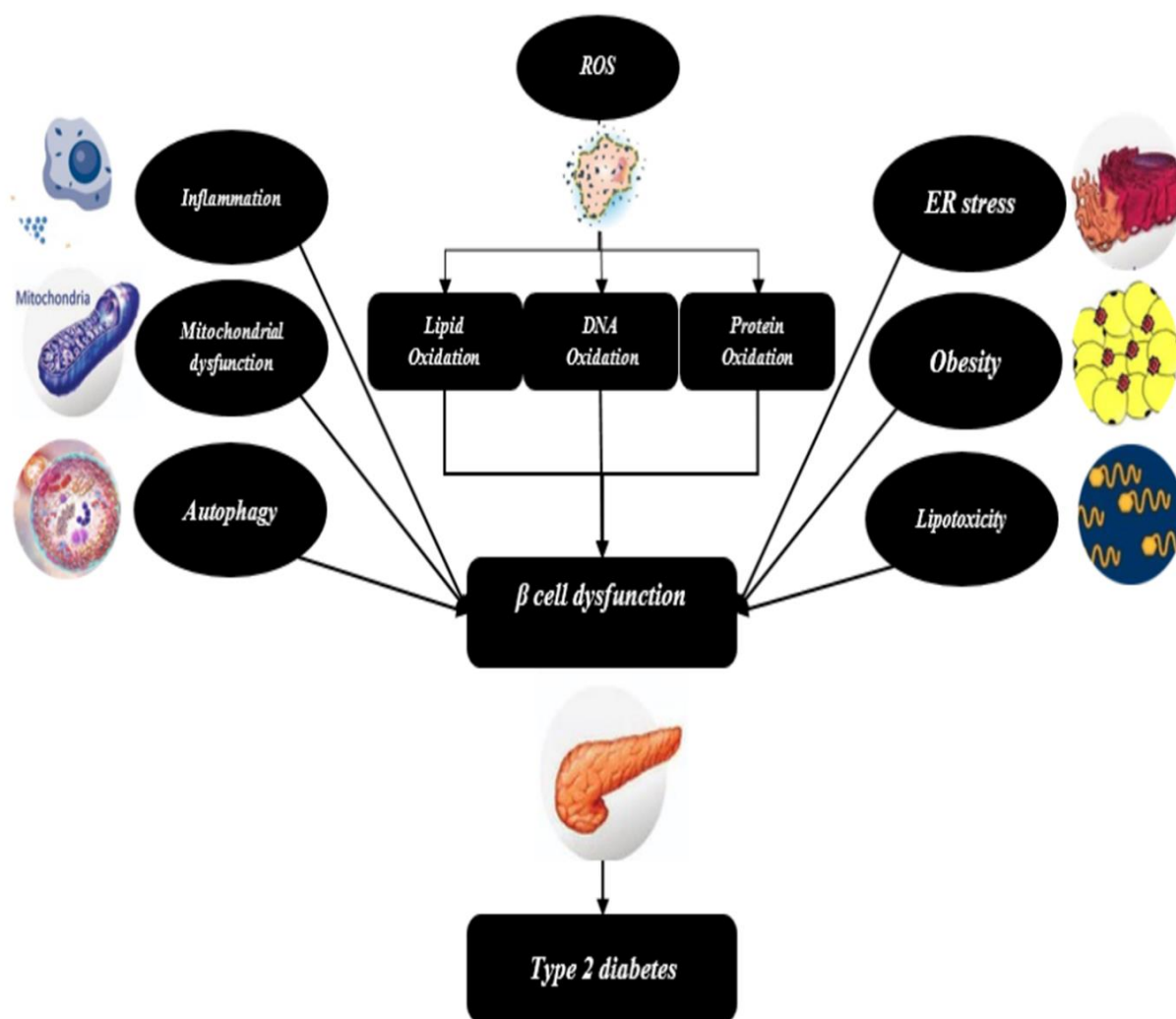


Figure 1. Factors involved in β -cell dysfunction and the pathogenesis of type 2 diabetes.

3. Effects of mitochondrial dysfunction on the pathogenesis of type 2 diabetes

Since mitochondrial DNA (mtDNA) encodes proteins that are part of the electron transport chain (ETC), ROS exposure increases the likelihood of an ETC deficiency and further increases the levels of ROS produced [45]. Oxidative stress is generally associated with diabetes and diabetes is characterized by mitochondrial disorders (Figure 1) [9]. Mitochondria produce ROS through the ETC and ER, mainly through the formation of disulfide bonds during the process of protein folding [45]. Interestingly, T2D patients have been shown to have reduced levels of mtDNA, suggesting a possible role of mitochondria in downstream cell signaling disorders [46]. The role of mitochondria is of significant importance for many aspects of cell metabolism in tissues implicated in the pathogenesis of diabetes mellitus, especially in pancreatic β cells. Mitochondrial oxidative activity inside these tissues must be appropriate for the maximum oxidation of nutrient loads, especially fatty acids. Total oxidation failure will result in aggregation of lipid mediators, fatty acid oxidation of the incomplete products, and production of ROS, causing IR in muscles, liver, and adipose tissue and altered secretion of β -cells (Figure 2) [47]. Many studies have shown changes in the number and morphology of mitochondria in diabetes [9, 48-50]. Insulin deficiency also occurs in diabetes and is related to changes in mitochondrial numbers and morphology [9]. Basal adenosine triphosphate (ATP) levels are elevated in the islets of T2D patients. This rise in the ATP:ADP ratio usually triggers insulin secretion; however, this is not seen in T2D [51]. Microarray results in T2D patients and their first-degree relatives support this hypothesis [7]. Peroxisome proliferator-activated receptor-coactivator α (PGC1 α) is one of the nuclear-encoded genes responsible for regulating the biogenesis of mitochondria and has been identified as a determinant factor in T2D in many studies. It should be noted that mitochondrial biogenesis and its density do not necessarily determine the oxidative function of muscular mitochondria. Different aspects of mitochondria should be considered in the study of mitochondrial function. However, many reports have claimed that the methodologies used *in vivo* or *ex vivo* were able to assess the oxidative activity of muscular mitochondria. The early hypothesis that reductions in mitochondrial function result in the accumulation of increased intramyocellular lipid and IR has not been confirmed by all published reports [52].

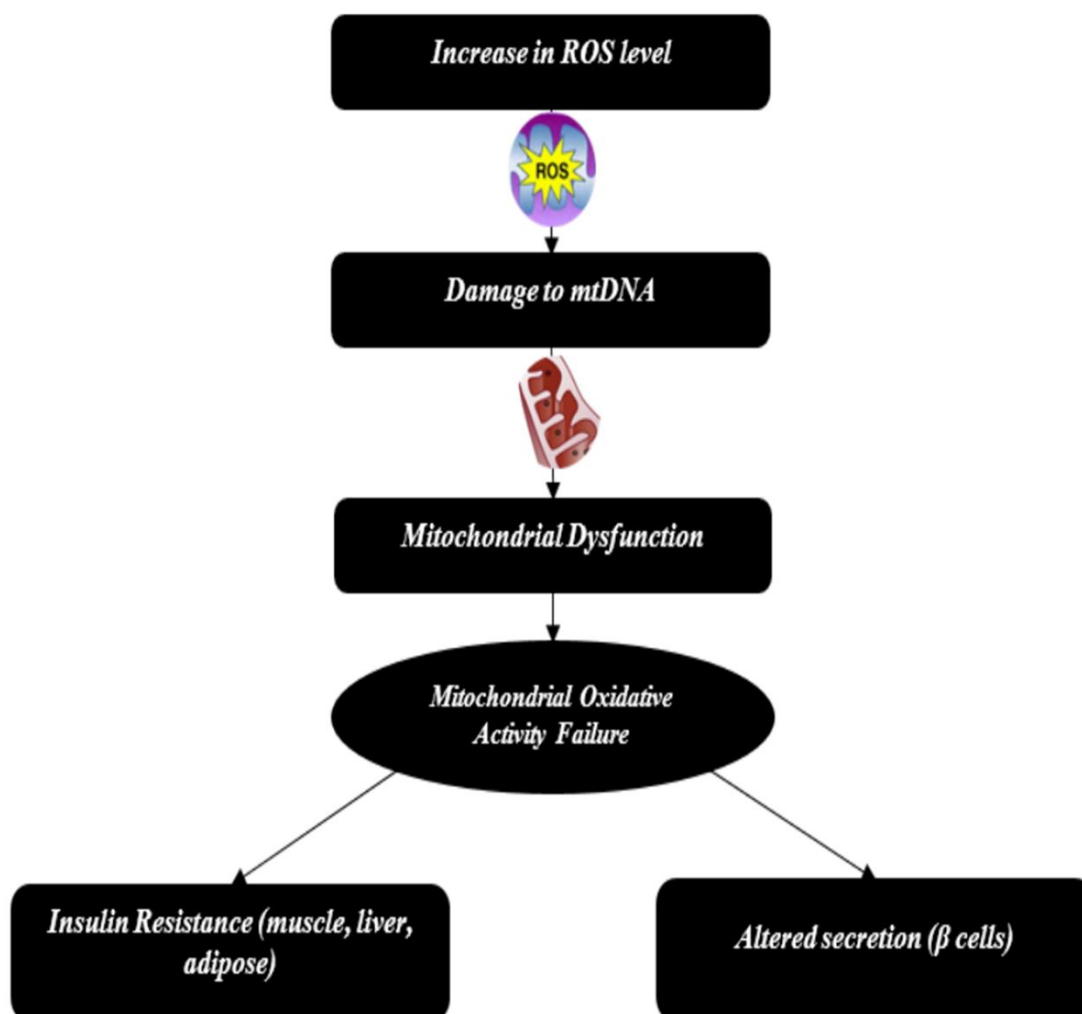


Figure 2. Factors causing mitochondrial oxidative activity failure and its consequences.

4. The role of ER stress in type 2 diabetes

ER plays a significant role in storing and secreting Ca^{2+} . A broad range of cellular functions, including organogenesis, transcriptional operation, stress responses, and apoptosis, are therefore regulated by ER through the use of Ca^{2+} [53]. Of all the specialized secretory cells in the body, β -cells are one of the most sensitive to ER stress, as it is heavily involved in the synthesis of proteins (including insulin). ER stress is regularly and frequently observed in diabetes and its complications [54]. In diabetic conditions, ER stress is also elevated, which results in c-Jun N-terminal kinase (JNK) pathway activation. JNK system activation has been suggested to occur in both IR and pancreatic β -cell dysfunction found in diabetes [55] (Table 1). About one-third of the proteome consists of soluble and transmembrane proteins that are first inserted into the ER during their biogenesis. Such proteins also undergo different posttranslational modifications within the ER. Enzymatic processes improve the possibility of correctly folding, modifying, and assembling secretory proteins into ER multiprotein complexes until they traffic into the secretory pathway further downstream. Given the availability of such protein-folding devices, a significant fraction of secretory proteins in the ER usually do not fold properly. Under ER stress conditions secretory proteins accumulating in incompletely modified and unfolded forms inside the ER [56]. During ER stress, an intracellular signaling pathway called the unfolded protein response (UPR) is activated by the presence of unfolded proteins in the ER [56]. A study has demonstrated that oxidative stress of the β -cells and ER are the main pathological features in T2D, resulting in inadequate insulin synthesis and secretion, immune activation, and apoptosis of β -cells [57]. Studies have revealed that both chronic hyperglycemia and hyperlipidemia cause insoluble UPR activation and β -cell death [58]. If ER stress continues at irretrievably high levels, the UPR switches from promoting adaptation to promoting self-destruction of its physiological outputs [56]. The development of inflammatory signals is an important consequence of oxidative and ER stress with strong or prolonged UPR signaling. ROS and RNS can both result in the activation of nuclear transcription factor kappa B (NF- κ B) in β -cells and, in the inflammatory pathway, activation of β -cell interleukin (IL)-1 β secretion. A probable important regulator of this function is the thioredoxin interacting protein, which binds thioredoxin, thus inhibiting its capacity to suppress thiol and scavenge oxidants [57]. ER homeostasis results from reactions of unfolded protein with molecular markers, such as C/EBP homologous protein, spliced X-box binding protein 1 and activating transcription factor 4, which improves stressed ER. However, ongoing ER stress activates the inflammatory response by stimulating NF- κ B and generating tumor necrosis factor (TNF)- α [59]. NF- κ B is an important inflammatory signaling regulator and thus ER stress can activate genes in β -cells that encode cytokines and chemokines [57].

5. Autophagy in type 2 diabetes

Autophagy failure in β -cells was reported in mice with a β -cell-specific defect for a key enzyme in autophagosome biogenesis, autophagy-related gene 7 (ATG7). The ATG7 knockout mice exhibit reduced β -cell mass owing to increased apoptosis and decreased proliferation, which ultimately leads to reduced insulin secretion and impaired glucose tolerance [60]. The β -cells are specialized to secrete insulin in reaction to elevated amounts of plasma glucose; they can boost their insulin synthesis and secretion by several folds to maintain glucose homeostasis. Consequently, they have to handle a high protein load on an ongoing basis. This is a challenge for their ER so β -cells are especially susceptible to ER stress. It has been shown that autophagy has a protective role against ER stress and promotes mitochondrial turnover [61]. In T2D, autophagy not only provides nutrients for the maintenance of cellular energy during fasting but also removes damaged organs, lipids, and misfolded proteins. Autophagy in T2D pancreatic β -cell death may act as a protective and prosurvival mechanism. Metformin protects against damage to β -cells in the pancreas through activating autophagy via AMP-activated protein kinase pathways [62]. There is only limited knowledge of the molecular pathway that governs autophagy. Mammalian target of rapamycin, a key kinase in the insulin receptor signaling pathway, is an autophagy regulator that prevents autophagosome formation by inhibiting ULK1 [63]. Studies results raise the likelihood that a deficiency in β -cell autophagy may be a factor in the progression from obesity to diabetes [64]. People with T2D have a large amount of a protein called islet amyloid polypeptide (IAPP). Accumulation of this protein is associated with the loss of pancreatic β -cells that produce insulin. Autophagy prevents the accumulation of toxic forms of IAPP in people without T2D, while in those with T2D it appears that this process does not work properly [65].

6. Role of obesity and inflammation in pathogenesis of type 2 diabetes

The rise in the mass of adipose tissue found in obesity can lead to IR and T2D over time (Figure 1) [66]. The first correlation between obesity, inflammation, and insulin activity is that the production of TNF- α mRNA in the obese animal's adipose tissue increases and TNF- α neutralization has increased the effect of insulin on glucose absorption [67, 68]. It has been shown that TNF- α is generated by adipose tissue and promotes IR. In addition to TNF- α , a variety of inflammatory cytokines, including adiponectin, leptin, IL-1 β , IL-6, resistin, monocyte chemo-attractant

protein 1, plasminogen activator inhibitor 1, angiotensinogen, visfatin, retinol-binding protein 4, and serum amyloid A, have been reported to be elevated in obese tissues [67]. There is increasing evidence associating obesity and IR with inflammation. T2D is now being redefined as an immune disorder, given the important role, inflammation plays in its pathogenesis [69]. In the case of obesity, adipose and muscle tissue, the liver, and the pancreas are themselves sources of inflammation. In these tissues, it has been observed that cell populations change from an anti-inflammatory profile to a proinflammatory profile allowing for the infiltration of macrophages and other immune cells. Such cells are highly involved in the processes for the generation of proinflammatory cytokines that interfere with insulin signaling in peripheral tissues or cause β -cell dysfunction, resulting in insulin shortage. Specifically, the proinflammatory protein IL-1 β is implicated in the pathogenesis of T2D by triggering the activation of the nucleotide-binding oligomerization domain like receptor family pyrin domain-containing 3 [70]. Gram-negative bacterial cell walls include lipopolysaccharides (LPS), which are among the most powerful and well-studied inflammatory inducers. LPS are recognized by the innate immune system through their association with special proteins that complex with toll-like receptor (TLR)-4 (the CD14/TLR4 complex). A study has shown that mice without functioning LPS receptors (CD14 knockout mice) are resistant to diet-induced obesity and associated disorders, such as hepatic IR [71]. *Helicobacter pylori* (*H. pylori*) infection is also strongly associated with the pathogenesis of T2D, which is associated with general activation of the innate immune system and a chronic, cytokine-mediated state of low-grade inflammation. The host's immune response to *H. Pylori* infection is complicated and involves the regulation of multiple proinflammatory cytokines, such as C-reactive protein, IL-6, and TNF- α . *H. pylori* infection infiltrates and activates neutrophils and macrophages. Increased ROS levels have been reported owing to neutrophil infiltration and increased DNA oxidative damage in *H. pylori*-infected patients [42].

7. The role of vitamin D in type 2 diabetes

Evidence indicates that vitamin D (VTD) plays roles in different mechanisms. 1,25(OH)₂D₃ has a defensive role for VTD and its respective metabolites against T2D [72]. VTD seems to be important for various endocrine, autocrine, and paracrine functions. There are several lines of evidence strongly suggesting a connection between VTD deficiency, reduced insulin secretion, and T2D pathogenesis [73, 74]. Analysis indicated that VTD deficiency could be vulnerable to glucose intolerance, altered insulin secretion, and T2D, either through direct or indirect intervention through activation of the vitamin D receptor (VDR) [72] (Ca-mediated) [75], through calcemic hormones, and by inflammation. VTD supplementation restores insulin secretion in models of both humans and animals, decreasing IR and plasma glucose levels. A human study showed an inverse link between dairy use and T2D risk [72]. VTD deficiency is associated with obesity, IR, and T2D [76]. Human studies have shown an inverse correlation between dairy use and T2D risk [72, 74]. *In vitro* and *in vivo* studies have proved that 1,25(OH)₂D₃ is vital for insulin secretion and glucose homeostasis. VDR mutant mice indicating that insulin synthesis might also require 1,25(OH)₂D₃ [72]. A research paper shows that low rates of 25(OH)D may have contributed to the prevalence of prediabetes or T2D [77].

CONCLUSION

Various factors can cause T2D in patients. ROS are involved in the pathogenesis of T2D via the oxidation of biological molecules, such as lipids, proteins, and DNA. Increased levels of oxidation of these biological molecules have been observed in T2D. Elevated ROS levels can damage the mitochondria and ER in β -cells, which can lead to T2D. Autophagy prevents ER stress and promotes mitochondrial turnover. Autophagy may act as a protective mechanism against the death of pancreatic β -cells and oxidative stress; thus, autophagy can be thought of as a mechanism to prevent the development of diabetes and β -cell dysfunction. Chronic inflammation plays an important role in T2D pathogenesis due to its relationship with obesity and IR. TNF- α , a proinflammatory cytokine, has been shown to boost IR. VTD deficiency reduces insulin secretion and the pathogenesis of T2D as it contributes to glucose intolerance and altered insulin secretion. Obesity is linked to IR and T2D. Therefore, obesity, ER stress, lipid peroxidation elevation, and oxidative DNA damage, inflammation, autophagy depression in β -cells, and VTD deficiency are important factors for the development of diabetes.

DECLARATIONS

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SKA and TV wrote the initial draft and SN and TV revised and edited the paper.

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Conflict of interest

The authors confirm that there are no conflicts of interest.

REFERENCES

1. Halim M and Halim A. The effects of inflammation, aging and oxidative stress on the pathogenesis of diabetes mellitus (type 2 diabetes). *Diabetes & Metabolic Syndrome: Clinical Research & Reviews*. 2019; 13 (2): 1165-1172. <https://doi.org/10.1016/j.dsx.2019.01.040>
2. Nowotny K, Jung T, Höhn A, Weber D and Grune T. Advanced glycation end products and oxidative stress in type 2 diabetes mellitus. *Biomolecules*. 2015; 5 (1): 194-222. <https://doi.org/10.3390/biom5010194>
3. Lowell BB and Shulman GI. Mitochondrial dysfunction and type 2 diabetes. *Science*. 2005; 307 (5708): 384-387. <https://doi.org/10.1126/science.1104343>
4. Shan P-F, Li Q, Khamaisi M and Qiang G-f. Type 2 diabetes mellitus and macrovascular complications. *International Journal of Endocrinology*. 2017; 2017. <https://doi.org/10.1155/2017/4301461>
5. Xia C, Rao X and Zhong J. Role of t lymphocytes in type 2 diabetes and diabetes-associated inflammation. *Journal of diabetes research*. 2017; 2017. <https://doi.org/10.1155/2017/6494795>
6. Gorogawa S-i, Kajimoto Y, Umayahara Y, Kaneto H, Watada H, et al. Probulcol preserves pancreatic β -cell function through reduction of oxidative stress in type 2 diabetes. *Diabetes research and clinical practice*. 2002; 57 (1): 1-10. [https://doi.org/10.1016/S0168-8227\(02\)00005-0](https://doi.org/10.1016/S0168-8227(02)00005-0)
7. Parish R and Petersen KF. Mitochondrial dysfunction and type 2 diabetes. *Current diabetes reports*. 2005; 5 (3): 177-183. <https://doi.org/10.1007/s11892-005-0006-3>
8. Hegde SV, Adhikari P, Kotian S, Pinto VJ, D'Souza S, et al. Effect of 3-month yoga on oxidative stress in type 2 diabetes with or without complications: A controlled clinical trial. *Diabetes care*. 2011; 34 (10): 2208-2210. <https://doi.org/10.2337/dc10-2430>
9. M Victor V, Rocha M, Herance R and Hernandez-Mijares A. Oxidative stress and mitochondrial dysfunction in type 2 diabetes. *Current pharmaceutical design*. 2011; 17 (36): 3947-3958. <https://doi.org/10.2174/138161211798764915>
10. Yan J, Feng Z, Liu J, Shen W, Wang Y, et al. Enhanced autophagy plays a cardinal role in mitochondrial dysfunction in type 2 diabetic goto-kakizaki (gk) rats: Ameliorating effects of (-)-epigallocatechin-3-gallate. *The Journal of nutritional biochemistry*. 2012; 23 (7): 716-724. <https://doi.org/10.1016/j.jnutbio.2011.03.014>
11. Ma ZA, Zhao Z and Turk J. Mitochondrial dysfunction and β -cell failure in type 2 diabetes mellitus. *Experimental diabetes research*. 2011; 2012. <https://doi.org/10.1155/2012/703538>
12. Özcan U, Yilmaz E, Özcan L, Furuhashi M, Vaillancourt E, et al. Chemical chaperones reduce er stress and restore glucose homeostasis in a mouse model of type 2 diabetes. *Science*. 2006; 313 (5790): 1137-1140. <https://doi.org/10.1126/science.1128294>
13. Kosacka J, Kern M, Klötting N, Paeschke S, Rudich A, et al. Autophagy in adipose tissue of patients with obesity and type 2 diabetes. *Molecular and cellular endocrinology*. 2015; 409: 21-32. <https://doi.org/10.1016/j.mce.2015.03.015>
14. De Felice FG and Ferreira ST. Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to alzheimer disease. *Diabetes*. 2014; 63 (7): 2262-2272. <https://doi.org/10.2337/db13-1954>
15. Mizushima N. Autophagy: Process and function. *Genes & development*. 2007; 21 (22): 2861-2873. <https://doi.org/10.1101/gad.1599207>
16. Yang J-S, Lu C-C, Kuo S-C, Hsu Y-M, Tsai S-C, et al. Autophagy and its link to type ii diabetes mellitus. *Biomedicine*. 2017; 7 (2). <https://doi.org/10.1051/bmdcn/2017070201>
17. Burgos-Morón E, Abad-Jiménez Z, Martínez de Marañón A, Iannantuoni F, Escibano-López I, et al. Relationship between oxidative stress, er stress, and inflammation in type 2 diabetes: The battle continues. *Journal of clinical medicine*. 2019; 8 (9): 1385. <https://doi.org/10.3390/jcm8091385>
18. Khemka VK, Choudhuri S, Ganguly A, Ghosh A, Bir A, et al. Lipid peroxidation and antioxidant status in nonobese type 2 diabetes mellitus. *Advances in Endocrinology*. 2014; 2014. <https://doi.org/10.1155/2014/830761>
19. Gerber PA and Rutter GA. The role of oxidative stress and hypoxia in pancreatic beta-cell dysfunction in diabetes mellitus. *Antioxidants & redox signaling*. 2017; 26 (10): 501-518. <https://doi.org/10.1089/ars.2016.6755>
20. Odegaard AO, Jacobs DR, Sanchez OA, Goff DC, Reiner AP, et al. Oxidative stress, inflammation, endothelial dysfunction and incidence of type 2 diabetes. *Cardiovascular diabetology*. 2016; 15 (1): 1-12. <https://doi.org/10.1186/s12933-016-0369-6>
21. Luc K, Schramm-Luc A, Guzik T and Mikolajczyk T. Oxidative stress and inflammatory markers in prediabetes and diabetes. *J. Physiol. Pharmacol*. 2019; 70: 809-824.

22. Ardeshirlarijani E, Tabatabaei-Malazy O, Mohseni S, Qorbani M, Larijani B, et al. Effect of probiotics supplementation on glucose and oxidative stress in type 2 diabetes mellitus: A meta-analysis of randomized trials. *DARU Journal of Pharmaceutical Sciences*. 2019; 27 (2): 827-837. <https://doi.org/10.1007/s40199-019-00302-2>
23. Uskova M and Kravchenko L. Antioxidant properties of lactic acid bacteria--probiotic and yogurt strains. *Voprosy pitaniia*. 2009; 78 (2): 18-23.
24. Mikelsaar M and Zilmer M. *Lactobacillus fermentum* me-3—an antimicrobial and antioxidative probiotic. *Microbial ecology in health and disease*. 2009; 21 (1): 1-27. <https://doi.org/10.1080/08910600902815561>
25. Leo EEM, Fernández JJA and Campos MRS. Biopeptides with antioxidant and anti-inflammatory potential in the prevention and treatment of diabetes disease. *Biomedicine & Pharmacotherapy*. 2016; 83: 816-826. <https://doi.org/10.1016/j.biopha.2016.07.051>
26. Willcox JK, Ash SL and Catignani GL. Antioxidants and prevention of chronic disease. *Critical reviews in food science and nutrition*. 2004; 44 (4): 275-295. <https://doi.org/10.1080/10408690490468489>
27. Asmat U, Abad K and Ismail K. Diabetes mellitus and oxidative stress—a concise review. *Saudi Pharmaceutical Journal*. 2016; 24 (5): 547-553. <https://doi.org/10.1016/j.jpsps.2015.03.013>
28. Blasiak J, Arabski M, Krupa R, Wozniak K, Zadrozny M, et al. DNA damage and repair in type 2 diabetes mellitus. *Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis*. 2004; 554 (1-2): 297-304. <https://doi.org/10.1016/j.mrfmmm.2004.05.011>
29. Abudawood M, Tabassum H, Almaarik B and Aljohi A. Interrelationship between oxidative stress, DNA damage and cancer risk in diabetes (type 2) in Riyadh, KSA. *Saudi Journal of Biological Sciences*. 2020; 27 (1): 177-183. <https://doi.org/10.1016/j.sjbs.2019.06.015>
30. Simone S, Gorin Y, Velagapudi C, Abboud HE and Habib SL. Mechanism of oxidative DNA damage in diabetes: Tuberin inactivation and downregulation of DNA repair enzyme 8-oxo-7, 8-dihydro-2'-deoxyguanosine-DNA glycosylase. *Diabetes*. 2008; 57 (10): 2626-2636. <https://doi.org/10.2337/db07-1579>
31. Sinaiko AR, Steinberger J, Moran A, Prineas RJ, Vessby B, et al. Relation of body mass index and insulin resistance to cardiovascular risk factors, inflammatory factors, and oxidative stress during adolescence. *Circulation*. 2005; 111 (15): 1985-1991. <https://doi.org/10.1161/01.CIR.0000161837.23846.57>
32. Vincent HK, Innes KE and Vincent KR. Oxidative stress and potential interventions to reduce oxidative stress in overweight and obesity. *Diabetes, obesity and metabolism*. 2007; 9 (6): 813-839. <https://doi.org/10.1111/j.1463-1326.2007.00692.x>
33. Bastard J-P, Maachi M, Lagathu C, Kim MJ, Caron M, et al. Recent advances in the relationship between obesity, inflammation, and insulin resistance. *European cytokine network*. 2006; 17 (1): 4-12.
34. Basu S. Novel cyclooxygenase-catalyzed bioactive prostaglandin f2 α from physiology to new principles in inflammation. *Medicinal research reviews*. 2007; 27 (4): 435-468. <https://doi.org/10.1002/med.20098>
35. Čolak E, Majkić-Singh N, Stanković S, Srecković-Dimitrijević V, Djordjević PB, et al. Parameters of antioxidative defense in type 2 diabetic patients with cardiovascular complications. *Annals of medicine*. 2005; 37 (8): 613-620. <https://doi.org/10.1080/07853890500330193>
36. Montonen J, Knekt P, Härkänen T, Järvinen R, Heliövaara M, et al. Dietary patterns and the incidence of type 2 diabetes. *American journal of epidemiology*. 2005; 161 (3): 219-227. <https://doi.org/10.1093/aje/kwi039>
37. Sugeçti S. Role of protein oxidation, lipid peroxidation and antioxidant defense systems on diabetes mellitus. *Aurum Journal of Health Sciences*. 1 (1): 47-54.
38. Abramsson-Zetterberg L, Vikström AC, Törnqvist M and Hellenäs K-E. Differences in the frequency of micronucleated erythrocytes in humans in relation to consumption of fried carbohydrate-rich food. *Mutation Research/Genetic Toxicology and Environmental Mutagenesis*. 2008; 653 (1-2): 50-56. <https://doi.org/10.1016/j.mrgentox.2008.03.007>
39. Pickup JC. Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. *Diabetes care*. 2004; 27 (3): 813-823. <https://doi.org/10.2337/diacare.27.3.813>
40. Filomeni G, De Zio D and Cecconi F. Oxidative stress and autophagy: The clash between damage and metabolic needs. *Cell Death & Differentiation*. 2015; 22 (3): 377-388. <https://doi.org/10.1038/cdd.2014.150>
41. Salmaninejad A, Kangari P and Shakoori A. Oxidative stress: Development and progression of breast cancer. *Tehran University Medical Journal TUMS Publications*. 2017; 75 (1): 1-9.
42. Nasif WA, Mukhtar MH, Eldein MMN and Ashgar SS. Oxidative DNA damage and oxidized low density lipoprotein in type ii diabetes mellitus among patients with helicobacter pylori infection. *Diabetology & metabolic syndrome*. 2016; 8 (1): 34. <https://doi.org/10.1186/s13098-016-0149-1>
43. Sifuentes-Franco S, Pacheco-Moisés FP, Rodríguez-Carrizalez AD and Miranda-Díaz AG. The role of oxidative stress, mitochondrial function, and autophagy in diabetic polyneuropathy. *Journal of diabetes research*. 2017; 2017. <https://doi.org/10.1155/2017/1673081>
44. Scherz-Shouval R and Elazar Z. ROS, mitochondria and the regulation of autophagy. *Trends in cell biology*. 2007; 17 (9): 422-427. <https://doi.org/10.1016/j.tcb.2007.07.009>
45. Burgos-Morón E, Abad-Jiménez Z, Martínez de Marañón A, Iannantuoni F, Escribano-López I, et al. Relationship between oxidative stress, inflammation, and inflammation in type 2 diabetes: The battle continues. *Journal of clinical medicine*. 2019; 8 (9): 1385. <https://doi.org/10.3390/jcm8091385>
46. Khan S, Raghuram GV, Bhargava A, Pathak N, Chandra DH, et al. Role and clinical significance of lymphocyte mitochondrial dysfunction in type 2 diabetes mellitus. *Translational Research*. 2011; 158 (6): 344-359. <https://doi.org/10.1016/j.trsl.2011.08.007>
47. Patti M-E and Corvera S. The role of mitochondria in the pathogenesis of type 2 diabetes. *Endocrine reviews*. 2010; 31 (3): 364-395. <https://doi.org/10.1210/er.2009-0027>
48. Sivitz WI and Yorek MA. Mitochondrial dysfunction in diabetes: From molecular mechanisms to functional significance and therapeutic opportunities. *Antioxidants & redox signaling*. 2010; 12 (4): 537-577. <https://doi.org/10.1089/ars.2009.2531>

49. Kelley DE, He J, Menshikova EV and Ritov VB. Dysfunction of mitochondria in human skeletal muscle in type 2 diabetes. *Diabetes*. 2002; 51 (10): 2944-2950. <https://doi.org/10.2337/diabetes.51.10.2944>
50. Morino K, Petersen KF, Dufour S, Befroy D, Frattini J, et al. Reduced mitochondrial density and increased irs-1 serine phosphorylation in muscle of insulin-resistant offspring of type 2 diabetic parents. *The Journal of clinical investigation*. 2005; 115 (12): 3587-3593. <https://doi.org/10.1172/JCI25151>
51. Fex M, Nicholas LM, Vishnu N, Medina A, Sharoyko VV, et al. The pathogenetic role of β -cell mitochondria in type 2 diabetes. *Journal of Endocrinology*. 2018; 236 (3): R145-R159. <https://doi.org/10.1530/JOE-17-0367>
52. Schrauwen-Hinderling VB, Roden M, Kooi ME, Hesselink MK and Schrauwen P. Muscular mitochondrial dysfunction and type 2 diabetes mellitus. *Current Opinion in Clinical Nutrition & Metabolic Care*. 2007; 10 (6): 698-703. <https://doi.org/10.1097/MCO.0b013e3282f0eca9>
53. Eizirik DL, Cardozo AK and Cnop M. The role for endoplasmic reticulum stress in diabetes mellitus. *Endocrine reviews*. 2008; 29 (1): 42-61. <https://doi.org/10.1210/er.2007-0015>
54. Balasubramanyam M, Singh LP and Rangasamy S. Molecular intricacies and the role of er stress in diabetes. *Experimental diabetes research*. 2012; 2012. <https://doi.org/10.1155/2012/958169>
55. Kaneto H, Katakami N, Matsuhisa M and Matsuoka T-a. Role of reactive oxygen species in the progression of type 2 diabetes and atherosclerosis. *Mediators of inflammation*. 2010; 2010. <https://doi.org/10.1155/2010/453892>
56. Papa FR. Endoplasmic reticulum stress, pancreatic β -cell degeneration, and diabetes. *Cold Spring Harbor perspectives in medicine*. 2012; 2 (9): a007666. <https://doi.org/10.1101/cshperspect.a007666>
57. Hasnain SZ, Prins JB and McGuckin MA. Oxidative and endoplasmic reticulum stress in b-cell dysfunction in diabetes. *J Mol Endocrinol*. 2016; 56 (2): 33-54. <https://doi.org/10.1530/JME-15-0232>
58. Back SH and Kaufman RJ. Endoplasmic reticulum stress and type 2 diabetes. *Annual review of biochemistry*. 2012; 81: 767-793. <https://doi.org/10.1146/annurev-biochem-072909-095555>
59. de Freitas Carvalho MM, Lage NN, de Souza Paulino AH, Pereira RR, de Almeida LT, et al. Effects of acai on oxidative stress, er stress, and inflammation-related parameters in mice with high fat diet-fed induced nafld. *Scientific reports*. 2019; 9 (1): 1-11. <https://doi.org/10.1038/s41598-019-44563-y>
60. Marasco MR and Linnemann AK. B-cell autophagy in diabetes pathogenesis. *Endocrinology*. 2018; 159 (5): 2127-2141. <https://doi.org/10.1210/en.2017-03273>
61. Bugliani M, Mossuto S, Grano F, Suleiman M, Marselli L, et al. Autophagy regulates the function and survival of human pancreatic beta cells under endoplasmic reticulum stress and in type 2 diabetes. *Frontiers in endocrinology*. 2019; 10: 52. <https://doi.org/10.3389/fendo.2019.00052>
62. Jiang Y, Huang W, Wang J, Xu Z, He J, et al. Metformin plays a dual role in min6 pancreatic β cell function through ampk-dependent autophagy. *International journal of biological sciences*. 2014; 10 (3): 268. <https://doi.org/10.7150/ijbs.7929>
63. Las G and Shirihai O. The role of autophagy in β -cell lipotoxicity and type 2 diabetes. *Diabetes, Obesity and Metabolism*. 2010; 12: 15-19. <https://doi.org/10.1111/j.1463-1326.2010.01268.x>
64. Quan W, Lim Y-M and Lee M-S. Role of autophagy in diabetes and endoplasmic reticulum stress of pancreatic β -cells. *Experimental & molecular medicine*. 2012; 44 (2): 81-88. <https://doi.org/10.3858/emm.2012.44.2.030>
65. Rivera JF, Costes S, Gurlo T, Glabe CG and Butler PC. Autophagy defends pancreatic β cells from human islet amyloid polypeptide-induced toxicity. *The Journal of clinical investigation*. 2014; 124 (8): 3489-3500. <https://doi.org/10.1172/JCI71981>
66. Calle M and Fernandez M. Inflammation and type 2 diabetes. *Diabetes & metabolism*. 2012; 38 (3): 183-191. <https://doi.org/10.1016/j.diabet.2011.11.006>
67. Chagas CEA, Borges MC, Martini LA and Rogero MM. Focus on vitamin d, inflammation and type 2 diabetes. *Nutrients*. 2012; 4 (1): 52-67. <https://doi.org/10.3390/nu4010052>
68. Hotamisligil GS, Shargill NS and Spiegelman BM. Adipose expression of tumor necrosis factor-alpha: Direct role in obesity-linked insulin resistance. *Science*. 1993; 259 (5091): 87-91. <https://doi.org/10.1126/science.7678183>
69. Zhong J, Gong Q and Mima A. Inflammatory regulation in diabetes and metabolic dysfunction. *Journal of diabetes research*. 2017; 2017. <https://doi.org/10.1155/2017/5165268>
70. Esser N, Legrand-Poels S, Piette J, Scheen AJ and Paquot N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. *Diabetes research and clinical practice*. 2014; 105 (2): 141-150. <https://doi.org/10.1016/j.diabres.2014.04.006>
71. Cani PD, Amar J, Iglesias MA, Poggi M, Knauf C, et al. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes*. 2007; 56 (7): 1761-1772. <https://doi.org/10.2337/db06-1491>
72. moreiraTs H. Theroleofvitamininddeficiencyinthepathogenesisoftype2diabetesmellitus. *Espen EurEJclinnutrmetab*. 2010; 5 (4): e155.
73. Scragg R. Vitamin d and type 2 diabetes: Are we ready for a prevention trial? *Diabetes*. 2008; 57 (10): 2565-2566. <https://doi.org/10.2337/db08-0879>
74. Ozfirat Z and Chowdhury TA. Vitamin d deficiency and type 2 diabetes. *Postgraduate medical journal*. 2010; 86 (1011): 18-25. <https://doi.org/10.1136/pgmj.2009.078626>
75. Cavalier E, Delanaye P, Souberbielle J-C and Radermecker R-P. Vitamin d and type 2 diabetes mellitus: Where do we stand? *Diabetes & metabolism*. 2011; 37 (4): 265-272. <https://doi.org/10.1016/j.diabet.2011.01.001>
76. Mousa A, Misso M, Teede H, Scragg R and de Courten B. Effect of vitamin d supplementation on inflammation: Protocol for a systematic review. *BMJ open*. 2016; 6 (4): e010804. <https://doi.org/10.1136/bmjopen-2015-010804>
77. Gao Y, Zheng T, Ran X, Ren Y, Chen T, et al. Vitamin d and incidence of prediabetes or type 2 diabetes: A four-year follow-up community-based study. *Disease markers*. 2018; 2018. <https://doi.org/10.1155/2018/1926308>