Original Article

Comparison of Serum Interleukin-37 Level in Obese, Nonobese Type II Diabetic Patients and Healthy Controls

Fadwa E. Alhayali[1], Ayşegül A. Yücel[1], Zainab F. Ashoor[2]

[1]Department of Immunology, Colleage of Medicine, Gazi University, Ankara, Turkiye, [2]Department of Microbiology, Colleage of Medicine, Al-Mustansriya University, Baghdad, Iraq

Abstract

Backgroud: Type 2 diabetes mellitus (DM2) is a metabolic disease resulting from the genetic and environmental factors and which causes insulin dysfunction on peripheral tissues, as well as in the pancreatic β-cell. Underlying pathologies such as overweight and obesity are the main factors for the development of T2DM. Interleukin-37 (IL-37) is an anti-inflammatory cytokine and also called as a "dual function." **Aim of study:** This study has demonstrated was elevated in the obese T2DM patients and IL-37 protects from obesity-induced leading to development of T2DM. Fifty-eight patients who visited to the National Center for Diabetes Research and Treatment in the İraq/Baghdad with the age of <40–>60 years were employed in this study. Patient groups were 29 obese T2DM and 29 nonobese T2DM patients, and they when compared with 29 individuals as healthy control groups. In this study, serum IL-37 levels were determined by enzyme linked immunosorbent assay. **Results:** In obese T2DM patients, the mean serum level of IL-37 was elevated and significantly higher (mean ± standard deviation [SD], 5.594 ± 3.421 pg/ml; $P < 0.0001$) in comparison with nonobese T2DM patients (mean ± SD, 1.851 ± 0.417 pg/ml; $P < 0.0001$) and healthy control group (mean ± SD, 0.777 ± 0.099 pg/ml). **Conclusions:** In this study, obese T2DM patients had higher serum IL-37 levels but lower serum IL-37 levels in nonobese diabetic patients as compared to the healthy controls. This result led to the supposition that the rise in serum IL-37 level is related with obesity. Further, it suggests that IL-37 being an anti-inflammatory mediator might be responsible for some underline changes, which may develop the progress of T2DM.

Keywords: Interleukin-37, obesity, type 2 diabetes mellitus

Introduction

The prevalence of type 2 diabetes mellitus (T2DM) increases globally and affects approximately one-third of the worldwide population.[1] T2DM, referred to as "*insulin-nondependent diabetes*" or "*adult-onset diabetes*," accounts for 90%–95% of all diabetes.[2,3] TDM2 is a complex metabolic and endocrine disorder resulting from the interaction between genetic and immunological factors. T2DM is most commonly related with insulin resistance and is a state of reduced insulin-mediated glucose uptake, in the incapacity presence of the pancreatic beta-cells to produce and promote sufficient insulin.[4-6] T2DM is a chronic metabolic disorder characterized by hyperglycemia. Chronic hyperglycemia in synergy with the other metabolic aberrations in patients with diabetes mellitus (DM) can cause damage to organ systems, leading to the development of their complications.[7,8] Overweight and obesity, particularly of the android type, are the main factors that lead to the development and progress of DM2.[9]

Obesity is characterized by an increase in the number and size of adipocytes. It is believe that the rapid increasing number of obese population is the major reason for the number of diabetic patients.[10] Obesity is a risk factor for developing diabetes and also a risk factor for diabetes complications.[4,11,12] Diabetes and obesity are public health concerns worldwide, especially with growth of Class II and III obesity. In this paragraph, it is important to explain the factors associated with T2DM,

Access this article online

Quick Response Code:

Website: http://www.mmjonweb.org

DOI: 10.4103/mj.mj_9_21

Address for correspondence: Dr. Fadwa E. Alhayali, Department of Immunology, Colleage of Medicine, Gazi University, Ankara, Turkiye.
E-mail: fadwaemad6@gmail.com

Submitted: 19-Jul-2021 **Revised:** 19-Jul-2021 **Accepted:** 20-Jul-2021 **Published:** 15-Dec-2021

How to cite this article: Alhayali FE, Yücel AA, Ashoor ZF. Comparison of serum interleukin-37 level in obese, nonobese type ii diabetic patients and healthy controls. Mustansiriya Med J 2021;20:76-81.

especially in classes of obesity.[13] Overweight in adults is defined as a body mass index (BMI) of ≥24 kg/m^2 and obese as a BMI of ≥30 kg/m^2.[14]

The immune response is classified into two main contents, innate and adaptive immunity. Adaptive immunity is defined by B-cells, which produce immunoglobulins, and T-cells are classified into CD4+ helper T-cells and cytotoxic CD8+ cells. Abnormal immune cell system and subsequent inflammatory parameters have an essential role in the progression of T2DM.[15] The immune response is closely related to the components that are altered in obesity and T2DM. The detection of immune cells in the metabolic tissues and organs, such as macrophages, has ongoing interaction that exists between immune and metabolism regulatory systems. Their interactions are termed "immunometabolism."[16] The innate immune system is the rapid first-line defense against environmental disorders, such as microbial infection and physical or chemical disorders. There is increasing evidence that an ongoing cytokine-induced acute-phase response is closely associated with the development of pathogenesis of T2DM.[17] The innate immune response is change in patients with obesity and T2DM. These changes include altered neutrophil function, increased of the pro-inflammatory cytokines, natural killer (NK) cell phenotypes abnormal, and an increase in inflammatory dendritic cell.[18] In previous studies, the role of adaptive immunity in T2DM pathogenesis has been demonstrated. However, increasing the role the adaptive immune system in the T2DM pathogenesis.[19] Lindsay *et al*. reported that increased serum total gammaglobulin levels are measure of the adaptive immune system and the development of T2DM. Pickup JC, *et al*. have also questioned whether both innate and adaptive immunity have a role in the development of T2DM.[17] The adaptive immune response changes during obesity and T2DM patients these changes include decreased gamma delta T-cell, increased inflammatory T helper cytokines, decreased regulatory T-cells, and dysfunction of B-cell.[18] In recent years, the role of the inflammatory system during diabetes has been increasingly investigated.[20]

T2DM is a chronic inflammatory disease in which increased levels of inflammatory cytokines are produced some stimuli such as over food, increasing age, and metabolic preprogramming. This chronic inflammation leads to diabetes and diabetic complications. Several reports show the association between increased inflammatory cytokines such as tumor necrosis factor-alpha (TNF-a), interleukin (IL)-6, and adipokines during the obesity, leading to the development of insulin resistance.[10] Proinflammatory cytokines and adipokines are raised due to the activation of macrophages and adipocytes in obese adipose tissue, which leads to a so-called "chronically inflamed adipose tissue." A disturbed lipid metabolism in overweight/obesity is also capable of inducing a chronic proinflammatory state. In sum, the literature contains numerous reports on increased levels of proinflammatory cytokines in the obesity and T2DM.[21]

IL-37 is isolated in silico in 2000 and and its anti-inflammatory actions by suppressing the innate system have been recognized.[22] IL-37 subtypes (IL-37a, IL-37b, and IL-37c) are expressed in NK cells, stimulated B-cells, monocytes, keratinocytes, epithelial cells, lymph node, and bone marrow.[23] During acute and chronic inflammation, IL-37 alters the cytokine balance away from excessive inflammation, thereby showing the key factor to the inflammatory balance in obesity.[22] Interestingly, IL-37 is also called as a "dual function" anti-inflammation cytokine. IL-37 is requires Smad3 when it takes a biological effect.[24] Recent studies have demonstrated mitogen-activated protein kinases and phosphatidylinositol 3-kinases signaling pathways as mediators of regulating agents in IL-37 expression. IL-37 is as an inhibition of both innate and adaptive immunity.[23] The study has been demonstrated that IL-37 protects from obesity-stimulated inflammation and T2DM. However, recent results were indicating that IL-37 showed protection role in the older T2DM patients.[22,25]

Thus, we conducted the present study to investigate the role of IL-37 in the obese and nonobese T2DM and compare with healthy control group. The results indicate that IL-37 showed elevated serum IL-37 level in the obese and nonobese T2DM patients.

Materials and Methods

Data and sample collection

Information about the samples

Routine examinations were performed in patients who were followed up with a diagnosis of T2DM, and measurements were made with height and weight. BMI was calculated as weight (kg)/height^2 (cm). In this study, the sum of the samples we collected is 87 examples. In addition, the age we collect is in the range between <40 and >60. During the sampling process, asking the patient about the following: patient'sage patient's weight, patient's height, smoking, other associated chronic diseases, taking any medications (insulin and other medications), and is there any associated allergies.

Blood collection

Blood samples were taken from diabetic patients aged <40–>60 years (obese and nonobese T2DM patients) and healthy subjects. Blood samples from all study groups were collected by venipuncture using plastic disposable 5 ml or 10 ml syringes. Whole blood samples were allowed to clot in an anticoagulant-free gel tube and then centrifuged at about 1500 rpm (10 min) to obtain at least 0.5 ml (nonhemolyzed cells free) serum. The remainder of the whole blood samples were collected in an ethylenediaminetetraacetic acid gel tube, these whole blood samples are stored at −20°C until used for genetic quantification of the samples.

Serum separation

Whole blood was collected in a test tube without anticoagulant and leave to clot, leaving it intact at 20 min. The clot was removed by centrifugation for 10 min (1500 × g) in a cooled

centrifuge. The supernatant obtained was called serum. After centrifugation, the liquid ingredient (serum) was transferred immediately to a clean test tube using a Pasteur pipette. Aliquots were stored at −20°C until serum samples were used for the measurement of immunological parameters by enzyme linked immunosorbent assay (ELISA) test. Avoid freeze-thaw cycles as this is detrimental to many serum components.

Determination of the level of interleukin-37 in serum by enzyme linked immunosorbent assay

IL-37 assay, the Endogen® Human IL-37 ELISA kit was used. Place in the ELISA wells (100 µl) from standard or samples. The plate was incubated at 37°C for 90 min and with wash solution washed 3 times (100 µl) of biotinylated antibody reagent adding to each well, with wash solution washed three times. Added to the ELISA wells (100 µl) of Streptavidin-HRP reagent. After a 30-min incubation at room temperature, the plate was washed three times. Following the addition of 90 µl of (TMB) substrate solution, the plate was left for another 15 min. Adding 50 µl of stop solution to each ELISA well. Optical density read on an ELISA at 450 nm. Sensitivity is 9.37 pg/ml and normal value is 15.65–1000 pg/ml. Standard curve of human serum IL-37 (pg/ml) ELISA test in the Table 1 and Figure 1.

Statistical analysis

Analysis of data is performed by using the available SPSS-27 application is applied by (Statistical Packages for Social Sciences-version 27). Data are presented in simple measures of frequency, percentage, means, and standard deviation (SD).

The significance of different means is tested by using Student's *t*-test. The significance of different percentages is shown by using Pearson's Chi-square test. Statistical significance is showed whenever the $P < 0.05$.

Results

Patient selection

In this study, Iraq's samples were collected from the endocrinology outpatient clinic of Al-Yermuk Training Hospital and the National Center for Diabetes Research and Treatment with an official agreement and with the permission of the Ethics Committee.

Study samples

The study groups were included in this study: Group I: Obese T2DM, Group II: Nonobese T2DM, and Group III: Healthy individuals. The 87 samples were collected in this study as a following 58 samples are T2DM patients, 29 samples are healthy controls [Table 2].

Distribution of the study groups according to of ages

When the distribution of the study groups by age is examined, Table 3 shows the numbers and percentages in different age groups in the study groups.

Among the obese T2DM patient group, In the <40 mean age was 3 (10.3%); 40–49 mean age was 9 (31.0%), 50–59 mean age was 11 (37.9%), ≥60 mean age was 6 (20.7%). The mean ± SD age within the obese T2DM patients was 51.4 ± 9.0.

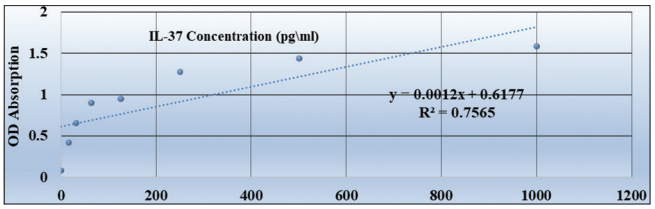

Figure 1: Serum interleukin-37 standard curve

Table 1: Human serum interleukin-37 (pg/ml) enzyme-linked immunosorbent assay test standard curve

IL-37 concentration (pg/ml)	Absorption
0	0.084
15.63	0.423
31.25	0.658
62.5	0.906
125	0.955
250	1.277
500	1.444
1000	1.592

IL: Interleukin

Table 2: Study groups classification

Group	Group name	Group number
Group I	Obese diabetes patients	29
Group II	Nonobese diabetes patients	29
Group III	Healthy controls	29

Among the nonobese patient group: In the <40 mean age was 5 (17.2%); 40–49 mean age was 5 (17.2%); 50–59 mean age was 9 (31.0%); in the ≥60 mean age was 10 (34.5%). The mean ± SD age within the nonobese T2DM patients was 53.7 ± 10.7.

Among the healthy control patient group: In the <40 mean age was 12 (41.4%); 40–49 mean age was 16 (55.2%); 50–59 mean age was 1 (3.4%). The mean ± SD age within the healthy control group was 40.1 ± 5.0.

The mean age of obese T2DM patients and nonobese T2DM patients is close to each other, but the mean age of healthy controls is lower than the other groups, because the mean age in the healthy control group might be younger.

In this study, serum IL-37 levels of study groups were measured by quantitative ELISA assay. In obese T2DM patients, the mean serum IL-37 level was 5.594 ± 3.421 pg/ml (min–max: 2.208–14.61 pg/ml), in nonobese T2DM patients was 1.851 ± 0.417 pg/ml (min–max: 1.300–2.999 pg/ml), and in the healthy control group was 0.777 ± 0.099 pg/ml (min–max: 0.636-1.009 pg/ml) [Table 4].

Serum IL-37 levels of obese T2DM patients were found to be higher compared to nonobese T2DM patients, the difference

Table 3: Distribution of the study groups according to of ages

Age (year)	Obese T2DM patients, *n* (%)	Nonobese T2DM patients, *n* (%)	Healthy control group, *n* (%)
<40	3 (10.3)	5 (17.2)	12 (41.4)
40-49	9 (31.0)	5 (17.2)	16 (55.2)
50-59	11 (37.9)	9 (31.0)	1 (3.4)
≥60	6 (20.7)	10 (34.5)	-
Mean±SD (minimum-maximum)	51.4±9.0 (36-70)	53.7±10.7 (35-70)	40.1±5.0 (30-50)

T2DM: Type 2 diabetes mellitus, SD: Standard deviation

being statistically significant ($P < 0.0001$). Serum IL-37 levels of obese T2DM patients were found to be higher when compared to the healthy control group, the difference being statistically significant ($P < 0.0001$). Serum IL-37 levels of nonobese T2DM patients were found to be higher when compared to the healthy control group, the difference being statistically significant ($P < 0.0001$) [Table 4].

Serum IL-37 levels are highest in obese T2DM patients and lowest in healthy control group. A significant difference was found between the three groups ($P < 0.0001$) [Table 4 and Figure 2].

Table 4: Compare between difference two groups in serum interleukin-37 pg/ml

	Obese T2DM patients		Nonobese T2DM patients
IL-37 level (pg/ml)	5.594±3.421 (2.208-14.61)		1.851±0.417 (1.300-2.999)
P		0.0001#	
	Obese T2DM patients		**Healthy control group**
IL-37 level (pg/ml)	5.594±3.421 (2.208-14.61)		0.777±0.099 (0.636-1.009)
P		0.0001#	
	Nonobese T2DM patients		**Healthy control group**
IL-37 level (pg/ml)	1.851±0.417 (1.300-2.999)		0.777±0.099 (0.636-1.009)
P		0.0001#	

#Significant difference between two independent paths using Student's *t*-test at 0.05 level. IL: Interleukin, T2DM: Type 2 diabetes mellitus

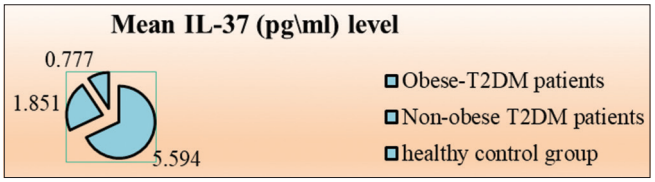

Figure 2: Comparison between difference groups in serum interleukin-37 pg/ml

Discussion

T2DM is a global public disease of the 21st century. T2DM is a metabolic impaired characterized by hyperglycemia with defect in carbohydrate, protein, and fat metabolism that are generally the result of insulin dysfunction. T2DM is an inflammatory disease; therefore, pro-inflammatory cytokines affect insulin resistance and promote apoptosis of b-cells, leading to the development of T2DM.[26] However, T2DM appears to be in a low-grade inflammation case; inflammation could be associated with pathogenesis of the type 2 diabetes.[27] The present study is an important link between T2DM and obesity research as it is one of the few studies to evaluate T2DM-associated factors, specifically in obesity and nonobesity individuals.[13]

Generally, obesity is linked to the development of insulin resistance. Abdominal obesity, where the fat is centrally distributed, is particularly an important determinant of insulin resistance. Obesity is strongly associated with lower levels of immunologic parameters and decrease in insulin sensitivity among diabetes patients.[28] The study found that, compared with normal BMI, overweight and obesity was significantly associated with the risk of T2DM.[29] İnflammation is critically included in the pathogenesis of obesity and insulin resistance, as well as associated with developed of T2DM. TNF-α is suggested to promote obesity-stimulated inflammation and insulin resistance based on human studies.[30]

Aging is considered a biological process key important in the metabolic processes.[25] In this study, comparison of İL-37 pg/ml level between different experiment groups according to age, The mean age of obese T2DM patients was 51.4 ± 9.0 years, the mean age of nonobese T2DM patients was 53.7 ± 10.7 years, and the mean age of healthy control group was 40.1 ± 5.0 years. The mean age of obese T2DM patients and nonobese T2DM patients is close to each other, but the mean age of healthy controls is lower than other groups, because the mean age in the healthy control group might be younger. Consistent with the literature, in our study, the mean age of obese T2DM patients was found to be higher than that of nonobese T2DM patients; the mean age of healthy controls was lower than other groups, because there was no one above 50 years of age in the completely healthy group who applied to the outpatient clinic. Human aging is characterized by both physical and physiological fragility. With advancing age, the immune system fundamentally changes and the tendency to immune pathologies increases. A weakened immune response and continued exposure to antigens in the elderly results in increased production of proinflammatory cytokines by T cells and macrophages, resulting in chronic low-level inflammation.[31]

IL-37 is of the IL-1 family. IL-37 is the fully studied. It has anti-inflammatory property. It appears widely. IL-37 is usually expressed in granule cells and T-cells, with the best degree of statement in regulatory T-cells (Treg cells).[32] Serum IL-37 levels of study groups were measured by quantitative ELISA method. Mean serum IL-37 level was 5.594 ± 3.421 pg/ml (min–max: 2.208–14.61 pg/ml) in obese T2DM patients, 1.851 ± 0.417 pg/ml (min–max: 1.300–2.999 pg/ml) in nonobese T2DM patients, and 0.777 ± 0.099 pg/ml (min–max: 0.636–1.009 pg/ml) in the healthy control group. Serum IL-37 levels of obese T2DM patients were found to be higher than nonobese T2DM patients compared to healthy control groups. In our study, a significant difference was found between the three groups examined in terms of serum IL-37 levels ($P < 0.0001$). The serum IL-37 levels of obese T2DM patients were found to be higher when compared to nonobese T2DM patients and healthy control group. Serum IL-37 levels were highest in obese T2DM patients and lowest in healthy control group; the reason for this can be explained by a study in the literature showing that IL-37 administration, at least by reducing local and systemic inflammation, corrects the established metabolic disorders caused by obesity and thus contributes to improved systemic insulin sensitivity. In addition, IL-37 causes a decrease in proinflammatory cytokines. In addition, in obesity, adipocytes produce proinflammatory cytokines and chemokines that can attract and activate macrophages and other immune cells; this causes chronic low-grade inflammation.[33] Inversely, reduced production of IL-37 may promote to the T2DM as the absence of IL-37 may promote inflammation that interferes with insulin signaling.[34]

Conclusion

In this study, it was reported that serum IL-37 levels were higher in obese T2DM patients and nonobese T2DM patients in comparison with healthy control individuals. This results in elevated serum IL-37 level associated with obesity among Iraqi T2DM patients. Further, it suggests that IL-37 being inflammatory mediator might be responsible for some underline changes which may donate for the progress of T2DM.

Acknowledgment

The authors are gratitude to the staff of National Center for Diabetes Research and Treatment with/Baghdad and all the patients who were participated in this work.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Shim K, Begum R, Yang C, Wang H. Complement activation in obesity, insulin resistance, and type 2 diabetes mellitus. World J Diabetes 2020;11:1-12.
2. American Diabetes Association. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes-2019. Diabetes Care 2019;42:S13-28.
3. Zhao C, Yang C, Wai ST, Zhang Y, *P* Portillo M, Paoli P, *et al.* Regulation of glucose metabolism by bioactive phytochemicals for the management of type 2 diabetes mellitus. Crit Rev Food Sci Nutr 2019;59:830-47.
4. Debrah Asiimwe, Godfrey O. Mauti, Ritah Kiconco, "Prevalence and Risk Factors Associated with Type 2 Diabetes in Elderly Patients Aged 45-80 Years at Kanungu District", Journal of Diabetes Research, vol. 2020, Article ID 5152146, 5 pages, 2020. https://doi.org/10.1155/2020/5152146.
5. Parmar MY. Obesity and type 2 diabetes mellitus. Integr Obes Diabetes 2018;4:1-2.
6. Cătoi AF, Pârvu A, Mureşan A, Busetto L. Metabolic mechanisms in obesity and type 2 diabetes: Insights from bariatric/metabolic surgery. Obes Facts 2015;8:350-63.
7. Al-Goblan AS, Al-Alfi MA, Khan MZ. Mechanism linking diabetes mellitus and obesity. Diabetes Metab Syndr Obes 2014;7:587-91.
8. Malek R, Hannat S, Nechadi A, Mekideche FZ, Kaabeche M. Diabetes and Ramadan: A multicenter study in Algerian population. Diabetes Res Clin Pract 2019;150:322-30.
9. Nieto-Martínez R, González-Rivas JP, Medina-Inojosa JR, Florez H. Are eating disorders risk factors for type 2 diabetes? A systematic review and meta-analysis. Curr Diab Rep 2017;17:138.
10. Yung-Luen S, Kuo-Ting H. Role of cyotkines in metabolism and type 2 diabetes mellitus. Int J Biomed Lab Sci 2013;2:1-6.
11. Franz MJ, Boucher JL, Rutten-Ramos S, VanWormer JJ. Lifestyle weight-loss intervention outcomes in overweight and obese adults with type 2 diabetes: A systematic review and meta-analysis of randomized clinical trials. J Acad Nutr Diet 2015;115:1447-63.
12. Damian DJ, Kimaro K, Mselle G, Kaaya R, Lyaruu I. Prevalence of overweight and obesity among type 2 diabetic patients attending diabetes clinics in northern Tanzania. BMC Res Notes 2017;10:515.
13. Silveira EA, de Souza Rosa LP, de Carvalho Santos ASEA, de Souza Cardoso CK, Noll M. Type 2 diabetes mellitus in class II and III obesity: Prevalence, associated factors, and correlation between glycemic parameters and body mass index. Int J Environ Res Public Health 2020;17:3930.
14. Al-Quwaidhi AJ, Pearce MS, Critchley JA, O'Flaherty M. Obesity and type 2 diabetes mellitus: A complex association. Saudi J Obes 2013;1:49-56.
15. 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;11:1582.
16. Shi J, Fan J, Su Q, Yang Z. Cytokines and abnormal glucose and lipid metabolism. Front Endocrinol (Lausanne) 2019;10:703.
17. Pickup JC. Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. Diabetes Care 2004;27:813-23.
18. Frydrych LM, Bian G, O'Lone DE, Ward PA, Delano MJ. Obesity and type 2 diabetes mellitus drive immune dysfunction, infection development, and sepsis mortality. J Leukoc Biol 2018;104:525-34.
19. Pedicino D, Giglio AF, Galiffa VA, Trotta F, Liuzzo G. Type 2 Diabetes, Immunity and Cardiovascular Risk: A Complex Relationship. Ch. 3. IntechOpen: InTech; 2012. p. 45-70. DOI: 10.5772/50611, Available from: https://www.intechopen.com/chapters/40641. [Last accessed on 2021 Aug 02].
20. Xiao J, Li J, Cai L, Chakrabarti S, Li X. Cytokines and diabetes research. J Diabetes Res 2014;2014:920613.
21. Pérez-Galarza J. Pro-ınflammatory cytokines, leptin and HGF in obese and type 2 diabetic patients. EC Diabetes Metab Res 2020;4:147-58.
22. Ballak DB, van Diepen JA, Moschen AR, Jansen HJ, Hijmans A, Groenhof GJ, *et al.* IL-37 protects against obesity-induced inflammation and insulin resistance. Nat Commun 2014;5:4711.
23. Wang L, Quan Y, Yue Y, Heng X, Che F. Interleukin-37: A crucial cytokine with multiple roles in disease and potentially clinical therapy. Oncol Lett 2018;15:4711-9.
24. Yan X, Xie B, Wu G, Hu J, Wang D, Cai X, *et al.* Interleukin-37: The effect of anti-inflammatory response in human coronary artery endothelial cells. Mediators Inflamm 2019;2019:2650590.
25. Li T, Li H, Li W, Chen S, Feng T, Jiao W, *et al.* Interleukin-37 sensitize the elderly type 2 diabetic patients to insulin therapy through suppressing the gut microbiota dysbiosis. Mol Immunol 2019;112:322-9.

26. Abdel-Moneim A, Abd El-Twab SM. Effect of antidiabetic therapy on TNF-α, IL-18, IL-23 and IL-35 levels in T2DM patients with coincidental *Helicobacter pylori* infection. J Taibah Univ Sci 2020;14:1377-85.
27. Al-Sharif FM. Association between insulin resistance and inflammatory cytokines among obese Saudi type 2 diabetic with vitamin D deficiency. Eur J Gen Med 2016;13:91-6.
28. Aleidi S, Issa A, Bustanji H, Khalil M, Bustanji Y. Adiponectin serum levels correlate with insulin resistance in type 2 diabetic patients. Saudi Pharm J 2015;23:250-6.
29. Ganz ML, Wintfeld N, Li Q, Alas V, Langer J, Hammer M. The association of body mass index with the risk of type 2 diabetes: A case-control study nested in an electronic health records system in the United States. Diabetol Metab Syndr 2014;6:50.
30. Tzanavari T, Giannogonas P, Karalis KP. TNF-alpha and obesity. Curr Dir Autoimmun 2010;11:145-56.
31. Fuentes E, Fuentes M, Alarcón M, Palomo I. Immune system dysfunction in the elderly. An Acad Bras Cienc 2017;89:285-99.
32. Hussain AA, Al-Rawi KF. Exploration of the relationship between interleukin 37 and folic acid in type 2 diabetic patients. Syst Rev Pharm 2020;11:143-8.
33. Jia H, Liu J, Han B. Reviews of interleukin-37: Functions, receptors, and roles in diseases. Biomed Res Int 2018;2018:3058640.
34. Gonzalez A, Merino B, Marroquí L, Ñeco P, Alonso-Magdalena P, Caballero-Garrido E, *et al.* Insulin hypersecretion in islets from diet-induced hyperinsulinemic obese female mice is associated with several functional adaptations in individual β-cells. Endocrinology 2013;154:3515-24.