Effects of diabetes on the development of radiation pneumonitis

Guangtong Dong1,2, Yuxiao Li3, Qiyao Zhao2, Bing Pang1, Xin Qi3, Junping Wei1* and Wei Hou3*

Abstract

Radiation pneumonitis (RP) is a common adverse reaction to radiation therapy in patients with chest tumors. Recent studies have shown that diabetes mellitus (DM), which can cause systemic multisystem damage, specifically targets lungs, and the incidence of RP in patients with a history of diabetes is higher than that in other patients with tumors who have undergone radiotherapy. DM is an important risk factor for RP in tumor patients undergoing RT, and patients with DM should be treated with caution. This article reviews research on the clinical aspects, as well as the mechanism, of the effects of diabetes on RP and suggests future research needed to reduce RP.

Keywords: Diabetes, Radiation therapy, Radiation pneumonia, Influence factors

Diabetes mellitus (DM) is a relatively common chronic metabolic disease [1]. The annual incidence of complications due to diabetes is increasing [2, 3]. Recent research has shown that diabetes is an important risk factor for radiation toxicity following radiotherapy for several tumors. Radiation-induced gastrointestinal and urogenital toxicity is more common in patients with DM [4, 5]. Radiation damage due to breast cancer treatment is also more common in patients with DM than in those without it [6].

Radiation therapy is a routine treatment for cancer after surgery. Radiation injury is one of the main adverse effects in patients who have undergone radiotherapy, and it is also the main limiting factor of the treatment [7]. When it occurs, radiation pneumonia (RP) usually presents within 1 to 6 months after completion of radiotherapy [8], with an incidence between 15 and 45% [4]. Patients with diabetes have shown a higher risk of radiation-induced damage [9], and many studies have indicated that lung tissue is a target for diabetes damage [10, 11], with an association between DM and RP. Glucocorticoids are the main drugs used to treat RP, but the administration of hormones can adversely affect blood glucose control and the insulin dosage required for diabetic patients. It also directly affects treatment of RP [12]. Therefore, some medical institutions exclude patients with severe diabetes from treatment with conventional radiation therapy [13]. The occurrence of RP in patients with breast tumors and DM has become a clinical concern. This article will review how DM affects RP based on clinical reports and mechanistic studies.

Clinical evidence that DM affects RP

Hsia et al. [14] retrospectively analyzed clinical data from 118 patients with lung cancer and reported that DM itself was not associated with a higher risk of RP. Similarly, Orton et al. evaluated the correlation between DM and RP in 66 lung cancer patients and reported that, although patients who had lung cancer and DM showed a higher incidence of RP than patients with lung cancer alone, this incidence was not significantly different from that in patients without DM [9]. However, both of these studies were reported as abstracts only; full reports were unavailable. In China, there is a number of
and TNF-α are significantly increased in patients with DM is considered a chronic inflammatory disease. Lev-

A 1993 article first described the relationship between tumor necrosis factor (TNF), inflammation, and insu-

Mechanism underlying the effects of DM on RP

Promotion of an inflammatory response

A 1993 article first described the relationship between tumor necrosis factor (TNF), inflammation, and insu-

immune dysregulation

In healthy individuals, immune responses are tempo-

DM is classified as a metabolic inflammatory disease [22, 23].

In the hyperglycemic environment of diabetic patients, anti-inflammatory cytokines such as IL-4, IL-5, and IL-13, which are typically maintained homeostatically in a microenvironment, lead to changes in the number and type of present cells [24, 25], presenting and releasing pro-inflammatory cytokines leading to chronic inflam-

DM can also cause nuclear factor kappa-B (NF-kB) activation through receptor for advanced glycaya-

Promotion of an inflammatory response

A 1993 article first described the relationship between tumor necrosis factor (TNF), inflammation, and insu-

DM, and type 2 DM (T2DM) is classified as a metabolic inflammatory disease [22, 23].

In the hyperglycemic environment of diabetic patients, anti-inflammatory cytokines such as IL-4, IL-5, and IL-13, which are typically maintained homeostatically in a microenvironment, lead to changes in the number and type of present cells [24, 25], presenting and releasing pro-inflammatory cytokines leading to chronic inflam-

DM can also cause nuclear factor kappa-B (NF-kB) activation through receptor for advanced glycaya-

Promotion of an inflammatory response

A 1993 article first described the relationship between tumor necrosis factor (TNF), inflammation, and insu-

DM, and type 2 DM (T2DM) is classified as a metabolic inflammatory disease [22, 23].

In the hyperglycemic environment of diabetic patients, anti-inflammatory cytokines such as IL-4, IL-5, and IL-13, which are typically maintained homeostatically in a microenvironment, lead to changes in the number and type of present cells [24, 25], presenting and releasing pro-inflammatory cytokines leading to chronic inflam-

DM can also cause nuclear factor kappa-B (NF-kB) activation through receptor for advanced glycaya-

Promotion of an inflammatory response

A 1993 article first described the relationship between tumor necrosis factor (TNF), inflammation, and insu-

DM, and type 2 DM (T2DM) is classified as a metabolic inflammatory disease [22, 23].

In the hyperglycemic environment of diabetic patients, anti-inflammatory cytokines such as IL-4, IL-5, and IL-13, which are typically maintained homeostatically in a microenvironment, lead to changes in the number and type of present cells [24, 25], presenting and releasing pro-inflammatory cytokines leading to chronic inflam-

DM can also cause nuclear factor kappa-B (NF-kB) activation through receptor for advanced glycaya-

Promotion of an inflammatory response

A 1993 article first described the relationship between tumor necrosis factor (TNF), inflammation, and insu-

DM, and type 2 DM (T2DM) is classified as a metabolic inflammatory disease [22, 23].

In the hyperglycemic environment of diabetic patients, anti-inflammatory cytokines such as IL-4, IL-5, and IL-13, which are typically maintained homeostatically in a microenvironment, lead to changes in the number and type of present cells [24, 25], presenting and releasing pro-inflammatory cytokines leading to chronic inflam-

DM can also cause nuclear factor kappa-B (NF-kB) activation through receptor for advanced glycaya-

Promotion of an inflammatory response

A 1993 article first described the relationship between tumor necrosis factor (TNF), inflammation, and insu-

DM, and type 2 DM (T2DM) is classified as a metabolic inflammatory disease [22, 23].

In the hyperglycemic environment of diabetic patients, anti-inflammatory cytokines such as IL-4, IL-5, and IL-13, which are typically maintained homeostatically in a microenvironment, lead to changes in the number and type of present cells [24, 25], presenting and releasing pro-inflammatory cytokines leading to chronic inflam-

DM can also cause nuclear factor kappa-B (NF-kB) activation through receptor for advanced glycaya-
not only in the formation and development of RP but also prediction of this condition [42]. Diabetic patients have a disorder of glucose, fat, and protein metabolism, and the acidic environment in diabetic patients’ tissues reduces patients’ cellular immune function, ultimately affecting the lungs [43] (Fig. 3).

**Oxidative stress**

In DM, glucose and its metabolites react with hydrogen peroxide in the presence of iron and copper ions, forming hydroxyl groups during auto-oxidation and generating a large amount of reactive oxygen species (ROS). ROS, in turn, promote the development of complications, such as hyperlipidemia, end-stage renal disease and apoptosis of islet cells [44]. Insulin resistance caused by chronic hyperglycemia is also thought to be related to the induction of oxidative stress [45]. Akash [46] et al. studied the level of 8-hydroxydeoxyribonucleic acid-modified protein in Goto Kakizaki rats, a model of T2DM, and showed that hyperglycemia is the main underlying factor of pancreatic β-cell oxidative stress, the type of stress caused by glucose that underlies glucotoxicity. In 309 diabetic patients vs. non-diabetic controls, Charles Sturt et al. observed significantly increased levels of glycosylated hemoglobin, lipids, and oxidative stress biomarkers, and suggested that these findings support a link between long-term hyperglycemia in T2DM and hyperglycemia-induced oxidative stress [47]. Chronic persistent hyperglycemia has also been reported to contribute to microvascular and macrovascular complications that occur through a series of mechanisms involving oxidative stress and inflammation [47]. Oxidative stress injury is involved in initiating RP. The “cytokine cascade theory [48]” promotes the idea that ROS damages lung parenchymal cells, causing these cells to secrete a large amount of inflammatory cytokines, chemokines, profibrotic cytokines, and other factors that cause RP. In addition, Ma [49] et al. found that, with increased production of oxygen free radicals, the activity of oxidative stress-sensitive kinases and transcription cytokines in macrophages increased rapidly, leading to the production

**Fig. 1** Diabetes induce NF-κB to promote inflammatory response. HMGB1 high mobility group 1 protein, RAGE receptor for advanced glycation endproducts, NF-κB nuclear facor kappa-B, TNF-α tumor necrosis factor α, IL-6 interleukin 6, IL-1β interleukin 1β

**Fig. 2** Inflammation and radiation pneumonia caused by diabetes. DM diabetes mellitus, TLR4 toll-like receptors 4, RP radiation pneumonia
of large numbers of inflammatory cytokine such as TNF-α, IL-6, and transforming growth factor-β (TGF-β) (Fig. 4).

**Microvascular endothelial injury**

As an important endocrine organ, the vascular endothelium produces cytokines that can regulate vascular tension, vascular wall inflammation, and smooth muscle cell proliferation and adhesion, which can lead to vascular disease [50]. Recently, vascular endothelial injury has been recognized as a common cause of various DM vascular lesions [51], particularly at their initiation [52]. Animal experiments have shown that the basement membrane of alveolar epithelial and capillary endothelial cells in diabetic rats is significantly thickened, and some rats showed focal nodular changes that were very similar to the nodular changes in diabetic glomerular basement membranes [53]. Sustained hyperglycemia can also chronically damage vascular structures by promoting apoptosis of vascular endothelial cells [54], increasing the permeability of these cells [55] and regulating endothelial cell gene expression [56], eventually leading to abnormal microvascular structure and function. Clinical studies have shown that in T2DM patients, the expression of some molecules that cause chronic structural damage to the vascular endothelium such as inflammatory factors (e.g., IL-6), vascular endothelial growth factor (VEGF), and angiopoietin (Ang) are upregulated, whereas the expression of molecules that exert vascular protective effects is significantly downregulated [57, 58]. The function and state of the endothelium depends not only on the extent of large numbers of inflammatory cytokine such as TNF-α, IL-6, and transforming growth factor-β (TGF-β) (Fig. 4).
of damage, but also on its ability to repair endogenously. In this regard, circulating endothelial progenitor cells (EPCs) play an important role because they can activate endothelial recovery [59]. In patients with diabetes, EPCs have been shown reduced ability to proliferate, adhere, and be incorporated into blood vessels [60]. In summary, DM causes endothelial dysfunction in many ways, but chronic damage to the structures and functions of vascular endothelial cells may be one of the main mechanisms underlying the development or aggravation of RP.

Microvascular occlusion
Microcirculation is the most basic structural and functional unit in the blood circulation system. It regulates vasomotor smooth muscle contraction and affects blood flow through nerves and Bodily fluids. Microvascular occlusive lesions are a general term for microcirculation duct, blood flow, and functional obstructive lesions. They mostly occur in pathological conditions such as metabolic disorders and inflammatory reactions. They are characterized by slowed microvascular blood flow, increased vascular permeability, endothelial cell damage, and leukocyte adhesion and migration [61]. Lungs are extremely rich in microvasculature. Microvascular endothelial cell damage and increased vascular permeability caused by DM may lead to thickening of the fused basal lamina of alveolar septal epithelial cells and alveolar capillary endothelial cell basal lamina. In addition, some studies have found that diabetic microangiopathy is related to an imbalance in the fibrinolytic system [62]. Tissue-type plasminogen activator (t-PA) is the initiating factor for the plasmin system [63]. It is regulated in the blood by plasminogen activator inhibitor type 1 (PAI-1). Patients with DM have long-term hyperglycemia, which causes an increase in PAI-1 that reduces the synthesis and secretion of t-PA, causing disorders of the fibrinolytic and coagulation systems, platelet activation, and microthrombosis, implicating peripheral nerve tissues and blood vessels corresponding tissue and organ lesions [64]. DM can cause microvascular occlusive lesions that lead to microcirculation disturbances in the lungs, which limit dissipation of local inflammatory reactions [65–67].

Discussion
In the 1970s, Schuylar et al. [68] first proposed that lungs were a target organ of DM. In the past 40 years, evidence has accumulated that shows lung injury caused or exacerbated by high glucose can result in chronic progressive effects in lungs, poor quality of life, and limitations on the use of hormone therapies [69, 70]. The Third National Health and Nutrition Survey in the United Kingdom showed that lung function declines with impaired glucose tolerance [71], and that the relationship between T2DM and lung-related damage was significant [72]. Through meta-analysis, Xiao-Jing Zhang et al. found that chronic lung disease or diabetes which lung cancer patients accompanied by were one of the important risk factors affecting the occurrence of RP [17]. Similarly, Sefika et al. found that DM was one of the important risk factors for the occurrence of RP by multivariate analysis and recursive zoning analysis [20]. In addition, the increase in X-ray volume and density of lung injury after radiotherapy was associated with the presence of diabetes mellitus and other clinical factors [18]. RP is one of the more common serious complications of chest radiotherapy [73]. At present, suitable and intensity-modulated radiation therapy is the main treatment for chest tumors, but the incidence of RP still reaches 30% of patients who undergo this treatment [74]. The pathophysiological processes of RP include inflammation, endothelial cell damage, microvascular circulation, and oxidative stress response [30]. DM is known to cause abnormal changes in the alveolar wall basement membrane, such as fibrinoid necrosis and fatty changes, thickening of the basement membrane of pulmonary capillary endothelial and alveolar epithelial cells, and increased permeability of blood vessel walls, exacerbating exudation at sites where inflammation occurs [75]. In addition, DM can result in microthrombi, leading to blood supply failure that cannot be repaired. Long-term hyperglycemia can also lead to cellular immune dysfunction and lymphocyte imbalances, resulting in low autoimmune function, susceptibility to various lung infections, and aggravated symptoms of RP [76]. In addition, patients with DM often experience autonomic neuropathy, parasympathetic activity with reduced bronchial adjusting tension resulting in reduced bronchial activity, bronchospasms, inflammatory exudation, retention of respiratory secretions, and reduced clearance by the airway ciliary mucosa, promoting conditions for local pathogen infection and reproduction and exacerbating RP [77] (Fig. 5).

DM is one of the most common endocrine diseases in the world. It is also the leading cause of death and disability worldwide [78]. Recent studies have shown that the prevalence of DM in lung cancer patients is higher than in the general population, and that patients with lung cancer should be more cautious about undergoing radiotherapy and adhering to post-treatment monitoring. DM is a risk factor for RP in cancer patients. Clinicians should fully consider this risk when developing radiotherapy plans and determining radiation doses. Maintaining fasting blood glucose levels within the normal range can reduce the occurrence of RP in patients with tumors and DM [79, 80]. However, there is still much that needs to be explored in interactions between DM and radiotherapy.
This article has several limitations. First, clinical studies reported in this article are mostly retrospective; therefore, there may be inherent biases. Specifically, we do not know how patients with DM fared long after treatment, with the potential for development of late-onset RP. Second, the sample sizes of these studies were relatively small. Third, patients and their tumors are heterogeneous. Despite these shortcomings, we believe that this article explores some important unresolved issues concerning the relationship between DM and RP.

**Conclusion**

DM is an important risk factor for RP in tumor patients undergoing RT, and patients with DM should be treated with caution when undergoing this therapy.

**Abbreviations**

DM: Diabetes mellitus; RP: Radiation pneumonia; RCTs: Randomized controlled trials; TNF: Tumor necrosis factor; NF-κB: Nuclear factor kappa-B; RAGE: Receptor for advanced glycation endproducts; EPCs: Endothelial progenitor cells; PAI-1: Plasminogen activator inhibitor type 1.

**Acknowledgements**

We would like to thank Editage (www.editage.cn) for English language editing.

**Authors’ contributions**

GD conceived of the study and wrote the manuscript, so he is the first author; YL reviewed and revised English grammar; QZ modified the figures; BP did the document finishing; XQ made corrections on the statement; JW and WH participated in the design of the study and coordination, both of them contributed equally to this work, so they are both co-corresponding author. All authors read and approved the final manuscript.

**Funding**

This article was funded by the Chinese National Health and Family Planning Commission Health Bureau Central Health Research Project (W2017BJ43).

**Availability of data and materials**

The datasets generated and/or analyzed in the current study are not publicly available due to state restrictions. Thus, information may compromise research participant privacy/consent but data are available from the corresponding author on reasonable request.

**Declarations**

**Ethics approval and consent to participate**

Not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare that there is no conflict of interest regarding the publication of this paper.

**Author details**

1. Department of Endocrinology, Guang’anmen Hospital of China Academy of Chinese Medical Sciences, 6 Floors of Inpatients Building, 5 Beixiange Street, Xicheng, Beijing 100053, China. 2. College of Traditional Chinese Medicine, Shandong University of Traditional Chinese Medicine, Jinan, China. 3. Department of Oncology, Guang’anmen Hospital of China Academy of Chinese Medical Sciences, 7 Floors of Inpatients Building, 5 Beixiange Street, Xicheng, Beijing 100053, China.

Received: 8 November 2020   Accepted: 17 May 2021

Published online: 24 May 2021

**References**

1. Unnikrishnan R, Anjana RM, Mohan V. Diabetes mellitus and its complications in India. Nat Rev Endocrinol. 2016;12(6):357–70.
2. Lutz SZ, Staiger H, Fritsche A, et al. Antihyperglycaemic therapies and cancer risk. Diabetes Vasc Dis Res. 2014;11(6):371–89.
3. Wu D, Hu D, Chen H, et al. Glucose-regulated phosphorylation of TET2 by AMPK reveals a pathway linking diabetes to cancer. Nature. 2018;559(7715):637–41.
4. Zaorsky NG, Shaikh T, Ruth K, et al. Prostate cancer patients with unmanaged diabetes or receiving insulin experience inferior outcomes and...
toxicities after treatment with radiation therapy. Clin Genitourin Cancer. 2017;15(2):326–35, e323.
5. Alashkham A, Paterson C, Hubbard S, Nabi G. What is the impact of diabetes mellitus on radiation induced acute proctitis after radical radiotherapy for adenocarcinoma prostate? A prospective longitudinal study. Clin Transl Radiat Oncol. 2019;14:59–63.
6. Pears KS, Barone BB, Snyder CF, et al. Diabetes mellitus and breast cancer outcomes: a systematic review and meta-analysis. J Clin Oncol. 2011;29(1):40–6.
7. Bledsoe TJ, Nath SK, Decker RH, et al. Radiation pneumonitis. Clin Chest Med. 2013;34(2):301–8.
8. Chang YJ, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol. 2015;16(6):630–7.
9. Oron MD, Mukhopadhyay ND, Weiss E. Evaluation of diabetes as a risk factor for the development of clinically symptomatic pneumonitis following Stereotactic Body Radiation Therapy (SBRT). Int J Radiat Oncol Biol Phys. 2013;87(2):S554.
10. Popov D, Simionescu M. Alterations of lung structure in ex-perimential diabetes, and diabetes associated with hyperlipidaemia in hamsters. Eur Respir J. 1997;10(18):1850–8.
11. Lin CC, Chang CT, Li TC, et al. Objective evidence of impair of alveolar integrity in patients with non-insulin-dependent mellitus using radionuclide inhalation lung scan. Lung. 2002;180(3):181–6.
12. Clore JN, Thurbay-Hay L. Glucocorticoid-induced hyperglycemia. Endocr Pract. 2009;15(5):469–74.
13. Yamashita H, Takahashi W, Haga A, et al. Radiation pneumonitis after stereotactic radiotherapy for lung cancer. World J Radiol. 2014;6(6):708–15.
14. Hisa WI, Jan N, Mukhopadhyay ND, Weiss E. Effect of diabetes mellitus and selected medications on the development of radiation pneumonitis in patients with locally advanced non-small cell lung cancer. Int J Radiat Oncol Biol Phys. 2015;93(3):403.
15. Luo W, Wang Y, Tang SM. Effect of different fractionated radiotherapy modes on radiation pneumonitis after radical mastectomy in patients with diabetes mellitus. J Modern Oncol. 2019;16(27):2879–82.
16. Guo F, Du AN, Shi JL, et al. Clinical study of radiation pneumonitis in patients with esophageal cancer and diabetes after intensity-modulated radiotherapy. Chin J Radiol Health. 2018;06(27):628–30.
17. Zhang X-J, Sun J-G, Sun J, et al. Prediction of radiation pneumonitis in lung cancer patients: a systematic review. J Cancer Res Clin Oncol. 2012;138(12):2103–16.
18. Kalman Noah S, Hugo Geoffrey D, Mahon Rebecca N, et al. Diabetes mellitus and radiation induced lung injury after thoracic stereotactic body radiotherapy. Radiat Oncother. 2018;129(2):270–6.
19. Kong M, Lim YJ, Kim Y, et al. Diabetes mellitus is a predictive factor for radiation pneumonitis after thoracic radiotherapy in patients with lung cancer. Cancer Manag Res. 2019;11:7103–10.
20. Ergen SA, Dinçbas FO, Yücel B, et al. Risk factors of radiation pneumonitis. Redox Rep. 2017;22:257–64.
21. Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006;444(7121):860–7.
22. Kim JH, Cho TS, Moon JH, et al. Serial changes in serum eosinophil-associated mediators between atopic and non-atopic children after mycoplasma pneumoniae pneumonia. Allergy Asthma Immunol Res. 2014;6(5):428–33.
23. He T, Tao J, Wang X, et al. Effects of cisatracurium in combination with ventilation on inflammatory factors and immune variants in sepsis rats. Exp Ther Med. 2018;15(3):4414–8.
24. Chen HY, Lee CH, Hsu TH, et al. Submerged-culture mycelia and broth of the maitake medicinal mushroom grifola frondosa (higher basidiomycetes) alleviate type 2 diabetes-induced alterations in immunocytocin function. Int J Med Mushrooms. 2015;17(6):541–56.
25. Cheekatla SS, Tripathi D, Venkatasubramanian S, et al. NK-CDC11c+ c cell crosstalk in diabetes enhances IL-6-mediated inflammation during Mycobacterium tuberculosis Infection. PLoS Pathog. 2016;12(10):e1005972.
26. Pitkiewicz P, Bernat-Karpinska M, et al. NK cell count and glucotransporter 4 (GLUT4) expression in subjects with type 2 diabetes and colon cancer. Diabetol Metab Syndr. 2016;8(1):38.
27. Naruishi K, Omori K, Maeda H, et al. Immune responses to porphyromonas gingivalis infection suppress systemic inflammatory response in experimental murine model. J Biol Regul Homeost Agents. 2011;25(2):195–202.
28. Path KH, Jo SK. Lasting effects of an impairment of Th1-like immune response iny-irradiated mice: a resemblance between irradiated mice and aged mice. Cell Immunol. 2011;267(1):1–8.
29. Tsoutsou PG. The interplay between radiation and the immune system in the field of post-radical pneumonitis and fibrosis and why it is important to understand it. Expert Opin Pharmacother. 2014;15(13):1781–3.
30. Sinclair AJ, Conroy SP, Bayer AJ. Impact of diabetes on physical function in older people. Diabetes Care. 2008;31(2):235–5.
31. Browne JL, Hooshmand S, Elam M, et al. The relationship between inflammation, oxidative stress, and metabolic risk factors in type 2 diabetic patients. Thyroid J Thyotto Physopharmacol. 2012;20(6):470–80.
32. Eriksson JW. Metabolic stress in insulin’s target cells leads to ROS accumulation—a hypothetical common pathway causing insulin resistance. FEBS Lett. 2007;581(19):3734–42.
33. Rehman K, Akash MSH. Mechanism of generation of oxidative stress and pathophysiology of type 2 diabetes mellitus: how are they interlinked? Oxidative stress and diabetes mellitus. J Cell Biochem. 2017;118(11):3577–85.
34. Butkowsk IG, Jelinek HF. Hyperglycaemia, oxidative stress and inflammation markers. Redox Rep. 2017;22:257–64.
35. Novakova-Jiresova A, Luijk PV, Goor HV, et al. Changes in expression of related mediators between atopic and non-atopic children after mycoplasma pneumoniae pneumonia. Allergy Asthma Immunol Res. 2014;6(5):428–33.
36. DiDonato JA, Hoath SB, Bertrand N, et al. NF-kappaB-mediated gene expression in diabetes mellitus. J Clin Invest. 2005;116(11):2957–66.
37. Anezinski E, Pelletier MC, et al. Oxidative stress and diabetes: endogenous and exogenous alcohol-induced changes in mitochondria. Diabetes Metab. 2013;39(1):9–11.
38. Clore JN, Thurbay-Hay L. Glucocorticoid-induced hyperglycemia. Endocr Pract. 2009;15(5):469–74.
39. Han B, Sohn DS, Chang MG, et al. High glucose exposure induces the activation of Akt in the liver, but not in adipose tissue, in streptozotocin-induced diabetic mice. J Pharmacol Sci. 2016;130(2):176–82.
40. Kotake K, Kuroki A, Masuda N, et al. Ultrasound diagnosis of lung cancer and diabetes mellitus. Jpn J Radiol. 2002;20(2):92–9.
41. Thiele JF, Ferrari AW Jr. Macrophages, fat, and the emergence of immunometabolism. J Clin Invest. 2013;123(12):4992–3.
42. Rehman K, Akash MSH. Mechanism of generation of oxidative stress and pathophysiology of type 2 diabetes mellitus: how are they interlinked? Oxidative stress and diabetes mellitus. J Cell Biochem. 2017;118(11):3577–85.
43. Butkowsk IG, Jelinek HF. Hyperglycaemia, oxidative stress and inflammation markers. Redox Rep. 2017;22:257–64.
44. Novakova-Jiresova A, Luijk PV, Goor HV, et al. Changes in expression of related mediators between atopic and non-atopic children after mycoplasma pneumoniae pneumonia. Allergy Asthma Immunol Res. 2014;6(5):428–33.
45. DiDonato JA, Hoath SB, Bertrand N, et al. Oxidative stress and diabetes: endogenous and exogenous alcohol-induced changes in mitochondria. Diabetes Metab. 2013;39(1):9–11.
46. Thiele JF, Ferrari AW Jr. Macrophages, fat, and the emergence of immunometabolism. J Clin Invest. 2013;123(12):4992–3.
47. Rehman K, Akash MSH. Mechanism of generation of oxidative stress and pathophysiology of type 2 diabetes mellitus: how are they interlinked? Oxidative stress and diabetes mellitus. J Cell Biochem. 2017;118(11):3577–85.
51. Xu F, Liu Y, Zhu X, et al. Protective effects and mechanisms of vaccarin on vascular endothelial dysfunction in diabetic angiopathy. Int J Mol Sci. 2019;20(18):4587–602.
52. Chen RF, Chang CH, Wang CT, et al. Suppression of oxygen radicals protects diabetic endothelium damage and tissue perfusion in a streptozotocin-induced diabetes rodent mode. Ann Plas Surg. 2019;82(15):18–22.
53. Guzik TJ, Musso S, Gastaldi D, et al. Mechanisms of increased vascular superoxide production in human diabetes mellitus: role of NAD(P)H oxidase and endothelial nitric oxide synthase. Circulation. 2002;105(14):1656–62.
54. Basmael YS, Al Subayil AM, Khatlani T, et al. Human chorionic villous mesenchymal stem/stromal cells protect endothelial cells from injury induced by high level of glucose. Stem Cell Res Ther. 2018;9(1):238–57.
55. Tonade D, Liu H, Palczewski K, Kern TS. Photoreceptor cells produce inflammatory products that contribute to retinal vascular permeability in a mouse model of diabetes. Diabetologia. 2017;60(10):2111–20.
56. Ishihme MR, Hamed M, Barthelmes D, et al. Identification of novel diabetest impaired miRNA-transcription factor co-regulatory networks in bone marrow-derived Lin−/VEGF−R2+ endothelial progenitor cells. PLoS ONE. 2018;13(7):e0200194.
57. Falkevall A, Mehlem A, Palombo I, et al. Reducing VEGF-B signaling ameliorates renal lipotoxicity and protects against diabetic kidney disease. Cell Metab. 2017;25(3):713–26.
58. Cui X, Chopp M, Zacharek A, et al. Angiopoietin/Tie2 pathway mediates type 2 diabetes induced vascular damage after cerebral stroke. Neurobiol Dis. 2011;43(1):285–92.
59. Aashara T, Murrah T, Sullivan A, et al. Isolation of putative progenitor endothelial cells for angiogenesis. Science. 1997;275(5302):964–7.
60. Tepper OM, Gallano RD, Capla JM, et al. Human endothelial progenitor cells from type II diabetes exhibit impaired proliferation, adhesion, and incorporation into vascular structures. Circulation. 2002;106(22):2781–6.
61. Tomaiuolo G. Biomechanical properties of red blood cells in health and disease towards microfluidics. Biomicrofluidics. 2014;8(5):89–110.
62. Chan K, Chen S, Chen P. Astataxanthin attenuated thrombotic risk factors in type 2 diabetic patients. J Funct Foods. 2019;53:22–7.
63. Opdenakker G, El-Asrar AA. Metalloproteinases mediate diabetes-induced retinal neuropathy and vasculopathy. Cell Mol Life Sci. 2019;76:3157–66.
64. Suzanne M. The full spectrum of Alzheimer’s disease is rooted in metabolic derangements that drive type 3 diabetes. Adv Exp Med Biol. 2019;1128:45–83.
65. Long J, He CJ, Ding H, et al. Effect of shock wave on vascular lesions in diabetic rats. Pain Phys. 2019;22(5):505–10.
66. Lee S, Lee MY, Nam JS, Kang S, Park JS, Shin S, Ahn CW, Kim KR. Hemorheological approach for early detection of chronic kidney disease and diabetic nephropathy in type 2 diabetes. Diabetes Technol Ther. 2015;17(11):808–15.
67. Domingoetti CP, Dusse LM, Carvalho M, et al. Diabetes mellitus: the linkage between oxidative stress, inflammation, hypercoagulability and vascular complications. J Diabetes Complicat. 2016;30(4):738–45.
68. Schuylor M, Niewoehner D, Inkleby S, et al. Abnormal lung elasticity in juvenile diabetes mellitus. Am Rev Respir Dis. 1976;113(1):37–41.
69. ALIMO. Pulmonary complications in diabetes mellitus. Mymensingh Med J. 2014; 23(3):603–605.
70. Mekov EV, Slavova YG, Genova MP, et al. Diabetes mellitus type 2 in hospitalized COPD patients: impact on quality of life and lung function. Folia Med. 2016;58(1):36–41.
71. Mckeever TM, Weston PJ, Hubbard R, et al. Lung function and glucose metabolism: an analysis of data from the Third National Health and Nutrition Examination Survey. Am J Epidemiol. 2005;161(6):546–56.
72. Ford ES, Mannino DM, National H, et al. Prospective association between lung function and the incidence of diabetes: findings from the National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. Diabetes Care. 2004;27(12):2966–70.
73. Pinnix C, Perkins GH, Strom EA, et al. Topical hyaluronic acid vs standard of care for the prevention of radiation dermatitis after adjuvant radiotherapy for breast cancer: single-blind randomized phase III clinical trial. Int J Radiat Oncol Biol Phys. 2012;83(4):1089–94.
74. Plama DA, Senan S, Tsujino K, et al. Predicting radiation pneumonitis after chemoradiation therapy for lung cancer: an international individual patient data meta-analysis. Int J Radiat Oncol Biol Phys. 2013;87(4):690–6.
75. Malenica M, Silar M, Dujic T, et al. Importance of inflammatory markers and IL-6 for diagnosis and follow up of patients with type 2 diabetes mellitus. Med Glas Ljek Komore Zenicko-doboj Kantona. 2017;14(2):169–75.
76. Wu HP, Chu CM, Lin CY, et al. Liver cirrhosis and diabetes mellitus are risk factors for staphylococcus aureus infection in patients with healthcare-associated or hospital-acquired pneumonia. Pulm Med. 2016;2016:4706150.
77. Walter RE, Beiser A, Givelier RJ, et al. Association between glycemic state and hung function. Am Respir Crit Care Med. 2003;167(5):911.
78. Niren K, Shah PD, Wasim E, et al. A novel sodiumglucose cotransporter type 2 inhibitor for the treatment of type 2 diabetes mellitus. Pharmaco-therapy. 2012;32(1):80–94.
79. Bernard L, Reix N, Benabu JC, et al. Breast cancer and diabetes mellitus: single-blind randomized phase III clinical trial. Int J Radiat Oncol Biol Phys. 2013;87(4):1089–94.
80. Mckeever TM, Weston PJ, Hubbard R, et al. Lung function and glucose metabolism: an analysis of data from the Third National Health and Nutrition Examination Survey Epidemiologic Follow-up Study. Diabetes Care. 2004;27(12):2966–70.

**Publisher’s Note**

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.