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Original Research Paper

The role of inflammation IL-6, TNF-α in type -2 Diabetes Mellitus

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Abstract: Diabetes mellitus is a broad term that refers to a group of metabolic disorders characterized by persistent hyperglycemia, The reason is either a disruption in insulin secretion, varying degrees of insulin resistance, or both. In type 2 diabetes, the pathways leading to β-cell death and malfunction are less clear, but the common denominator seems to be inadequate β-cell insulin production, which often occurs in the context of insulin resistance. An essential indicator of long-term glycemic control and an accurate biomarker for the diagnosis and prognosis of diabetes is HbA1c. The glycation process produces HbA1c, which is a byproduct of Amadori rearrangement and accumulates up in red blood cells. Tumor necrosis factor-alpha (TNF-α) is a cytokine implicated in systemic inflammation that is generated by activated macrophages, CD4+ lymphocytes, natural killer cells, neutrophils, mast cells, eosinophils, and neurons. It usually causes an acute phase response. TNF-α was the first proinflammatory cytokine identified as having a role in the etiology of insulin resistance and type 2 diabetes. T2DM patients have been discovered to have higher levels of circulating inflammatory markers such TNF-α and IL6.In patients with One of the most prevalent metabolic diseases in the world, type 2 diabetes mellitus as a long-term metabolic condition marked by high blood glucose levels that eventually damages the heart, blood vessels, eyes, kidneys, and nerves. T2DM, which accounts for more than 90% of cases of diabetes mellitus, is characterized by tissue insulin resistance (IR), insufficient compensatory insulin secretory response, and insufficient insulin secretion by pancreatic islet β-cells that cause it elevated risk for mortality, CVD and the advancement of type 2 diabetes mellitus.

Methods: For this research, 120 blood samples were collected from patients with DM type 2 and 60 volunteers. A sandwich ELISA was used to estimate the serum levels of human TNF-α, and IL-6 and the results were statistically processed in SPSS.

Results: The study showed no significant difference (p>0.407) in the mean age among patient groups was (44.51±12.33) years, while the control group was (41.13±10.22) years. The study also examined body weight distribution, finding no significant difference(p->0.32) between patients (24.54±3.44) and the control group (25.11±3.21), serum IL-6 patient groups was (6.44±2.11) while the control group was (1.43±0.32) and TNF-α patient groups was (16.22±2.45) while the control group was (2.34±0.33) in type 2 diabetes mellitus patients compared to the healthy control group.

Conclusions: The disease known as T2DM is complex One of the most prevalent metabolic diseases in the world, type 2 diabetes mellitus as a long-term metabolic condition marked by high blood glucose levels association with increase inflammatory biomarkers that leads to developments CVD and kidney failure.

Keywords: diabetes mellitus, TNF-α, insulin resistance, β-cell, IL-6

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1. Introduction

The two main causes of type 2 diabetes mellitus (T2DM), one of the most common metabolic illnesses worldwide, are the tissues' inability to respond to insulin and the decreased ability of the pancreatic β-cells to release insulin [1]. Diabetes mellitus is a chronic metabolic disease characterized by elevated blood glucose levels that ultimately harms the heart, blood vessels, eyes, kidneys, and nerves, according to the World Health Organization (WHO). Insufficient compensatory insulin secretory response, tissue insulin resistance (IR), and insufficient insulin secretion by pancreatic islet β-cells are the hallmarks of type 2 diabetes, which makes up over 90% of cases of diabetes mellitus [2]. Body-mass index [BMI] ≥30 kg/m2 indicates obesity, which is the most potent risk factor for type 2 diabetes[3]. and is linked to metabolic disorders that cause IR [4]. β-cell physiology requires cellular integrity, proper activity, and strict regulation of pathways and activities [5]. Diabetes is a chronic metabolic condition characterized by high blood glucose levels. Type 2 diabetes (T2D) is characterized by impaired insulin secretion and physiological insulin resistance, and it is frequently accompanied by a number of other conditions, such as impaired glucagon production, a diminished gut incretin effect, excessive adipocyte lipolysis, increased hepatic glucose output, impaired renal glucose reabsorption, decreased muscular glucose uptake, and abnormalities in hypothalamic neurotransmitter function [6]. Metabolites, particularly glucose, have a role in the physiology of beta cells and insulin-sensitive tissues. When the need for insulin varies, the beta cells adjust, or compensate. The prevalence of type 2 diabetes rises with age, and it is typically diagnosed in middle-aged people[7]. Clinical research on young people with prediabetes and type 2 diabetes has revealed a substantial β-cell malfunction before to or at the time of the diagnosis, which quickly worsens in conjunction with rising insulin resistance[8]. The synthesis of insulin by β-cells and glucagon by α-cells is delicately balanced to maintain glucose homeostasis, and the disruption of this balance may be a major factor in the pathophysiology of type 2 diabetes[8]. For many years, type 2 diabetes mellitus (T2DM) was known as non-insulin dependent diabetes or adult-onset diabetes with insulin resistance that could eventually progress to complete resistance. However, in the last ten years, One of the main problems with type 2 diabetes has been shown to be impaired β-cell function [9, 10]. Type 2 diabetes is often diagnosed in conjunction with another medical condition. When symptoms are not present, the disease is diagnosed by measuring the oral glucose tolerance test (OGTT) at 200 mg/dL, fasting plasma glucose (FPG) at 126 mg/dL or higher, or glycated hemoglobin (HbA1c) at 48 mmol/mol (6.5%) Diabetes is diagnosed when blood glucose levels are 200 mg/dL or above and the symptoms are present. Chronic exposure to hyperglycemia increases the likelihood of developing comorbidities, namely micro and macrovascular problems, and is a major contributor to the pathology, particularly in blood vessels[10]. Numerous inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α), contribute to damage to glomerular and vascular endothelial cells and have an impact on urine albumin levels in individuals with type 2 diabetes [11].

2.Methodology

Samples collection

Samples were collected at Al-Sadr Teaching Hospital in Najaf Al-Ashraf and were from men aged 40-70 years. Patients' dependent on external insulin, diabetic foot patients, and women were excluded.

The enzyme-linked immunosorbent assay (ELISA) was used to evaluate serum levels of interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-α) and Insulin. In simple terms, within 24 hours after admission, 5 mL of fasting cubital venous blood was drawn from each patient. For fifteen minutes, the blood samples were centrifuged at 2000 g. Following centrifugation, commercially available ELISA kits (Company: China Beijing Solarbio Science & Technology) used to measure the levels of IL-6 and TNF-α. We gathered clinical and demographic data, including each patient's age, body mass index (BMI), sex, and length of diabetes mellitus. In whole blood, a spectrophotometer was used to quantify the following: triglycerides (TG), total cholesterol (TC), HDL-C, LDL-C, and fasting plasma glucose (FPG).

Participants

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A total of 120 participants were enrolled in the study, comprising 60 individuals diagnosed with Type 2 Diabetes Mellitus (T2DM) and 60 age- and sex-matched healthy controls. The mean age was 54.2 ± 9.1 years in the diabetic group and 52.7 ± 8.5 years in the control group, with no significant difference ($p = 0.34$). Body Mass Index (BMI) and waist circumference were significantly higher in the T2DM group ($p < 0.01$), suggesting a higher degree of central obesity.

3.Results and discussion

Inflammatory Cytokine Levels

The diabetic group had considerably higher serum levels of tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) than the control group, as shown in Table 1.

Table 1: Inflammatory Cytokine Levels in T2DM and Control Groups

Marker	T2DM Group (Mean ± SD)	Control Group (Mean ± SD)	p-value
IL-6 (pg/mL)	6.8 ± 2.1	2.9 ± 1.2	< 0.001
TNF-α (pg/mL)	8.1 ± 2.5	3.4 ± 1.3	< 0.001

Correlation Analysis

Correlation analysis showed that both IL-6 and TNF-α levels were positively associated with key metabolic indicators:

- Fasting Blood Glucose: IL-6 ($r = 0.68$), TNF-α ($r = 0.71$), $p < 0.001$
- HbA1c: IL-6 ($r = 0.59$), TNF-α ($r = 0.65$), $p < 0.001$
- HOMA-IR: IL-6 ($r = 0.73$), TNF-α ($r = 0.76$), $p < 0.001$

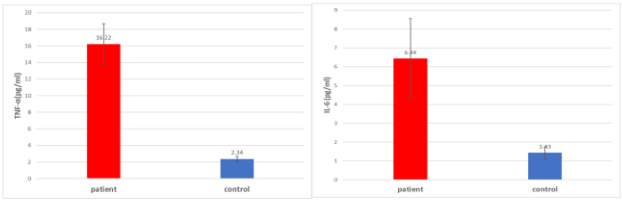

Fig 1: The mean concentration of IL-6 and TNF-α in diabetic patients' comparison with control group.

These findings indicate a strong relationship between systemic inflammation and glycemic control.

This study offers strong evidence that individuals with type 2 diabetes have considerably higher levels of the inflammatory cytokines TNF-α and IL-6, and that these levels are positively connected with indicators of insulin resistance and poor glycemic control, these results support the hypothesis that a major contributing factor to the development and progression of type 2 diabetes is chronic low-grade inflammation [12].

IL-6 has been shown to interfere with insulin receptor signaling through activation of the JAK/STAT pathway and serine phosphorylation of IRS-1, ultimately contributing to insulin resistance[13]. Our findings of elevated IL-6 and its strong correlation with HOMA-IR are in agreement with previous studies[14].

In immunological responses, macrophages are important immune modulator cells. By releasing cytokines and activating NF-κB signaling, the pathophysiology of insulin resistance induced on by obesity is significantly influenced by macrophages. Adipose tissue macrophages (ATMs) are the main source of pro-inflammatory cytokines and chemokines in adipose tissue, including MCP-1, IL-1β, IL-6, and TNF-α. These molecules are associated with inflammation and insulin resistance [15].

Proinflammatory pathways are activated after TNF-alpha exposure, which prevents insulin signaling at the level of the insulin receptor substrate (IRS) proteins, resulting in insulin resistance with regard to glucose absorption in myocytes and adipocytes [16]. According to our research, TNF-α levels were considerably higher in T2DM patients than in controls ($p = 0.008$). Serum levels of TNF-α were substantially greater in obese diabetes patients than in nonobese diabetic patients ($p < 0.018$) and obese nondiabetic individuals ($p < 0.001$)[17]. The elevated TNF-α levels in our diabetic cohort, alongside strong correlations with fasting glucose and HbA1c, align with prior evidence indicating its role in metabolic dysregulation[18].

Both cytokines are closely linked to adiposity, particularly visceral fat accumulation. As observed in our cohort, individuals with T2DM exhibited significantly higher BMI and waist circumference. Adipose tissue in obese individuals serves as an active endocrine organ, secreting pro-inflammatory mediators that exacerbate insulin resistance[19]. Numerous lines of evidence have demonstrated the involvement of cytokines in the pathophysiology of atherosclerosis,

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including IL-6, IL-18, interferon-gamma, and tumor necrosis factor alpha (TNF-α) [20].

Multiple regression analysis revealed a significant correlation between the serum IL-6 concentration and the HbA1C level (β = 0.58, P = 0.04) [21]. According to these findings, in patients with type 2 diabetes mellitus, elevated serum IL-6 and hyperglycemia may raise the concentration of plasma fibrinogen, a known risk factor for atherosclerosis [21]. Both diabetic and non-diabetic patients with coronary artery disease (ACS) had higher serum IL-6 levels [22].

Patients with type 2 diabetes or cardiovascular disease frequently have high levels of the cytokine interleukin-6 (IL-6), which binds to the IL-6 receptor to control inflammatory responses [23].

One cytokine that contributes to both the innate and adaptive immune responses is IL-6. In reaction to bacteria and other cytokines, primarily interleukin-1 (IL-1) and TNF-a, monocytes, endothelial cells, fibroblasts, and other cells manufacture it. A newly identified cytokine from the IL-1 family, IL-18 has a pleiotropic effect and is involved in both the innate and acquired immune responses [22].

Compared to the NDM group, the IL-6 level of the diabetic mellitus group and the TNF-α level of the impaired fasting glucose group were both higher [24]. When diabetic patients have nephropathy, their IL-6 levels increases [25]. Proinflammatory cytokine plasma levels, including IL-6, were shown to be higher in T2DM patients than in non-T2DM[26]. The protein level of IL-6 shown a strong correlation with T2DM, particularly in the insulin resistance (IR) group (p-value 0.03) when compared to the control group[27]. showed that increasing levels of IL-6, leptin, CRP, and TNF-α were highly linked to diabetes overall, while increasing levels of IL-6 and leptin were positively and linearly correlated with impaired glucose control [28]. elevated levels of TNF-α and inflammatory cytokines (IL-1β, IL-6, IL-18, and CRP) were substantially linked to the overall risk of type 2 diabetes[29]. Increased TNF-α production has been seen in adipose tissue taken from obese humans or rodents, and TNF-α has been linked to the pathophysiology of type 2 diabetes and obesity-related insulin resistance [30]. TNF-α seems to directly affect glomerular cells by causing apoptosis and cytotoxicity [31]. In participants with abdominal obesity, elevated levels of TNF-α, IL-6, hs-CRP, and insulin resistance were substantially linked to type 2 diabetes [32]. Increased truncal fat mass is linked to elevated plasma levels of TNF-alpha and IL-6 in both type 2 diabetic patients and older, healthy individuals [33]. TNF-α and IL-6 levels were strongly positively correlated with HbA1C (P > 0.05). The development of atherosclerosis can be predicted by the levels of TNF-α and IL-6 [34]. Insulin resistance has been linked to IL-6 and TNF-alpha [33]. According to multiple findings, CRP levels are increased in those with type 2 diabetes [35] and proinflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor (TNF)-α [36]. Type 2 diabetes and insulin resistance are predicted by elevated CRP and IL-6 levels[14, 37] Although oxidative stress may be at least largely to blame, the processes underlying the increase in serum levels of proinflammatory molecules in type 2 diabetes are yet unknown [38]. Insulin resistance was associated with elevated levels of pro-inflammatory cytokines, including TNF-α, IL-6, IL-1β, IFNγ, and fetuin A [39]. There were no significant differences in serum CRP (p >.05), but the exercise group's levels of inflammatory markers, TNF-α, and IL-6 were significantly lower than the control group's (p <.05) [40].

Clinical Implications

Therapeutic Targeting: The data underscore the therapeutic potential of anti-inflammatory agents targeting IL-6 and TNF-α pathways in the management of T2DM. These cytokines may be helpful indicators for monitoring the course of the illness and identifying those who are at high risk for type 2 diabetes.

Conclusion

The elevated levels of IL-6 and TNF-α in patients with T2DM and their significant correlations with insulin resistance and glycemic markers emphasize the role of inflammation in the etiology of T2DM. Targeting these pathways could improve diagnostic and therapeutic strategies.

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Author's Contributions

The manuscript was prepared with input from each contributing author. The text was examined, revised, and approved in its final form by all authors.

Ethics

The University of Kufa's medical ethics committee gave its consent for this study to be carried out (2025). Adults gave their verbal and written approval, and researchers and participants both agreed to be published.

References

1. Roden, M., & Shulman, G. I. (2019). The integrative biology of type 2 diabetes. *Nature*, 576(7785), 51-60. https://doi.org/10.1038/s41586-019-1790-0

2. Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., Ostolaza, H., & Martín, C. (2020). Pathophysiology of type 2 diabetes mellitus. *International Journal of Molecular Sciences*, 21(17), 6275. https://doi.org/10.3390/ijms21176275

3. Bellou, V., Belbasis, L., Tzoulaki, I., & Evangelou, E. (2018). Risk factors for type 2 diabetes mellitus: An exposure-wide umbrella review of meta-analyses. *PLOS ONE*, 13(3), e0194127. https://doi.org/10.1371/journal.pone.0194127

4. Sinha, R., Dufour, S., Petersen, K. F., LeBon, V., Enoksson, S., Ma, Y.-Z., Savoye, M., Rothman, D. L., Shulman, G. I., & Caprio, S. (2002). Assessment of skeletal muscle triglyceride content by 1H nuclear magnetic resonance spectroscopy in lean and obese adolescents: Relationships to insulin sensitivity, total body fat, and central adiposity. *Diabetes*, 51(4), 1022-1027. https://doi.org/10.2337/diabetes.51.4.1022

5. Cerf, M. (2013). Beta cell dysfunction and insulin resistance. *Frontiers in Endocrinology*, 4, 37. https://doi.org/10.3389/fendo.2013.00037

6. Meur, G., Anindya, R., & Rutter, G. A. (2024). Chapter 10 - Biochemistry and immunology of inflammation-mediated responses in the development of diabetes mellitus. In P. Tripathi, R. P. Tripathi, & M. P. Kaushik (Eds.), *Biochemical Immunology of Diabetes and Associated Complications* (pp. 169-207). Academic Press.

7. Khin, P. P., Lee, J. H., & Jun, H.-S. (2023). Pancreatic beta-cell dysfunction in type 2 diabetes. *Journal of Diabetes Research*, 2023, 1721727. https://doi.org/10.1155/2023/1721727

8. Serbis, A., Giapros, V., Tsamis, K., Balomenou, F., Galli-Tsinopoulou, A., & Siomou, E. (2023). Beta cell dysfunction in youth- and adult-onset type 2 diabetes: An extensive narrative review with a special focus on the role of nutrients. *Nutrients*, 15(9), 2217. https://doi.org/10.3390/nu15092217

9. Saisho, Y. (2014). Importance of beta cell function for the treatment of type 2

diabetes. *Journal of Clinical Medicine*, 3(3), 923-943. https://doi.org/10.3390/jcm3030923

10. Artasensi, A., Pedretti, A., Vistoli, G., & Fumagalli, L. (2020). Type 2 diabetes mellitus: A review of multi-target drugs. *Molecules*, 25(8), 1987. https://doi.org/10.3390/molecules25081987

11. Liu, C., Li, Q., Feng, X., Zhu, J., & Li, Q. (2021). Deterioration of diabetic nephropathy via stimulating secretion of cytokines by atrial natriuretic peptide. *BMC Endocrine Disorders*, 21(1), 204. https://doi.org/10.1186/s12902-021-00766-5

12. Hotamisligil, G. S. (2006). Inflammation and metabolic disorders. *Nature*, 444(7121), 860-867. https://doi.org/10.1038/nature05485

13. Pickup, J. C. (2004). Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. *Diabetes Care*, 27(3), 813-823. https://doi.org/10.2337/diacare.27.3.813

14. Pradhan, A. D., Manson, J. E., Rifai, N., Buring, J. E., & Ridker, P. M. (2001). C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA*, 286(3), 327-334. https://doi.org/10.1001/jama.286.3.327

15. Zand, H., Morshedzadeh, N., & Naghashian, F. (2017). Signaling pathways linking inflammation to insulin resistance. *Journal of Research in Medical Sciences*, 11, S307-S309. https://doi.org/10.4103/1735-1995.204123

16. Nieto-Vazquez, I., Fernández-Veledo, S., Krämer, D. K., Vila-Bedmar, R., Garcia-Guerra, L., & Lorenzo, M. (2008). Insulin resistance associated to obesity: The link TNF-alpha. *Archives of Biochemistry and Biophysics*, 114(3), 183-194. https://doi.org/10.1016/j.abb.2008.01.013

17. Alzamil, H. (2020). Elevated serum TNF-α is related to obesity in type 2 diabetes mellitus and is associated with glycemic control and insulin resistance. *Journal of Obesity and Overweight*, 2020(1), 5076858. https://doi.org/10.1155/2020/5076858

18. Fernández-Real, J. M., & Ricart, W. (2003). Insulin resistance and chronic cardiovascular inflammatory syndrome. *Endocrine Reviews*, 24(3), 278-301. https://doi.org/10.1210/er.2002-0011

19. Wellen, K. E., & Hotamisligil, G. S. (2005). Inflammation, stress, and diabetes. *The Journal of Clinical Investigation*, 115(5), 1111-1119. https://doi.org/10.1172/JCI24696

20. Fadaei, R., Bagheri, N., Heidarian, E., Nouri, A., Hesari, Z., Moradi, N., Ahmadi, A., & Ahmadi, R. (2020).

Serum levels of IL-32 in patients with type 2 diabetes mellitus and its relationship with TNF-α and IL-6. *Cytokine*, 125, 154832. https://doi.org/10.1016/j.cyto.2019.154832

21. Kado, S., Nagase, T., & Nagata, N. (1999). Circulating levels of interleukin-6, its soluble receptor and interleukin-6/interleukin-6 receptor complexes in patients with type 2 diabetes mellitus. *Diabetes Research and Clinical Practice*, 36, 67-72. https://doi.org/10.1016/S0168-8227(98)00145-0

22. Souza, J. R. M., Oliveira, R. T., Blotta, M. H. S., & Coelho, O. R. (2008). Serum levels of interleukin-6 (IL-6), interleukin-18 (IL-18) and C-reactive protein (CRP) in patients with type-2 diabetes and acute coronary syndrome without ST-segment elevation. *Archives of Brazilian Medicine and Health Sciences*, 90, 94-99. https://doi.org/10.1590/S0066-782X2008000100010

23. Su, H., Lei, C. T., & Zhang, C. (2017). Interleukin-6 signaling pathway and its role in kidney disease: An update. *Frontiers in Immunology*, 8, 405. https://doi.org/10.3389/fimmu.2017.00405

24. Zheng, M., Wang, X., Guo, H., Fan, Y., Song, Z., Lu, Z., Wang, J., Zheng, C., Dong, L., & Ma, Y. (2021). The cytokine profiles and immune response are increased in COVID-19 patients with type 2 diabetes mellitus. *Journal of Diabetes Research*, 2021, 9526701. https://doi.org/10.1155/2021/9526701

25. Reddy, V. K. K., Shiddapur, G., Jagdale, N., Kondapalli, M. P., Adapa, S., & Shiddapur, G. (2024). Investigating interleukin-6 levels in type 2 diabetes mellitus patients with and without diabetic nephropathy. *Journal of Clinical Medicine*, 16(8). https://doi.org/10.3390/jcm16082000

26. Çelik, S. P., Parilti, D. N., Açik, L., Yalçin, M. M., Yetkin, İ., & Yunusov, E. (2024). NAMPT, IL-6, and vaspin gene expressions and serum protein levels in type 2 diabetes mellitus and related complication. *Turkish Journal of Biology*, 48(2), 133-141. https://doi.org/10.3906/biy-2301-1

27. Khdaer, H. M., Aldabagh, M. A. H., & Altai, G. A. (2022). Function role of IL-6-174 gene polymorphisms in association with IL-6 levels in type 2 diabetes mellitus. *Wiadomosci Lekarskie*, 75(3), 659-663. https://doi.org/10.36740/WLek202203113

28. Mirza, S., Hossain, M., Mathews, C., Martinez, P., Pino, P., Gay, J. L., Rentfro, A., McCormick, J. B., & Fisher-Hoch, S. (2012). Type 2-diabetes is associated with elevated levels of TNF-alpha, IL-6 and adiponectin and low levels of leptin in a population of Mexican Americans: A cross-sectional

study. *Cytokine*, 57(1), 136-142. https://doi.org/10.1016/j.cyto.2011.10.013

29. Liu, C., Feng, X., Li, Q., Wang, Y., Li, Q., & Hua, M. (2016). Adiponectin, TNF-α and inflammatory cytokines and risk of type 2 diabetes: A systematic review and meta-analysis. *Cytokine*, 86, 100-109. https://doi.org/10.1016/j.cyto.2016.06.001

30. Moller, D. E. (2000). Potential role of TNF-α in the pathogenesis of insulin resistance and type 2 diabetes. *Trends in Endocrinology & Metabolism*, 11(6), 212-217. https://doi.org/10.1016/S1043-2760(00)00306-0

31. Navarro-González, J. F., Mora-Fernández, C., Muros de Fuentes, M., & García-Pérez, J. (2011). Inflammatory molecules and pathways in the pathogenesis of diabetic nephropathy. *Nature Reviews Nephrology*, 7(6), 327-340. https://doi.org/10.1038/nrneph.2011.12

32. Tangvarasittichai, S., Pongthaisong, S., & Tangvarasittichai, O. (2016). Tumor necrosis factor-α, interleukin-6, C-reactive protein levels and insulin resistance associated with type 2 diabetes in abdominal obesity women. *International Journal of Clinical Biochemistry*, 31, 68-74. https://doi.org/10.1016/j.ijcb.2016.01.001

33. Pedersen, M., Bruunsgaard, H., Weis, N., Hendel, H. W., Andreassen, B. U., Eldrup, E., Dela, F., & Pedersen, B. K. (2003). Circulating levels of TNF-alpha and IL-6-relation to truncal fat mass and muscle mass in healthy elderly individuals and in patients with type-2 diabetes. *Mechanisms of Ageing and Development*, 124(4), 495-502. https://doi.org/10.1016/S0047-6374(03)00012-5

34. Wu, W., Wang, M., Sun, Z., Wang, X., Miao, J., & Zheng, Z. (2012). The predictive value of TNF-α and IL-6 and the incidence of macrovascular complications in patients with type 2 diabetes. *Archives of Medical Science*, 49, 3-7. https://doi.org/10.5114/aoms.2012.27563

35. Festa, A., D'Agostino, R. Jr, Howard, G., Mykkänen, L., Tracy, R. P., & Haffner, S. M. (2000). Inflammation and microalbuminuria in nondiabetic and type 2 diabetic subjects: The Insulin Resistance Atherosclerosis Study. *Diabetes Care*, 58(4), 1703-1710. https://doi.org/10.2337/diabetes.58.4.1703

36. Pickup, J. C., Chusney, G. D., Thomas, S. M., & Burt, D. J. (2000). Plasma interleukin-6, tumour necrosis factor α and blood cytokine production in type 2 diabetes. *Diabetes & Metabolism*, 67(3), 291-300. https://doi.org/10.1016/S0676-

6370(00)00112-0

37. Festa, A., D'Agostino, R. Jr, Howard, G., Mykkänen, L., Tracy, R. P., & Haffner, S. M. (2000). Chronic subclinical inflammation as part of the insulin resistance syndrome: The Insulin Resistance Atherosclerosis Study (IRAS). *Journal of Clinical Endocrinology & Metabolism*, 102(1), 42-47. https://doi.org/10.1210/jc.2000-0101

38. Arnalich, F., Hernanz, A., Lopez-Maderuelo, D., Pena, J., Camacho, J., Madero, R., Vazquez, J., & Montiel, J. (2000). Enhanced acute-phase response and oxidative stress in older adults with type II diabetes. *Hematology Research*, 32(10), 407-412. https://doi.org/10.1016/S0301-472X(00)00112-0

39. Reinehr, T. (2019). Inflammatory markers in children and adolescents with type 2 diabetes mellitus. *Clinica Chimica Acta*, 496, 100-107. https://doi.org/10.1016/j.cca.2019.01.014

40. Su, X., He, J., Cui, J., Li, H., & Men, J. (2022). The effects of aerobic exercise combined with resistance training on inflammatory factors and heart rate variability in middle-aged and elderly women with type 2 diabetes mellitus. *Annals of Noninvasive Electrocardiology*, 27(6), e12996. https://doi.org/10.1111/anec.12996