All Kerala Govt. Ayurveda College Teacher's Association
KERALA JOURNAL OF AYURVEDA
An International Journal of Ayurveda Specialties

ISSN 2583-8555 (ONLINE)
Vol 2(4): 20–26 (2023)
https://doi.org/10.55718/kja.204

REVIEW ARTICLE

Impact of non-communicable diseases on immunity and *Ojas* focussing on type 2 Diabetes Mellitus – A scoping review

Reshma M A [1] Pradeep K [2] Abhilash M [3] Dhanya N S [3] Anjali Sivaram [4]

[1] Senior Research Fellow Dept of Kriyasarira GAVC Tripunithura
[2] Associate Professor Dept of Kriyasarira GAVC Kannur
[3] Assistant Professor GAVC Tripunithura
[4] Associate Professor GAVC Tripunithura

*Email: reshmaantony88@gmail.com

ARTICLE HISTORY

Received: 24 September 2023
Accepted: 29 November 2023

Available online
Version 1.0 : 30 December 2023

Keywords

Non-communicable diseases, Immunity, *Ojas*, Type 2 Diabetes Mellitus, Gut microbiome

Additional information

Peer review: Publisher thanks Sectional Editor and the other anonymous reviewers for their contribution to the peer review of this work.

Reprints & permissions information is available at https://keralajournalofayurveda.org/index.php/kja/open-access-policy

Publisher's Note: All Kerala Govt. Ayurveda College Teacher's Association remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

CITE THIS ARTICLE

Reshma M A, Pradeep K, Abhilash M, Dhanya N S, Sivaram A . Impact of non-communicable diseases on immunity and Ojas focussing on type 2 Diabetes Mellitus – A scoping review. Kerala Journal of Ayurveda. 2023; 2(3): 01-05. https://doi.org/10.55718/kja.204

Abstract

Non communicable diseases (NCDs)are recognised as a major challenge in sustainable development. Among different types of NCDs, diabetes is connected to a number of other serious health problems. The projected rapid increase in diabetes prevalence, incidence, morbidity and mortality shows the necessity of developing new treatment strategies to combat the problem. In addition, diabetic patients are more susceptible to infections like urinary tract infections, lower respiratory tract infections and skin and soft tissue infections. Various studies were conducted to define the diabetes- associated mechanisms that impair the host's defence against pathogens. These mechanisms mainly include defects in phagocytosis, suppression of cytokine production, failure to kill microbes, dysfunction of immune cells etc. Both innate and adaptive immunity are severely hampered in diabetes. The disease severity is associated with severe gut microbiota dysbiosis. In Ayurveda classics, *ojakshaya*is described in the pathogenesis of *madhumeh a*and there is both qualitative and quantitative *kshaya* of *aparaojas.* This article discusses about different effects of T2DM on immune system which in turn promotes the different infections, gut microbiota dysbiosis and status of *ojakshaya* in *Prameha.*

Introduction

Non communicable diseases (NCDs) were recognised as a major challenging issue in the 2030 agenda of sustainable development. As a part of this, heads of state and government were dedicated to develop ambitious national responses to reduce mortality by one third. NCDs are also known as chronic diseases as they have a tendency to be of long duration. They were developed as a result of combination of genetic, environmental, physiological and behavioural factors. Diabetes, cardiovascular diseases, chronic respiratory diseases and cancers are the four leading types of NCDs. These diseases create major social concern, especially in low- and middle-income countries. NCDs eradicate 41 million people each year which is equal to 74% of total deaths worldwide. Among the four leading types of NCDs, diabetes account for 2 million of NCD deaths including kidney disease deaths caused

by diabetes.[1] In India, NCDs contribute to 60% of total deaths. In this, 3% is due to diabetes.[2] Diabetes is also associated with number of other serious health issues including obesity, hypertension, stroke, cardiovascular diseases, diabetic complications etc. It also imposes large economic burden on disease affected people, their families, societies and national health care system. The projected rapid increase in diabetes prevalence, incidence, morbidity and mortality shows the necessity of developing new treatment strategies to combat the problem.[3] Immune system plays a central role in all these NCDs. Diabetes being a chronic condition deteriorates the immunity of the person in its long run. In Ayurveda the symptoms of diabetes can be seen in *Prameha* which is a *Vasthigata roga*. During the progression of *Prameha* it causes gradual depletion of *Ojas* and the person becomes susceptible to various infections. This article is aimed at presenting and discussing the impact of type 2 diabetes on immunity and *Ojas*.

Methodology

For this scoping review, relevant articles were selected from PubMed using the advanced searching option using keywords Diabetes Mellitus and Immunity or *Ojas*. From these articles, 44 were selected applying the criteria of dealing with immune related changes, pathophysiological changes that directly or indirectly affect immunity as well as integrative approaches in dealing with *Ojas*, immunity and Diabetes Mellitus. Finally, these findings were compared with the classical concepts of *Ojas* and *Prameha*.

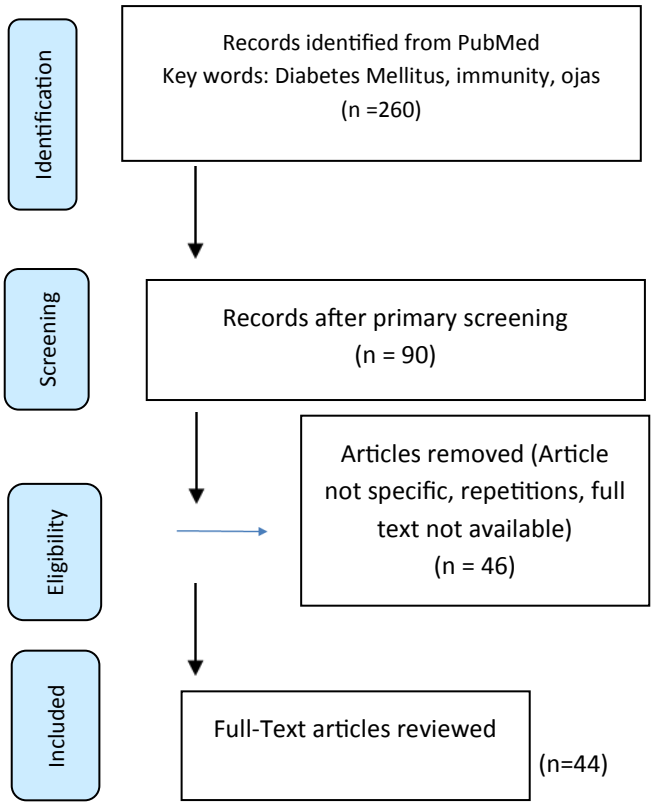

Figure 1 – Flow chart showing the review process

Impact of T2DM on immunity

Generally, immunity is of two types, innate immunity and adaptive immunity. Innate immunity is the first line of defence against invading pathogens. Adaptive immunity is mediated by both B cells and T cells. B cells produces antibodies and T cells are classified in to helper T cells and cytotoxic T cells. Unusual immune cell activation and consequent inflammatory environment plays important role in the progression of T2DM. The host's immune response is disrupted in diabetes. There is damage of natural barrier and cellular immunity. As per American Diabetes Association, the chief issue in diabetes are development of infections due to defective immune system. Already many studies were done to define diabetes- related mechanisms that damage the host's defence. The main mechanisms which play crucial role in defective host's defence are mainly dysfunction of immune cells, suppression of cytokine production, defects in phagocytosis, failure to kill microbes etc.[4]

Complement system, dendritic cells, macrophages, neutrophils, natural killer (NK) cells, natural killer T (NKT) cells, innate lymphoid cells (ILCs) etc are the central constituents of innate immunity. Complement system acts through classical, alternative and lectin pathways. Dendritic cells are specific antigen presenting cells (APCs) which play as a connecting link between innate and adaptive immune system. Macrophages have a critical role in T2DM related atherosclerosis. Diabetes patients become pro-inflammatory due to the modification of lipoproteins in arterial wall. Due to this monocytes are recruited to the site and become differentiated into macrophages and further internalise the accumulated lipoproteins to generate cholesterol- laden foam cells. It further promotes progression of disease through the synthesis of chemokines, cytokines, matrix metallo proteinases (MMPs) and reactive oxygen species (ROS). Foam cells die by apoptosis and produce necrotic core within atherosclerotic plaque. Macrophages also play important role in tissue repair. Initially they are pro- inflammatory to clear debris and pathogens, but later they stimulate tissue repair. Neutrophils are predominant leukocytes and they reach infection sites by chemotaxis. Activated neutrophils phagocytose and kill pathogens. NK cells sense and directly destroy tumour cells and virus infected cells. NKT cells express markers of both NK cells and T cells. They produce many cytokines. ILCs yields pro- inflammatory and regulatory cytokines to encourage immunity, inflammation and tissue repair.[4]

Table no 1: Effect of T2DM on immunity

Total leukocytes	Leukocytes number increases.[5]They become large, more granular and express less level of antioxidant
	Innate immunity
Complement system	Decreased attachment of C- type lectin to mannose residues[7], impaired lectin pathway, reduced CD59 activity, increased deposition of membrane attack complex (MAC) in vascular walls.[8]
Dendritic cells	Both the number and activity of DCs are reduced.[9,10]
Macrophages	Decreased cholesterol efflux and dysfunctional generation of foam cells.[11]
Neutrophils	Neutrophil become activated and release neutrophil extracellular traps (NETs)[12,13], production of high levels of myeloperoxidase (MPO)[14], ROS[15], and calprotectin (S100A8/A9).[16] They become susceptible to apoptosis. There will be impairment in their migration, phagocytosis and microbial killing.
NK cells	Increase in number of NK cells, but they are dysfunctional. Expression of high levels of GLUT4 (glucose transporter type 4).[17,18] Decreased levels of NKG2D, NKp46 and degranulation capacity. They become
NKT cells	Increase in number of NKT cells, produce high levels of IFN-γ, IL-4, IL-17[20], NKp39, NKG2D (natural killer group 2d) and NKp44 and low levels of NKG2A and 158b.[21]
Innate lymphoid cells	Increase in ILCs.[22,23] Production of high levels of IFN-γ.[23]
	Adaptive immunity
Humoral immunity	Reduced germinal centres[24], antibody (Ab) production. Defective isotype switching. Antibodies become glycated and fail to activate complement.[25-27]
Cellular immunity	Decreased number of pathogen specific Th17 helper cells.[29] Elevated number of Th1 cells, but decreased expression of granzyme B (GrB), perforin and CD107a.[28,29]

Effect of T2DM on susceptibility to infections

T2DM has an elevated risk of infections like urinary tract infections, pyelonephritis, balanitis, vulvo- vaginal infections etc with a complicated course. Defects in the innate immune responses are responsible for this.

Bacteria

Cutaneous microbiome is altered in T2DM patients. Staphylococcus epidermidis become dominant and increases the incidence of skin and soft tissue infections. Defective neutrophil causes increased infections with Staphylococcus aureus, Klebsiella pneumonia etc. The basal phenotype of macrophages is altered and they have a diminished capacity to control Mycobacterium tuberculosis. Both the severity and risk of progression to active form increased in diabetes. There is an increase in serum levels of inflammatory cytokines like IFN-γ, TNF-α, IL-1β, IL-17A, IL-2, IL-6 and IL-18, but decreased levels of IL-22. This contributes to poor control of TB infection. Both inflammatory microenvironment and dysfunctional immune responses increases the complications in diabetic TB. Wounds of diabetic patients are more prevalent in infections caused by Staphylococcus aureus, Enterococcus faecalis etc. T2DM patients are vulnerable to UTIs due to antibiotic resistant Escherichia coli, Klebsiella spp, Enterococci and Helicobacter pylori infections.

Viruses

There is a positive correlation with viral load and antibody titres with blood glucose levels. Infections with severe acute respiratory syndrome coronavirus (SARS-CoV), SARS corona virus2, hepatitis C virus (HCV) are increased in T2DM. Diabetic patients have elevated levels of adipose tissue derived adipokines, interferon, TNF-α, impaired viral clearance and impaired T cell function. Elevated levels of IL-6, IL-7, IL-8, IL-10, IFN-γ, fibrinogen, plasminogen, C-reactive protein and D-dimer have been seen in COVID-19 patients. COVID-19 patients also have lymphopenia, decreased Tcells, B cells and NK cells. Surviving T cells are of an exhausted phenotype. There is a higher prevalence of HBV infection. Influenza virus can induce severe form of disease in diabetic patients. Prevalence of cytomegalovirus, Herpes simplex virus and Varicella zoster are also increased.

Parasites

T2DM patients have an increased risk of infection with Plasmodium Falciparum, Ascaris lumbricoides and Giardia lamblia etc.

Fungi

There is higher prevalence of fungal wound infections in diabetic patients and it is correlated with levels of HbA1c. Candida albicans, Candida parapsilosis, Candida tropicalis, Aspergillus species are the widely observed fungal isolates. They are resistant to antifungal medications. Diabetic patients are also susceptible to UTIs caused by Candida albicans.[30]

Table no 2: Effect of T2DM on susceptibility to infections

	Infective agent
Innate immunity dysfunction	
Complement system	*Streptococcus pneumonia, Candida albicans, Candida tropicalis, Candida lusitaniae, Candida lipolytica, Candida krusei, Escherichia coli and Borrelia burgdorferi*[31-34]
NK cells	*Mycobacterium tuberculosis*[29,35]
Neutrophil	*Klebsiella pneumonia, Staphylococcus aureus and Burkholderia pseudomallei*[36-40]
Macrophage	*Mycobacterium tuberculosis*[41]
ILC3	*Mycobacterium tuberculosis*[42]
Adaptive immunity dysfunction	
B cells	*Streptococcus pneumonia, Staphylococcus aureus*[43,44]
T cells	*Mycobacterium tuberculosis*[29,35]

Human microbiome

Human microbiome includes diverse types of microbes and the utmost studied ones are gut microbiome. Gut microbiome carries a complex community of over 100 trillion bacteria, viruses, yeasts and parasites. It influences the host physiology, gut barrier permeability, metabolism, immune functions and brain functions. Gut microbiome plays crucial role in NCDs as it actively involves in gut homeostasis. This vision can lead to new advances in gut microbiome modulation which in turn can produce good results in management and avoidance of NCDs. Suitable therapeutic immunomodulatory nutritional interventions have the potential to re-establish homeostasis in NCDs.

Alterations in gut microbiome have been perceived in preclinical animal models and T2DM patients. T2DM patients have an increase in multiple pathogenic bacteria such as Escherichia coli, Clostridium hathewayi, Clostridium symbiosum. The disease severity is associated with severity of gut microbiome dysbiosis. Administration of probiotics in animal models and humans showed improvement in disease progression.[45] Additional research is still necessary to find out the missing links between altered physiological and immunological mechanisms and amplified proneness to infections in T2DM.

Diabetes in Ayurveda- *Prameha* and *Madhumeha*

Ayurveda explains *Prameha* as a group of disorders characterized by increase in frequency of micturition, increase in volume and turbidity of urine. *Acharya* include *Prameha* in the eight major incurable diseases. The disease was considered one among the *vasthighatarogas* and has twenty types.Among twenty types, ten are caused by *kapha*, six by *pitta* and four by *vata*. *Madhumeha* or *kshaudrameha* is explained as one type of *vatameha*. This term *Madhumeha* is used synonymously to Diabetes mellitus by many people. The three *doshik* types *kapha*, *pitta* and *vata*can be considered as three stages of one disease. *Kaphajaprameha* is the early stage and *vatajaprameha* is the final stage. *Sahaja pramehi* has the *vata* predominant stage of disease in the very beginning. So,*Madhumeha* is a *vatapradhanatridoshajavyadhi* which occurs either independently as in *sahajapramehi* or as a final stage due to inadequate treatment.[46]

Status of *Ojas* in *Prameha*

In Ayurveda,*Ojas* is considered as the essence of seven *dhatus*. It represents biological strength or *bala*. It is the purest product of digestion, absorption and metabolism. *Charaka* explains *Ojas* in *dasapranayatana*. *Vyadhikshamatva* is the main task done by*Ojas*. *Vyadhikshamatva* is the capability of the body to battle against developed disease and resists new disease production. It is the resistance to decay and degeneration. It can be equated to immunity.[47]

As per *Ayurveda* classics, the vitiation of*Ojas*is broadly classified as *ojovisramsa*, *ojovyapat* and *ojakshaya*. This *ojakshaya* is in turn described in the pathogenesis of *Madhumeha.*[48]*Oja kshaya* is also seen in *sannipatajwara*, *pandu*, *grahani, kshatsheen, rajayakshma* etc.According to *Charaka*,the etiopathogenesis of *Prameha* begin as *kaphaja*; vitiates 10 *dushyas meda*, *mamsa*, *kleda* etc.,and gradually it undergoes *pittaja* stage and finally it attains *vataja* nature. During the progression through each stage,*Prameha* manifest with its various systemic effects and attain the name *Madhumeha*. The *Madhumeha* becomes very difficult to cure due to its progression to the deeper *dhatus*. During the progression of *Prameha*, it affects all the *dhatuvahasrotas* and cause *dhatukshaya* and finally results in *kshaya* of *Ojas*. Hence it can be called as *Ojomeha*.[49] Gradual depletion of *Ojas* makes the person susceptible to opportunistic infections and compromises the quality of life.

Chakrapani while explaining *Ojas* states that it exists in 2 forms- *para ojas* and *aparaojas*. The "*para*" means superior and "*apara*" means inferior. Though they are mentioned so, each has its own significance. Both *para* and *apara ojas* are mutually dependent for maintaining the

health and life. The *para ojas* formed during the time of fertilization is responsible for the viability and growth and development of the zygote through different stages. The *para ojas* located in *hridaya* having 8 *bindupramana*. It's highly vital as even a fractional decrease of it may cause instantaneous death. The *para ojas*is essential for the existence of healthy life till death. In *Madhumeha,*there is qualitative and quantitative *kshaya* of *Apara ojas*.*Apara ojas* traverses all over the body through minute channels. The quantity of *apara ojas* is half *anjali*(*swaprasruta*) and varies between individuals.[49]*Apara ojas* is derived from the *poshaka dhatus*. The quantitative and qualitative *dhatu kshaya* ultimately causes *ojakshaya*. The defective *aparaojas* gradually deteriorate the quality of *para ojas*. The improper *Ojas* disrupt the homeostasis of various systems of the body. Ultimately the person becomes weak, prone to many systemic diseases and infections.

Ojas is also mentioned as one of the *dushyas* of *Prameha*.*Prameha* begins as *kaphapradhana tridoshadushti*. Increased *kapha* and *meda* along with *kleda* and *shithilamamsa* is dragged to *vasti* and expressed as *prabhootavila mutrata*.[50]*Prabhootamutrata* indicates both the quantity and frequency of urine. *Avilatwa* is the turbidity of urine due to excretion of *dosha* and *dushya*. In *Madhumeha*, *vata* by its *ruksha guna* changes the quality of *Ojas* from *madhura* into *kashaya* and transports it to *vasti*. So, the *Ojas* produced in *Madhumeha* is deficient in quality. The qualitatively deficient *Ojas* is also lost through urine.[48]

Discussion

NCDs have direct impact on the immune system as well as there can be indirect influence through other factors like gut microbiome. There is decline in both innate and adaptive immune mechanisms in cases of type 2 Diabetes Mellitus. Although the direct mentioning of *Ojas* in *Prameha* is limited, as any other disease;*dosha*, *dushya*, *prakriti*, *aahara*, *agni*, *koshta*, *satvam*, *nidra* etc has its own role in development and progression of *ojakshaya*. *Ativyayama* (excessive exercise), *chinta*(excessive thought) , *bhaya* (worry)*, kshayam*(loss of tissues) , *abhigata*(injury), *kopa* (anger) , *soka (grief)* are the main factors responsible for reduction of *Ojas.* The nature of *Ojas* both in quality and quantity is different in every individual depending on *prakriti*, *agni*, *satva* etc. Even though *Prameha* develops in a person due to its specific *nidanas* the progression of the disease will depend on the inbuilt nature of these *prakriti*, *agni*, *satva* etc. For example, the rate of progression of the disease will be slow in *kaphasariraprakriti*, *satvikamanasa prakriti*, *samagni*, *madhyakoshta*, *pathyaaharaseelitha*individual. If these factors are also favorable for the disease, the progression of disease will be faster.

Conclusion

Diabetes is one of the important threats to the public health. For countries like India, burden of diabetes has been already increased significantly and will continue to increase in future. The current pandemic, COVID-19 has been exposed how the susceptible populations with high rates of NCDs including diabetes are to disease severity. This in turn advocates the need to recalibrate and reframe the diabetic management strategies once again. At present all the treatments target at the control of blood glucose level only. So after some time patient suffers from severe diabetic complications. But Ayurveda as a holistic medicine approaches a disease in a broad aspect. It addresses the root cause and tries to prevent or delay the complications that may happen in future. So conservation of immunity is an important factor to prevent the complications. So the treatment should be based on increasing the *Ojas* or immunity along with controlling disease. A better understanding of how immune dysfunctions occur in diabetes will help an *Ayurvedic* physician to manage the disease without further complications.

References

1. Damasceno A. Noncommunicable Disease. Heart of Africa: Clinical Profile of an Evolving Burden of Heart Disease in Africa. 2016. 155–157 p.
2. National Health Mission. Module for multi purpose workers (mpw) female/male on prevention, screening and control of common non communicable diseases. 2018;68. Available from: http://nhsrcindia.org/sites/default/files/Multi-Purpose Workers on Prevention Screening Control of NCDs-English.pdf
3. Balasopoulou A, Kokkinos P, Pagoulatos D, Plotas P, Makri OE, Georgakopoulos CD, et al. Symposium Recent advances and challenges in the management of retinoblastoma Globe saving Treatments. BMC Ophthalmol [Internet]. 2017;17(1):1. Available from: http://www.ncbi.nlm.nih.gov/pubmed/28331284 http://www.pubmedcentral.nih.gov/article PMC5354527
4. Berbudi A, Rahmadika N, Tjahjadi AI, Ruslami R. Type 2 Diabetes and its Impact on the Immune System. Curr Diabetes Rev. 2019;16(5):442–9.
5. Kwilas AR, Donahue RN, Tsang KY, Hodge JW. Immune consequences of tyrosine kinase inhibitors that synergize with cancer immunotherapy , HHS Public Access. Cancer Cell. 2015;2 (1):1–17.
6. de Souza Prestes A, dos Santos MM, Ecker A, de Macedo GT, Fachinetto R, Bressan GN, et al. Methylglyoxal disturbs the expression of antioxidant, apoptotic and glycation responsive genes and triggers programmed cell death in human

leukocytes. Toxicol Vitr [Internet]. 2019;55:33–42. Available from: https://doi.org/10.1016/j.tiv.2018.11.001

7. Ilyas R, Wallis R, Soilleux EJ, Townsend P, Zehnder D, Tan BK, et al. High glucose disrupts oligosaccharide recognition function via competitive inhibition: A potential mechanism for immune dysregulation in diabetes mellitus. Immunobiology. 2011;216(1–2):126–31.

8. Qin X, Goldfine A, Krumrei N, Grubissich L, Acosta J, Chorev M, et al. Glycation Inactivation of the Complement Regulatory Protein CD59. Diabetes. 2004;53(10):2653–61.

9. Hinkmann C, Knerr I, Hahn EG, Lohmann T, Seifarth CC. Reduced frequency of peripheral plasmacytoid dendritic cells in type 1 diabetes. Horm Metab Res. 2008;40(11):767–71.

10. Seifarth CC, Hinkmann C, Hahn EC, Lohmann T, Harsch IA. Reduced frequency of peripheral dendritic cells in type 2 diabetes. Exp Clin Endocrinol Diabetes. 2008;116(3):162–6.

11. Gonzalez L, Trigatti BL. Macrophage Apoptosis and Necrotic Core Development in Atherosclerosis: A Rapidly Advancing Field with Clinical Relevance to Imaging and Therapy. Can J Cardiol [Internet]. 2017;33(3):303–12. Available from: http://dx.doi.org/10.1016/j.cjca.2016.12.010

12. Wong SL, Demers M, Martinod K, Gallant M, Wang Y, Goldfine AB, et al. Diabetes primes neutrophils to undergo NETosis, which impairs wound healing. Nat Med [Internet]. 2015;21(7):815–9. Available from: http://dx.doi.org/10.1038/nm.3887

13. Joshi MB, Baipadithaya G, Balakrishnan A, Hegde M, Vohra M, Ahamed R, et al. Elevated homocysteine levels in type 2 diabetes induce constitutive neutrophil extracellular traps. Sci Rep. 2016;6(October):1–15.

14. García AG, Rodríguez MR, Alonso CG, Ochoa DYR, Aguilar CA. Myeloperoxidase is associated with insulin resistance and inflammation in overweight subjects with first-degree relatives with type 2 diabetes mellitus. Diabetes Metab J. 2015;39(1):59–65.

15. Ridzuan N, John CM, Sandrasaigaran P, Maqbool M, Liew LC, Lim J, et al. Preliminary study on overproduction of reactive oxygen species by neutrophils in diabetes mellitus. World J Diabetes. 2016;7(13):271.

16. Kraakman MJ, Lee MKS, Al-Sharea A, Dragoljevic D, Barrett TJ, Montenont E, et al. Neutrophil-derived S100 calcium-binding proteins A8/A9 promote reticulated thrombocytosis and atherogenesis in diabetes. J Clin Invest. 2017;127(6):2133–47.

17. Piątkiewicz P, Miłek T, Bernat-Karpińska M, Ohams M, Czech A, Ciostek P. The dysfunction of nk cells in patients with type 2 diabetes and colon cancer. Arch Immunol Ther Exp (Warsz). 2013;61(3):245–53.

18. Piątkiewicz P, Bernat-Karpińska M, Miłek T, Rabijewski M, Rosiak E. NK cell count and glucotransporter 4 (GLUT4) expression in subjects with type 2 diabetes and colon cancer. Diabetol Metab Syndr. 2016;8(1):1–8.

19. Berrou J, Fougeray S, Venot M, Chardiny V, Gautier JF, Dulphy N, et al. Natural Killer Cell Function, an Important Target for Infection and Tumor Protection, Is Impaired in Type 2 Diabetes. PLoS One. 2013;8(4).

20. Coquet JM, Chakravarti S, Kyparissoudis K, McNab FW, Pitt LA, McKenzie BS, et al. Diverse cytokine production by NKT cell subsets and identification of an IL-17-producing CD4-NK1.1- NKT cell population. Proc Natl Acad Sci U S A. 2008;105(32):11287–92.

21. Lv X, Gao Y, Dong T, Yang L. Role of natural killer T (NKT) cells in type II diabetes-induced vascular injuries. Med Sci Monit. 2018;24:8322–32.

22. Liu F, Wang H, Feng W, Ye X, Sun X, Jiang C, et al. Type 1 innate lymphoid cells are associated with type 2 diabetes. Diabetes Metab. 2019;45(4):341–6.

23. Jiska Cohen-Mansfield, Maha Dakheel-Ali, MDb, Marcia S. Marx, PhDb, Khin Thein, MDb, and Natalie G. Regier P, Waage et al HHS Public Access. Physiol Behav. 2017;176(1):139–48.

24. Farnsworth CW, Schott EM, Benvie A, Kates SL, Schwarz EM, Gill SR, et al. Exacerbated Staphylococcus aureus Foot Infections in Obese/Diabetic Mice Are Associated with Impaired Germinal Center Reactions, Ig Class Switching, and Humoral Immunity . J Immunol. 2018;201(2):560–72.

25. Diepersloot RJA, Bouter KP, Beyer WEP, Hoekstra JBL, Masurel N. Humoral immune response and delayed type hypersensitivity to influenza vaccine in patients with diabetes mellitus. Diabetologia. 1987;30(6):397–401.

26. McMichael a J, Gotch F, Cullen P, Askonas B, Webster RG. The human cytotoxic T cell response to influenza A vaccination. Clin Exp Immunol [Internet]. 1981;43(2):276–84. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1537292&tool=pmcentrez&rendertype

27. Sheridan PA, Paich HA, Handy J, Karlsson EA, Schultz-Cherry S, Hudgens M, et al. The antibody response to influenza vaccination is not impaired in type 2 diabetics. Vaccine [Internet]. 2015;33(29):3306–13. Available from: http://dx.doi.org/10.1016/j.vaccine.2015.05.043

28. Martinez PJ, Mathews C, Actor JK, Hwang SA, Brown EL, De Santiago HK, et al. Impaired CD4+ and T-helper 17 cell memory response to Streptococcus pneumoniae is associated with elevated glucose and percent glycated hemoglobin A1c in Mexican Americans with type 2 diabetes mellitus. Transl Res [Internet]. 2014;163(1):53–63. Available from: http://dx.doi.org/10.1016/j.trsl.2013.07.005

29. Kumar NP, Sridhar R, Nair D, Banurekha V V., Nutman TB, Babu S. Type 2 diabetes mellitus is associated with altered CD8+ T and natural killer cell function in pulmonary tuberculosis. Immunology. 2015;144(4):677–86.

30. Daryabor G, Atashzar MR, Kabelitz D, Meri S, Kalantar K. The Effects of Type 2 Diabetes Mellitus on Organ Metabolism and the Immune System. Front Immunol. 2020;11(July).

31. Barkai LJ, Sipter E, Csuka D, Prohászka Z, Pilely K, Garred P, et al. Decreased ficolin-3-mediated complement lectin pathway activation and alternative pathway amplification during bacterial infections in patients with type 2 diabetes mellitus. Front Immunol. 2019;10(MAR):1–10.

32. Patel PN, Sah P, Chandrashekar C, Vidyasagar S, Venkata Rao J, Tiwari M, et al. Oral candidal speciation, virulence and antifungal susceptibility in type 2 diabetes mellitus. Diabetes Res Clin Pract [Internet]. 2017;125:10–9. Available from: http://dx.doi.org/10.1016/j.diabres.2017.01.001

33. Jhugroo C, Divakar DD, Jhugroo P, Al-Amri SAS, Alahmari AD, Vijaykumar S, et al. Characterization of oral mucosa lesions

and prevalence of yeasts in diabetic patients: A comparative study. Microb Pathog [Internet]. 2019;126:363–7. Available from: https://doi.org/10.1016/j.micpath.2018.11.028

34. Javid A, Zlotnikov N, Pětrošová H, Tang TT, Zhang Y, Bansal AK, et al. Hyperglycemia impairs neutrophil-mediated bacterial clearance in mice infected with the Lyme disease pathogen. PLoS One. 2016;11(6):1–20.

35. Kumar S, Ramachandran R, Mete U, Mittal T, Dutta P, Kumar V, et al. Acute pyelonephritis in diabetes mellitus: Single center experience. Indian J Nephrol. 2014;24(6):367–71.

36. Yano H, Kinoshita M, Fujino K, Nakashima M, Yamamoto Y, Miyazaki H, et al. Insulin treatment directly restores neutrophil phagocytosis and bactericidal activity in diabetic mice and thereby improves surgical site staphylococcus aureus infection. Infect Immun. 2012;80(12):4409–16.

37. Lin JC, Siu LK, Fung CP, Tsou HH, Wang JJ, Chen CT, et al. Impaired phagocytosis of capsular serotypes K1 or K2 Klebsiella pneumoniae in type 2 diabetes mellitus patients with poor glycemic control. J Clin Endocrinol Metab. 2006;91 (8):3084–7.

38. Chanchamroen S, Kewcharoenwong C, Susaengrat W, Ato M, Lertmemongkolchai G. Human polymorphonuclear neutrophil responses to Burkholderia pseudomallei in healthy and diabetic subjects. Infect Immun. 2009;77(1):456–63.

39. Riyapa D, Buddhisa S, Korbsrisate S, Cuccui J, Wren BW, Stevens MP, et al. Neutrophil extracellular traps exhibit antibacterial activity against Burkholderia pseudomallei and are influenced by bacterial and host factors. Infect Immun. 2012;80(11):3921–9.

40. Easton A, Haque A, Chu K, Lukaszewski R, Bancroft GJ. A critical role for neutrophils in resistance to experimental infection with Burkholderia pseudomallei. J Infect Dis. 2007;195(1):99–107.

41. Lopez-Lopez N, Martinez AGR, Garcia-Hernandez MH, Hernandez-Pando R, Castañeda-Delgado JE, Lugo-Villarino G, et al. Type-2 diabetes alters the basal phenotype of human macrophages and diminishes their capacity to respond, internalise, and control Mycobacterium tuberculosis. Mem Inst Oswaldo Cruz. 2018;113(4):1–11.

42. Tripathi D, Radhakrishnan RK, Thandi RS, Paidipally P, Devalraju KP, Neela VSK, et al. Erratum: IL-22 produced by type 3 innate lymphoid cells (ILC3s) reduces the mortality of type 2 diabetes mellitus (T2DM) mice infected with Mycobacterium tuberculosis (PLoS Pathogens (2019) 15:12 (e1008140) DOI: 10.1371/journal.ppat.1008140). PLoS Pathog. 2021;17(5):1–21.

43. Farnsworth CW, Shehatou CT, Maynard R, Nishitani K, Kates SL, Zuscik MJ, et al. A humoral immune defect distinguishes the response to Staphylococcus aureus infections in mice with obesity and type 2 diabetes from that in mice with type 1 diabetes. Infect Immun. 2015;83(6):2264–74.

44. Mathews CE, Brown EL, Martinez PJ, Bagaria U, Nahm MH, Burton RL, et al. Impaired function of antibodies to pneumococcal surface protein A but Not to capsular polysaccharide in Mexican American adults with type 2 diabetes mellitus. Clin Vaccine Immunol. 2012;19(9):1360–9.

45. Iatcu CO, Steen A, Covasa M. Gut microbiota and complications of type-2 diabetes. Nutrients. 2022;14(1).

46. Kumar R, Mishra D, Kumar M, others. Madhumeha: A Term Often Misused for Diabetes Mellitus. Int J Heal Sci Res. 2018;8 (5):272–6.

47. Bagde AB, Sawant RS, Yanpallewar SU, Nikumbh MB, Dhimdhime RS. Ojas: the Vital Nectar of Life. J Biol Sci Opin. 2014;2(2):203–6.

48. Charaka samhita of agnivesh elaborated by Caraka & Dridhabala, Ayurveda dipika commentary by Chakrapanidatta, edited by jadavji trikamji Acharya, Chaukhambha publications, Nidanasthana 4th, 37th verse.p.215.

49. Charaka samhita of agnivesh elaborated by Caraka & Dridhabala, Ayurveda dipika commentary by Chakrapanidatta, edited by jadavji trikamji Acharya, Chaukhambha publications, Chikitsasthana 6th.p.445.

50. Charak samhitha with Charak Chandrika Hindi commentary by Dr Brahmanand Tripathi and Dr Ganga Sahay Pandey, Sutrasthana 30th, verse 7th. p.560.

§§§