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TLR3 and its roles in the pathogenesis of type 2 diabetes

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Abstract

Type 2 diabetes (T2D) is the most prevalent non-infectious disease and leads to several complications including nephropathy and retinopathy. The mechanisms and signaling molecules responsible for the development and progression of T2D, as well as its associated complications are yet to be identified. It would appear that genetic backgrounds and immunological parameters of people susceptible to T2D may play important roles in induction of T2D. TLRs participate in several cellular pathways which can induce activation of proliferation. However, in contradiction, these pathways can also be associated with apoptosis. The multiple roles of TLRs and their signaling molecules associated with T2D pathways makes them candidates for the induction of immune-regulated diseases like T2D. TLR3 has been identified as an intracellular ligand and subsequently activates signaling molecules via the TRIF pathway. Therefore, the alteration of expression of TLR3 and their functions may lead to inappropriate induction of immune system functions that are related to T2D disease. The aim of this review was to collect recent data regarding the roles of TLR3 in the progression and pathogenesis of T2D.

Key words: Type 2 Diabetes, Toll Like Receptor 3, TRIF.

Introduction

The frequencies of type 2 diabetes (T2D) make it the most prevalent type of diabetes, and its incidence continues to increase globally (1). It is expected that T2D and its complications will affect 300 million people by 2025 (1). Recent investigations showed that genetic, immunologic and environmental parameters play a major role in the pathogenesis of T2D and its complications (2, 3). It has been proposed that T2D is an immune system dependent disorder in which the expression or activation profiles of immune related molecules are altered (4). Toll like receptors (TLRs), are important intra/extra-innate immunity sensors and are involved in crucial cellular pathways via the activation of intracellular signaling molecules (5). TLRs are evolutionarily conserved proteins expressed in phagocytic cells such as macrophages, dendritic cells and neutrophils. TLRs consist of 14 members including TLR1, 2, 4, 5 and 6 which are expressed on cytoplasmic membranes whereas TLR3, 7, 8 and 9 are expressed inside the endosomes of human cells (6). At least 10 different TLRs are found in humans, while, other members are not expressed on/in human cells. TLRs recognize various pathogen associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), which lead to activation of two important intracellular signaling pathways including Toll/IL-1R-domain-containing adaptor inducing IFN-β (TRIF) and myeloid differentiation primary response gene 88 (MYD88) dependent pathways (6). Activation of the signaling pathways can regulate several functions of human immune cells including expression of inflammatory cytokines, MHC and homing molecules (7).

TLR3 is a unique intracellular TLR which recognizes several ligands such as dsRNA viruses and regulates cell functions in a TRIF dependent manner (8, 9). It has been documented that TLR3 can regulate the functions of immune cells, pancreatic β-cell, adipocytes and also glucose homeostasis (10, 11). So, altered expression or function of TLR3 may not only be associated with altered immune responses but it may also participate in β-cell function and glucose homeostasis which are associated with T2D. Based on research which identifies T2D is an immune system related disease and the pivotal roles played by TLR3 in the function of immune cells and β-cells, it is hypothesized that the TLR3 may participate in the development of T2D and its complications. Therefore, the present review article was designed to review the recent data regarding the plausible mechanisms that associate TLR3 and its signaling molecules in the development and pathogenesis of T2D and its complications.

TLR3; introducing, ligands and intracellular signaling

The TLR3 gene (also known as CD283) is located

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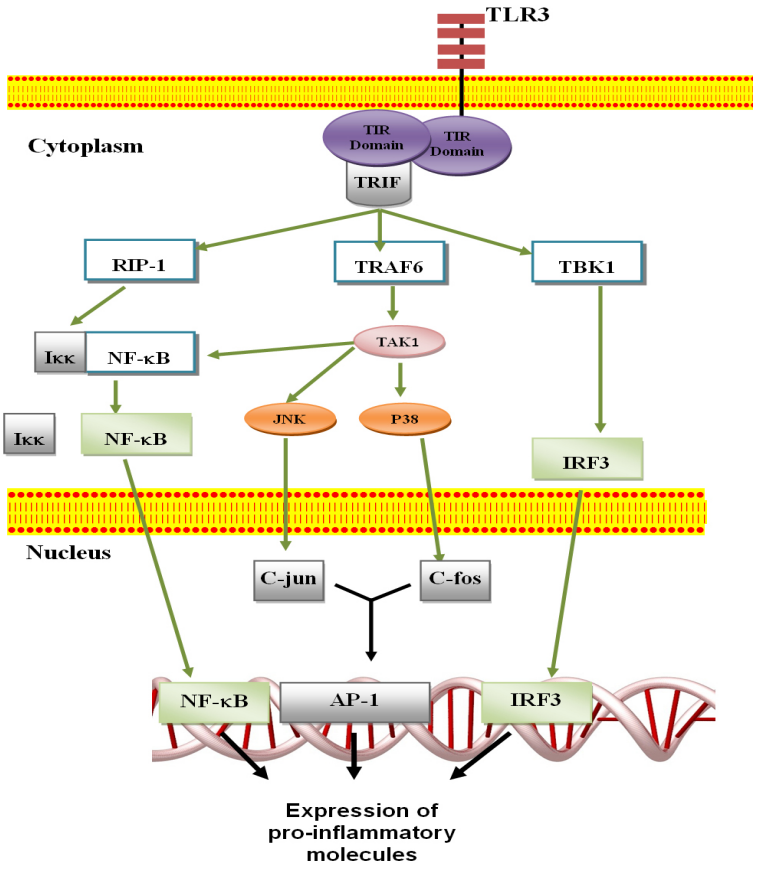

Figure 1. TLR3 intracellular signaling. The figure demonstrated that TLR3 activate pro-inflammatory transcription factors (IRF3, AP-1 and NF-κB) via TRIF signaling pathway.

on 4q35 (12) and is highly conserved in several species (13). TLR3 plays a key role in the recognition of PAMPs and DAMPs which leads to phosphorylation and activation of several transcription factors including interferon regulatory factor 3 (IRF3), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and activator protein 1 (AP-1). These transcription factors participate in several cell functions including activation of signal transduction, proliferation and in some cases apoptosis (14-16). Like other TLRs, the structure of TLR3 consists of three sections including the extracellular N-terminal domains, a hydrophobic transmembrane domain and an intracellular Toll/interleukin-1 receptor (TIR) domain (17). TLR3 localizes to the endoplasmic reticulum (ER), the lysosome and the endosome (18). TLR3 is expressed in several immune cells, such as monocytes, dendritic cells and NK cells, however, it is also expressed in non-immune cells including epithelial cells and β cells of the pancreas (10, 19).

The main ligand for TLR3 is endogenous dsRNA, however, TLR3 can also be activated by polyriboinosinic polyribocytidylic acid (poly I:C), which is a stable synthetic dsRNA analogue (20, 21). Interestingly, it has been demonstrated that TLR3 preferentially binds synthetic poly I:C compared to viral dsRNA, leading to the proposal that TLR3 recognizes unique dsRNA structures (22). Furthermore, TLR3 detects cell-associated poly I:C more efficiently than soluble dsRNA. Leading to a further hypothesis that TLR3 detects dsRNA from dying cells preferentially to that of live cells (23).

In contrast to other TLRs, TLR3 uses TRIF as the unique adaptor factor, thereby activating transcription factors via the TRIF pathway (24). The association of TLR3 with its ligand leads to interactions between the TIR domain of TLR3 and TRIF (25) and subsequent activation of downstream intracellular signaling molecules such as TNF receptor associated factor 6 (TRAF6), receptor-interaction protein 1 (RIP-1) and tank-binding kinase 1 (TBK1) (26). These events lead to activation of IRF3, AP-1 and NF-κB, which are transcription factors that regulate inflammation (27, 28) and are responsible for transcription from several genes which are involved in cell activation, proliferation and apoptosis (Figure 1) (29).

TLR3 and type 2 diabetes

There is some controversy in the literature regarding the potential functions of TLR3 and its intracellular signaling in the progression and pathogenesis of T2D. There is some evidence which demonstrates that TLR3 acts directly on the function and replication of pancreatic β-cells. For instance, Wang and colleagues (2013) revealed that TLR3 and its related signaling molecules like TRIF and p38 play a negative role in the proliferation of pancreatic β-cell lines (30). Accordingly, they have stimulated TLR3, using poly I:C, and found that cyclin D1/2 protein levels were decreased in pancreatic β-cell lines which led to inhibited proliferation of these cells (30). They also reported that MG132, a proteasome inhibitor, resolved the inhibitory function of poly I:C (30). Leading to the speculation that TLR3 inhibits pancreatic β-cell line proliferation by regulating the degradation of cyclin D in a ubiquitin/proteasome-dependent manner. More evidence for the role of TLR3 was shown in, RIP-B7.1 transgenic mice that express B7.1, which is an important costimulatory molecule, in pancreatic islets. These mice developed diabetes after treatment with

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poly I:C (31). Furthermore, it was reported that TLR3$^{-/-}$ mice were protected from diabetes after treatment with poly I:C (31). Wu et al., (2012) reported that loss of TLR3 function led to improve glucose tolerance and declined liver steatosis in obese mice (32). Moreover, another study demonstrated that dsRNA induces apoptosis in pancreatic β-cells by activation of TLR3 (33). Interestingly, up-regulation of TLR3 in peripheral blood mononuclear cells (PBMCs) derived from T2D patients has been reported previously (34) suggesting that the TLR3 pathway is active in these patients. Several molecules which participate in the pathogenesis of T2D, such as apo-proteins, have interactions with TLRs. For instance, it has been reported that apolipoprotein E suppresses activation of monocytes by TLR3 ligands (35). Clearly, further studies are needed to understand the relationship between TLR3 and known macromolecules which participate in the pathogenesis of T2D before we have a clear understanding of molecular mechanisms of T2D. However, the data suggests that TLR3 plays an important role in metabolic homeostasis focusing on the pancreatic β-cells as one of the cellular targets for this regulation. But these are not the only cells in which insulin pathways are regulated, because defects in TLR3 expression leads to diminish insulin resistance in muscle cells of obese patients (36).

As mentioned previously, TRIF is a unique adaptor protein for TLR3 to facilitate phosphorylation of signaling molecules (16). This data is supported by results in mice lacking TRIF which exhibit increased fasting blood glucose in comparison to healthy controls. It has been also reported that TRIF$^{-/-}$ mice were unable to produce normal ranges of insulin (10). Interestingly, the loss of TLR3 was not associated with islet dysfunction or hyperglycemia (10). Hussey et al., demonstrated that a prolonged mild increase in plasma levels of non-esterified fatty acids (NEFA) led to upregulation of TLRs and their related intracellular signaling molecules such as NF-κB and Mitogen-activated protein kinase (MAPK) in muscle tissue of healthy individuals (37). Interestingly, it has been found that increased expression of TLRs and their related signaling molecules led to mild inflammation, insulin resistance and exacerbate islet dysfunction (37). In parallel with pro-inflammatory cytokines, expression levels of TRIF were significantly increased in the monocytes of T2D subjects compared with a healthy control group (38). Komura and colleagues reported that expression levels of TLR3 and responsiveness of monocytes to TLR3 ligands were not different between T2D patients and healthy controls under *in vitro* conditions (39). Thus, the difference between T2D and healthy controls regarding TLR3 expression is controversial. In spite of all that, it seems that inflammation as a result of TLR3 activation may be considered as an important candidate for inducing pancreatic β-cell dysfunction. Surprisingly, there are limited clinical studies regarding the role of TLR3 in the pathogenesis of T2D complications. Accordingly, Rojo-Botello revealed that expression of TLR3 increased in gingival tissue from T2D patients with and without chronic periodontitis (34).

The data compiled in this review suggests that research into future lead therapies may explore the use of TLR3 agonists/antagonists as a beneficial therapeutic approach for the treatment of metabolic diseases including T2D.

It has been documented that T2D is associated with several complications such as nephropathy (40), retinopathy (41), periodontitis (42), cognitive dysfunction and dementia (43), cystic fibrosis (44) and hypertension (45). The main mechanisms which lead to the development of these complications during T2D are yet to be fully comprehended. However, one immerging theme is that inflammation is a common factor in these complications and that this may be induced by TLRs including TLR3. For example, it has been documented that serum levels of downstream molecules of the TLR3 pathway, including pro-inflammatory cytokines increased in patients with T2D complications such as periodontitis (42), nephropathy (40) and cardiovascular diseases (46).

It has been documented that inflammation is strongly associated with T2D and its complications (40). For instance, previous studies demonstrated that expressions of pro-inflammatory cytokines are elevated during T2D (40). Additionally, as mentioned in previous sections and also figure 1, TLR3 plays significant roles in induction of inflammation, hence, it seems that the expression status, genetic variations and the molecular roles of TLR3 in the development and pathogenesis of T2D complications should be explored further.

Conclusion remarks

According to the all data presented in this review, some hypothesizes may be proposed; firstly, TLR3 potentially participates in proliferation, function and apoptosis of pancreatic β-cells. Secondly, TLR3 and its molecular signaling may induce inflammation which leads to progression and deterioration of T2D and its related complications. Thirdly, TLR3 and the expression of its signaling molecules are altered in immune cells and/or pancreatic β-cells of T2D patients which may be induced by several factors including environmental, host genetic and epigenetic factors. However, further studies are required to confirm these hypotheses and improve our knowledge regarding the roles of TLR3 in the development and pathogenesis of T2D. Potentially, agonists/antagonists of TLR3 may be considered as leads for the treatment of T2D and its complications.

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References

1. Joost H-G. Diabetes and cancer: Epidemiology and potential mechanisms. Diabetes and Vascular Disease Research. 2014: 11(6):390-4. doi: 10.1177/1479164114550813..

2. Arababadi MK, Naghavi N, Hassanshahi G, Mahmoodi M. Is CCR5-Delta32 mutation associated with diabetic nephropathy in type 2 diabetes? Ann Saudi Med. 2009, 29(5):413. doi: 10.4103/0256-4947.55177

3. Arababadi MK, Mirzaei M, Sajadi SMA, Hassanshahi G, Ahmadababdi BN, Salehabadi VA, Derakhshan R, Kennedy D. Interleukin (IL)-10 gene polymorphisms is associated with type 2 diabetes with and without nephropathy: a study of patients from the South-East

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region of Iran. Inflammation. 2012; 35(3):797-802. doi: 10.1007/s10753-011-9376-7
4. Wu Y, Ding Y, Tanaka Y, Zhang W. Risk Factors Contributing to Type 2 Diabetes and Recent Advances in the Treatment and Prevention. International journal of medical sciences. 2014, 11(11):1185. doi: 10.7150/ijms.10001. eCollection 2014.
5. Shahrakyvahed A, Sanchooli J, Sanadgol N, Arababadi MK, Kennedy D. TLR9: an important molecule in the fight against hepatitis B virus. Postgraduate medical journal. 2014, 90(1065):396-401. doi: 10.1136/postgradmedj-2013-132309.
6. Carpenter S, O'Neill L. Recent insights into the structure of Toll-like receptors and post-translational modifications of their associated signalling proteins. Biochem J. 2009, 422:1-10. doi: 10.1042/BJ20090616.
7. Zare-Bidaki M, Hakimi H, Abdollahi SH, Zainodini N, Kazemi Arababadi M, Kennedy D. TLR4 in Toxoplasmosis; friends or foe? Microbial pathogenesis. 2014, 69:28-32. doi: 10.1016/j.micpath.2014.03.006.
8. Yu M, Lam J, Rada B, Leto TL, Levine SJ. Double-Stranded RNA Induces Shedding of the 34-kDa Soluble TNFR1 from Human Airway Epithelial Cells via TLR3–TRIF–RIP1-Dependent Signaling: Roles for Dual Oxidase 2-and Caspase-Dependent Pathways. The Journal of Immunology. 2011, 186(2):1180-8. doi: 10.4049/jimmunol.1001499.
9. Yamamoto M, Sato S, Hemmi H, Hoshino K, Kaisho T, Sanjo H, Takeuchi O, Sugiyama M, Okabe M, Takeda K. Role of adaptor TRIF in the MyD88-independent toll-like receptor signaling pathway. Science Signaling. 2003, 301(5633):640. doi: 10.1126/science.1087262.
10. Hutton MJ, Soukhatcheva G, Johnson JD, Verchere CB. Role of the TLR signaling molecule TRIF in beta-cell function and glucose homeostasis. Islets. 2010, 2(2):104-11. doi: 10.4161/isl.2.2.11209.
11. Brenner C, Simmonds RE, Wood S, Rose V, Feldmann M, Turner J. TLR signalling and adapter utilization in primary human in vitro differentiated adipocytes. Scand J Immunol. 2012, 76(4):359-70. doi: 10.1111/j.1365-3083.2012.02744.x.
12. Beutler B. Toll-Like Receptor Genes. Genetic Susceptibility to Infectious Diseases. 2008:165.
13. Choe J, Kelker MS, Wilson IA. Crystal structure of human toll-like receptor 3 (TLR3) ectodomain. Science Signaling. 2005, 309(5734):581. doi: 10.1126/science.1115253.
14. Youn HS, Lee JY, Saitoh SI, Miyake K, Kang KW, Choi YJ, Hwang DH. Suppression of MyD88-and TRIF-dependent signaling pathways of toll-like receptor by (S)-epigallocatechin-3-gallate, a polyphenol component of green tea. Biochemical pharmacology. 2006, 72:850-9. doi: 10.1016/j.bcp.2006.06.021.
15. Muzio M, Bosisio D, Polentarutti N, D'amico G, Stoppacciaro A, Mancinelli R, van't Veer C, Penton-Rol G, Ruco LP, Allavena P. Differential expression and regulation of toll-like receptors (TLR) in human leukocytes: selective expression of TLR3 in dendritic cells. The Journal of Immunology. 2000, 164(11):5998-6004. doi: 10.4049/jimmunol.164.11.5998.
16. Karimi-Googheri M, Arababadi MK. TLR3 plays significant roles against hepatitis B virus. Mol Biol Rep. 2014, 41(5):3279-86. doi: 10.1007/s11033-014-3190-x.
17. Bell JK, Botos I, Hall PR, Askins J, Shiloach J, Segal DM, Davies DR. The molecular structure of the Toll-like receptor 3 ligand-binding domain. Proceedings of the National Academy of Sciences of the United States of America. 2005, 102(31):10976-80. doi: 10.1073/pnas.0505077102.
18. Latz E, Schoenemeyer A, Visintin A, Fitzgerald KA, Monks BG, Knetter CF, Lien E, Nilsen NJ, Espevik T, Golenbock DT. TLR9 signals after translocating from the ER to CpG DNA in the lysosome. Nat Immunol. 2004, 5(2):190-8. doi:10.1038/ni1028.
19. Nicodemus CF, Berek JS. TLR3 agonists as immunotherapeutic agents. Immunotherapy. 2010, 2(2):137-40. doi: 10.2217/imt.10.8.
20. Alexopoulou L, Holt AC, Medzhitov R, Flavell RA. Recognition of double-stranded RNA and activation of NF-kappaB by Toll-like receptor 3. Nature. 2001, 413(6857):732-8. doi:10.1038/35099560.
21. Kariko K, Ni H, Capodici J, Lamphier M, Weissman D. mRNA is an endogenous ligand for Toll-like receptor 3. J Biol Chem. 2004, 279(13):12542-50.
22. Gauzzi MC, Del Corno M, Gessani S. Dissecting TLR3 signalling in dendritic cells. Immunobiology. 2010, 215(9-10):713-23. doi: 10.1074/jbc.M310175200.
23. McBride S, Hoebe K, Georgel P, Janssen E. Cell-associated double-stranded RNA enhances antitumor activity through the production of type I IFN. J Immunol. 2006, 177(9):6122-8. doi: 10.4049/jimmunol.177.9.6122.
24. Ayoobi F, Hassanshahi G, Zainodini N, Khorramdelazad H, Arababadi MK, Kennedy D. Reduced expression of TRIF in chronic HBV infected Iranian patients. Clin Res Hepatol Gastroenterol. 2013. doi: 10.1016/j.clinre.2012.11.005.
25. Wu JF, Chen CH, Ni YH, Lin YT, Chen HL, Hsu HY, Chang MH. Toll-like receptor and hepatitis B virus clearance in chronic infected patients: a long-term prospective cohort study in Taiwan. J Infect Dis. 2012, 206(5):662-8. doi: 10.1093/infdis/jis420.
26. Chang WJ, Toledo-Pereyra LH. Toll-like receptor signaling in liver ischemia and reperfusion. J Invest Surg. 2012, 25(4):271-7. doi: 10.3109/08941939.2012.687802.
27. Szatmary Z. Molecular biology of toll-like receptors. Gen Physiol Biophys. 2012, 31(4):357-66. doi: 10.4149/gpb_2012_048.
28. Li X, Jiang S, Tapping RI. Toll-like receptor signaling in cell proliferation and survival. Cytokine. 2010, 49(1):1-9. doi: 10.1016/j.cyto.2009.08.010.
29. Tuosto L. NF-kappaB family of transcription factors: biochemical players of CD28 co-stimulation. Immunol Lett. 2011, 135(1-2):1-9. doi: 10.1016/j.imlet.2010.09.005.
30. Wang Y, Wu H, Gao L, Chen S, Gu L, Ding Z, Guo J. Elevated toll-like receptor 3 inhibits pancreatic β-cell proliferation through G1 phase cell cycle arrest. Molecular and cellular endocrinology. 2013, 377(1):112-22. doi: 10.1016/j.mce.2013.07.003.
31. Alkanani AK, Hara N, Lien E, Ir D, Kotter CV, Robertson CE, Wagner BD, Frank DN, Zipris D. Induction of diabetes in the RIP-B7.1 mouse model is critically dependent on TLR3 and MyD88 pathways and is associated with alterations in the intestinal microbiome. Diabetes. 2014, 63(2):619-31. doi: 10.2337/db13-1007.
32. Wu LH, Huang CC, Adhikarakunnathu S, San Mateo LR, Duffy KE, Rafferty P, Bugelski P, Raymond H, Deutsch H, Picha K, Ward CK, Alexoupolou L, Flavell RA, Mbow ML, Susulic VS. Loss of toll-like receptor 3 function improves glucose tolerance and reduces liver steatosis in obese mice. Metabolism. 2012, 61(11):1633-45. doi: 10.1016/j.metabol.2012.04.015.
33. Dogusan Z, García M, Flamez D, Alexopoulou L, Goldman M, Gysemans C, Mathieu C, Libert C, Eizirik DL, Rasschaert J. Double-stranded RNA induces pancreatic β-cell apoptosis by activation of the toll-like receptor 3 and interferon regulatory factor 3 pathways. Diabetes. 2008, 57(5):1236-45. doi: 10.2337/db07-0844.
34. Rojo-Botello N, García-Hernández A, Moreno-Fierros L. Expression of toll-like receptors 2, 4 and 9 is increased in gingival tissue from patients with type 2 diabetes and chronic periodontitis. Journal of periodontal research. 2012, 47(1):62-73. doi: 10.1111/j.1600-0765.2011.01405.x.
35. Ali K, Middleton M, Puré E, Rader DJ. Apolipoprotein E suppresses the type I inflammatory response in vivo. Circulation research. 2005, 97(9):922-7. doi: 10.1161/01.RES.0000187467.67684.43.
36. Fabre O, Breuker C, Amouzou C, Salehzada T, Kitzmann M, Mercier J, Bisbal C. Defects in TLR3 expression and RNase L acti-

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vation lead to decreased MnSOD expression and insulin resistance in muscle cells of obese people. Cell Death Dis. 2014, 5:e1136. doi: 10.1038/cddis.2014.104.
37. Hussey SE, Lum H, Alvarez A, Cipriani Y, Garduno-Garcia J, Anaya L, Dube J, Musi N. A sustained increase in plasma NEFA upregulates the Toll-like receptor network in human muscle. Diabetologia. 2014, 57(3):582-91. doi: 10.1007/s00125-013-3111-x.
38. Dasu MR, Devaraj S, Park S, Jialal I. Increased toll-like receptor (TLR) activation and TLR ligands in recently diagnosed type 2 diabetic subjects. Diabetes Care. 2010, 33(4):861-8. doi: 10.2337/dc09-1799.
39. Komura T, Sakai Y, Honda M, Takamura T, Matsushima K, Kaneko S. CD14+ monocytes are vulnerable and functionally impaired under endoplasmic reticulum stress in patients with type 2 diabetes. Diabetes. 2010, 59(3):634-43. doi: 10.2337/db09-0659.
40. Arababadi MK, Nosratabadi R, Hassanshahi G, Yaghini N, Pooladvand V, Shamsizadeh A, Hakimi H, Derakhshan R. Nephropathic complication of type-2 diabetes is following pattern of autoimmune diseases? Diabetes Res Clin Pract. 2009, 87(1):33-7. doi: 10.1016/j.diabres.2009.09.027.
41. Gholamhossein Y, Behrouz H, Asghar Z. Diabetic retinopathy risk factors: plasma erythropoietin as a risk factor for proliferative diabetic retinopathy. Korean J Ophthalmol. 2014, 28(5):373-8. doi: 10.3341/kjo.2014.28.5.373.
42. Longo PL, Artese HP, Rabelo MS, Kawamoto D, Foz AM, Romito GA, Dib SA, Mayer MP. Serum levels of inflammatory markers in type 2 diabetes patients with chronic periodontitis. J Appl Oral Sci. 2014, 22(2):103-8. doi: 10.1590/1678-775720130540
43. Lee JH, Choi Y, Jun C, Hong YS, Cho HB, Kim JE, Lyoo IK. Neurocognitive changes and their neural correlates in patients with type 2 diabetes mellitus. Endocrinol Metab (Seoul). 2014, 29(2):112-21. doi: 10.3803/EnM.2014.29.2.112
44. Perano S, Rayner CK, Couper J, Martin J, Horowitz M. Cystic fibrosis related diabetes-a new perspective on the optimal management of postprandial glycemia. J Diabetes Complications. 2014;28(6):904-11. doi: 10.1016/j.jdiacomp.2014.06.012.
45. Castro Torres Y, Katholi RE. Novel treatment approaches in hypertensive type 2 diabetic patients. World J Diabetes. 2014, 5(4):536-45. doi: 10.4239/wjd.v5.i4.536.
46. Mahmoud F, Al-Ozairi E. Inflammatory cytokines and the risk of cardiovascular complications in type 2 diabetes. Dis Markers. 2013, 35(4):235-41. doi: 10.1155/2013/931915.

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