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Original Article

Effect of *IL-23 Receptor* Gene Polymorphism (Rs1884444) on the Prevalence of Oral Fungal Infection in Patients with Type 2 Diabetes Mellitus: A Case-Control Study in Iraqi Patients

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Abstract

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder linked to several genetic disorders. Over the last decade, advancements in genetic association studies have resulted in the identification of at least 75 distinct genetic loci associated with T2DM, allowing for a better understanding of the genetic architecture of this disease. Recently, there has been a positive association between the prevalence of oral fungal infection and T2DM. The current study aimed to assess the effect of single nucleotide polymorphism in *IL23R* (rs1884444) on oral fungal infection and the distribution of alleles in T2DM patients compared to healthy controls. A total of 150 specimens, including oral swabs and whole blood samples, were collected from the Endocrinology and Diabetes Center in Baghdad. Oral swabs were collected via AIMS transport media. Routine tests and the Vitek 2 system carried out fungal identification; moreover, the tetra-primer amplification refractory mutation system-polymerase chain reaction (ARMS-PCR) was used for molecular detection. The findings revealed that the O blood group was positively associated with T2DM and oral fungal infection. Moreover, the TT genotype for *IL23R* SNP (rs1884444G/T) increased significantly in patients, as compared to that in healthy control. Furthermore, the T allele was increased in patients suffering from T2DM ($P<0.001$). The GT and TT were more frequent in oral fungal infection in patients with T2DM. The TT and T alleles were positively associated with the risk of developing T2DM. Moreover, GT and TT were associated with oral fungal infection and T2DM.

Keywords: IL23R.rs (rs1884444), Oral fungal infection, Polymorphism

1. Introduction

Diabetes is one of the most perplexing health conditions of the twenty-first century. Type 2 Diabetes Mellitus (T2DM) accounts for 90%-95% of all diabetes cases, ranging from insulin resistance with relative insulin deficiency to insulin secretory defect (1). The abnormal insulin secretion or impairment in insulin action could affect blood sugar and its deficient action on target tissues, leading to DM (2, 3). The DM is divided into two main categories: T1DM, caused by an absolute deficiency of insulin secretion, and T2D, caused by insulin resistance and insufficient compensative insulin increased production.

Regarding the epidemiology of T2DM**,** in developing countries, 87%-91%, 7%-12%, and 1%-3% of people with DM have T2DM, T1DM, and other types of DM, respectively. Moreover, 425 million people with DM worldwide are aged 20-79 years, half (49.7%) of people who live with DM have not been diagnosed, and 352 million people live with impaired glucose tolerance (IGT). Moreover, 7.3% of 20-79-year-old adults in the urban areas are familiar with DM, compared to those

residing in villages (10.2 vs. 6.9%) (4). Hyperglycemia is caused by insufficient insulin, insulin deficiency, or both (5). Inflammation is commonly inferred as a crucial etiological factor that plays an essential role in developing IR that contributes significantly to T2DM (6). Nowadays, T2DM pathogenesis is related to innate and adaptive immune factors recognized as important etiological components in IR production (7-9).

The *IL23R* encodes a protein called IL-23 receptor located on (chr1P31.3:67,138,639-67,259,979), Size: 121,341 bases. The gene contains 12 exons and 10 Intron (10). This protein is found on the surface of various immune system cells, including Tc, NKc, monocytes, and DCs. These cells recognize foreign substances and protect the body from infection and illnesses (11). A variation known as serum soluble IL23R (sIL23R) lacked the transmembrane and intracellular domains but retained the extracellular domain. It may compete with IL23R for IL23 binding on the membrane or secreted by the cell due to an alternative reading frame for IL12R. In addition, it controlled the Th17 cell pathway, which contributed to the inflammation and immunological function of microbial foreign invaders (12).

Several studies suggested that *IL23R* genetic variations may contribute to general problems, such as immune system regulation, which may help explain why these variations are related to several different disorders characterized by immune system dysfunction (13, 14). On the other hand, IL-23 and/or IL-1 activate differentiation of human Th17 cells that express IL-23R and CCR6. The IL23R has a role to play in the pathogenesis of T2DM (15). Periodontitis (PD) is the sixth significant complication of diabetes. The PD and DM are considered complex (or multifactorial) diseases. Genetic and environmental factors contribute significantly to this disease (16). A significant characteristic of complicated diseases is their polygenic nature; several genes are implicated in disease susceptibility (17). In light of the aforementioned issues, the current study aimed to investigate the effect of single nucleotide polymorphism in *IL23R* (rs1884444) on oral infection and the distribution of alleles in patients in comparison with healthy controls.

2. Materials and Methods

2.1. Participants and Sampling

This case-control study was conducted from October to December 2020. A total of 150 specimens, including oral swabs and whole blood samples, were collected from the Endocrinology and Diabetes Center in Baghdad. A number of 75 T2DM patients, as well as 75 healthy controls of approximately the same age and gender, were included in the present study. Oral swabs were collected via AIMS transport media, and blood samples were collected via EDTA coated tube. The isolation and identification of fungal isolates were performed accordingly. The smears were obtained using swabs from the oral cavity. All smears collected from patients and healthy participants were subjected to microscopic evaluations and germ tube growth at 45°C. Vitek 2 Compact system can be used for the identification and differentiation of hyphae, yeast forms, shape, and arrangement**.**

2.2. Genomic DNA Extraction

The genomic DNA was extracted from EDTA blood according to the manufacturer's instructions using the blood gSYNC DNA extraction kit (Geneaid Company, Taiwan) intended for DNA isolation from whole blood. The measurement of DNA purity and concentration was performed using Nanodrop Software (Bioneer, North Korea). The tetra-primer amplification refractory mutation system-polymerase chain (ARMS-PCR) was used for genotyping the tested single-nucleotide polymorphisms (SNPs) observed in the table 1. Reaction Mix for T-ARMS-PCR included 4 µl template DNA, 1 µl paired Outer primer, 2 µl paired inner primer, master mix 5 µl, and 10 µl DW. The amplification condition encompassed five steps: pre-denaturation at 95°C for 5 min, denaturation at 95°C for 30 sec, annealing at 53°C-57°C for 40 sec, extension at 72°C for 40 sec, and final extension at 72°C for 5 min. The number of cycles was 35.

Table 1. Primer and two pairs of primers with amplicons of polymerase chain reaction

genes / SNPs		Primer	Pcr product	*Ta*
IL23R, rs1884444	IF	GCTTCCAGACATGAATCGGT	175 223 350	56
	IR	CTATTACTGCATCCCATTGAATAGTAAC		
	OF	CTCTGTTTCCTTCCTTCCTTTCT		
	OR	TTCAGAGATTCTAACATAAAACCATGA		

The PCR product size was three bands, and each SNP had three bands different in size from other SNPs. Apantly, bands from top to bottom. The first large band was SNPs and flanks. If one band appeared in addition to the first, that was homozygote, while if two bands appeared in addition to the first, it was a heterozygote. Wild or mutant genotypes could be detected depending on the size of the bands.

2.3. Statistical Analysis

The data were analyzed in SPSS software (version 26.0). The scale data were subjected to a normality test, and other variables were tested using chi-square (X2). The scale variable data are presented as mean±standard deviation. The significance level was set at ≤ 0.05, and it was utilized to compare categorical variables. Alleles and genotypes were presented as percentage frequencies. A two-tailed Fisher's exact probability (P) test was used to determine if there were significant changes in the distributions between T2DM patients and healthy controls. In addition, an odds ratio was calculated to emphasize the association between an allele or genotype and disease. The OR value may be less than one (indicating a negative correlation) or greater than one (indicating a positive correlation) (positive association). Simultaneously, an H-W calculator determined that two genotypes were significantly out of Hardy-Weinberg Equilibrium (HWE).

3. Results

3.1. Distribution of Participants according to Age and Gender

The recorded data demonstrated that there were no significant differences in participants' age range in this study (Figure 1). The mean scores of male subjects in the experimental and control groups were 40.2±13.4 and. 43.1±13.8, respectively. The mean scores of female subjects in the experimental and control groups were obtained at 43.1±14.7 and 46.0±13.2, respectively. The distribution of participants according to gender is displayed in figure 2, demonstrating that female patients (57.3%) outnumbered the male ones (42.7%). While in healthy controls, the majority of participants were male (56%). According to Chi-square analysis (X^2), there was no statistically significant difference between the gender of patients (X^2=1.6, p=0.204).

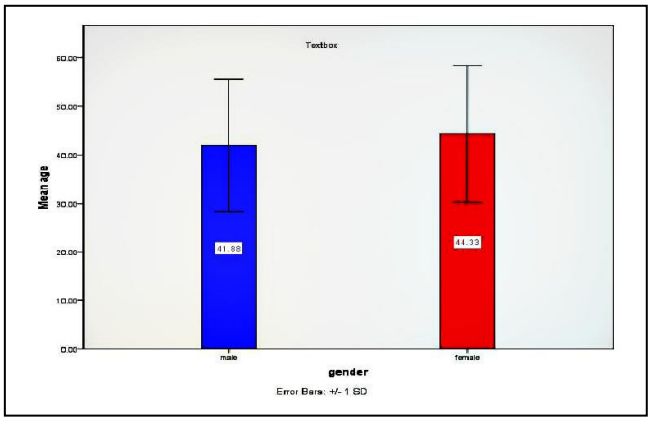

Figure 1. Distribution of patients and healthy control according to their age

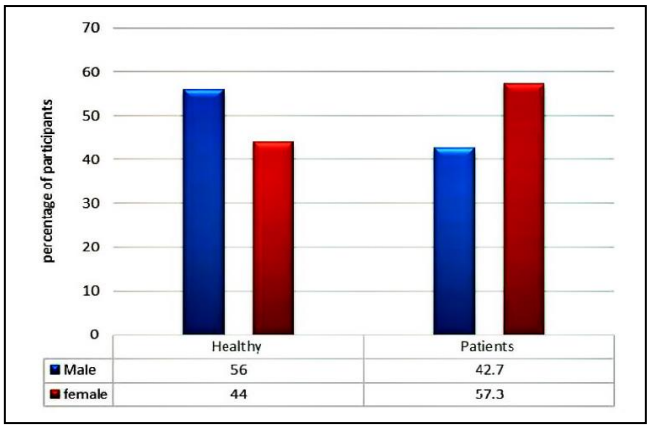

Figure 2. Distribution of patients and healthy control according to their gender

3.2. Blood Groups

The phenotypic "ABO" blood types are defined by the presence of antigenic substances on the surface of red blood cells. The current study examined the association between antigens and T2DM, as presented in figure 3.

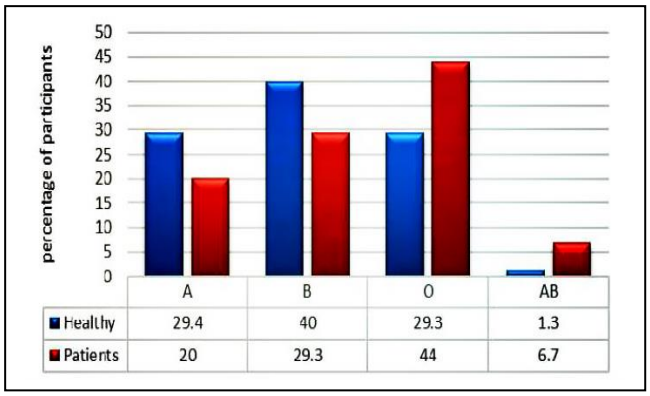

Figure 3. Distribution of patients and healthy controls according to an ABO blood group

The association between ABO blood groups and T2DM revealed that the O group was more prevalent in patients 33(44%) compared to healthy controls 22 (29.3%). Moreover, the results showed that the B group increased significantly in healthy controls 30 (40.0%), compared to patients 22(29.3). However, other groups did not display a significant difference. Statistically, the O groups indicated a significant difference in percentage between patients and healthy controls. At the same time, other groups of ABO illustrated were not significantly different.

The frequency of the O group was illustrated to be associated with T2DM (Table 2). It was revealed that the O group was significantly associated with the disease (p=0.04) with an OR value of (2.0) and (95 % CI: 0.96- 3.71). Other groups (A, B, and AB) were not statistically correlated with the disease with OR (0.6-0.9). The O groups were significantly linked to the disease based on an odd ratio analysis.

Table 2. Stratification of ABO gropes with T2DM patients and healthy controls

ABO	Patient n (%)	Healthy n (%)	OR	95%CI	*P*
A	15(20)	22(29.4)	0.60	0.28- 1.27	0.187
B	22(29.3)	30(40.0)	0.62	0.31- 1.22	0.171
O	33(44)	22(29.3)	2.0	0.96 - 3.71	0.043
AB	5(6.7)	1(1.3)	0.98	0.60 -46.37	*P*

3.3. IL23R rs1884444 G/T

In *IL-23R* (rs1884444), the lengths of a fragment of specific amplicons as (T allele) was (223 bp), and the G allele was (175 bp). There are two specific heterozygosity amplicons; moreover, amplicons (non-indicative) result from the primer pairs (350 bp for the Two outer primers), as depicted in figure 4.

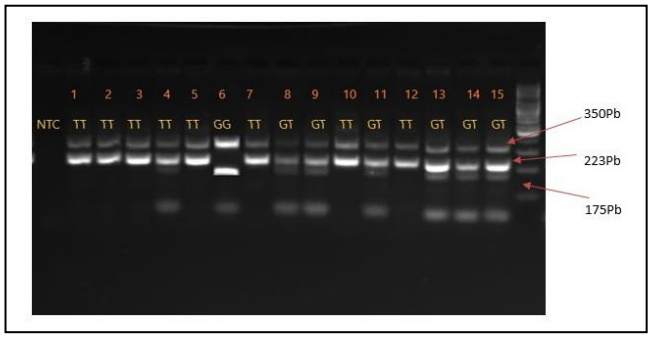

Figure 4. Electrophoresis profile of *IL-23R* (rs1884444) locus genotyping by T-ARMS-PCR on a 2.5% agarose gel stained by EtBr with the following conditions: 30 min, 150 (5V/cm), 15 min, 75 (5V/cm), and 1X Tris-acetic buffer. Lanes (8,9,11,13,14,15) showed three bands sized 350 bp , 223bp, and 175pb, indicating GT heterozygous. Lanes (1,2,3,4,5,7,10,12) displayed two bands sized 350, 223 bp, signifying TT homozygote. Lane 6 illustrated two bands sized 350pb and 175pb, demonstrating GG homozygote; M: ladder as DNA marker (100pbs) (Bioneer, Korea)

As illustrated in table 3, GG genotype decreased in patients 13(17.3), as compared to 30(40.0%) in healthy controls with a significant increase (*P=0.003*). There was no significant difference between those groups with the frequency of GT genotype 22(29.3) vs. 29(38.7%) (*P=0.228*). On the contrary, TT genotype was increased in

T2DM-P 40 (53.3) compared to healthy controls 16(21.3%) with a high OR value of 4.2 (95%CI:2.21 to 8.62, *P*<0.001). The T allele was increased in patients 102(68%) compared to healthy controls 61(40.7%) with a high OR value of 3.1 (*P<0.001*).

3.4. Correlation between Genotypes and Oral Fungal Infection in T2DM Patients

We investigated the possible effects of *IL-23R* genes Polymorphism and immunopathogenic on T2DM patients with Oral fungal infection.

3.4.1. *IL23R* rs 1884444 G /T

For *IL23R* rs (1884444 G/T), the first position has three genotypes (GG, GT, and TT), with GT being significantly associated with an oral fungal infection in T2DM patients where it was accounted for (17.0) positive, vs. 5.0 negative(X^2=21.9; *P*=0.001). The TT was highly significant in the influence between them when it was accounted for (33.0 positives vs. 7.0 negative; X^2=38.4, *P<0.001*). On the other hand, for GG genotypes, it was a non-significant influence, as displayed in table 4.

Table 3. Stratification analysis and Hardy Weinberg equilibrium (HWE) of IL23R (1884444 G/T) genotype and alleles in T2DM patients and healthy controls

Genotype/alleles	patients	Healthy	HWE	OR	95%CI	*P*
GG	13 (17.4)	30 (40.0)		0.31	0.14 to 0.66	0.003
GT	22 (29.3)	29 (38.7)		0.65	0.33 to 1.30	0.228
TT	40 (53.3)	16 (21.3)	0.09	4.2	2.21 to 8.62	<0.001
G	48 (32)	89 (59.3)		0.35	0.22-0.57	< 0.001
T	102 (68)	61(40.7)		3.1	1.93- 4.9	

Table 4. Distribution Genotypes of IL-23R rs(1884444 G/T) in T2DM patients with oral fungal infection

Genotype	*IL23R* rs (1884444 G/T)					
	GG		GT		TT	
Oral fungal infection	+ve	-ve	+ve	-ve	+ve	-ve
Total no. patients	8	5	17	5	33	7
X^2	7.3		21.9		38.4	
P-value	0.117		0.001		<0.001	

4. Discussion

The current investigation indicated that T2DM females aged 43.1±14.7 outnumbered the male ones. This finding can be attributed to a genetic propensity to develop the disease and its combination with specific environmental or lifestyle variables, highlighting the role of age and gender in developing this disease. Mature adults are at a higher risk of developing T2DM compared to younger ones. The present study results agree with those obtained by Zimny, Starczewska (18), who suggested that female T2DM patients outnumbered the male ones. However, the development and progression of T2DM have been subjected to some risk factors related to patients' age, gender, immunological status, and genetic background (19). On the contrary, Floss, Moll (14) observed that males (51.4%) surpassed females (39.6%) in the patient group, and there was no significant difference in their ages (*P*=0.09). Furthermore, it has been observed that mature adult males and the female gender are more susceptible to this disease. A comparable investigation pointed out that females were more susceptible to developing T2DM, in comparison with males.

In the present study, the O group was positively associated with and increased the risk of T2DM development. In contrast, blood groups A, B, and AB were negatively associated with this disease. In addition, the diversity in the frequency can be ascribed

to the fact that the Iraqi population is mostly O groups depending on the inherited alleles. This difference between blood groups and their association with the disease may need a large sample size to determine the disease positively. This finding is consistent with those obtained by Aggarwal, Singh (20), who indicated that blood group "O" had a high incidence of T2DM. Nonetheless, blood group B was decreased in patients. However, all other blood groups were comparable between patients and healthy controls. Along the same lines, in their study, Legese, Abebe (21) pointed to a greater risk of antigen B in patients' blood groups and a reduced risk of O antigen .

On the other hand, a study performed by Waseem, Iqbal (22) in Pakistan indicated that the blood groups B and A had a less significant impact on illness development. In a study on 8,126 subjects in Iran, although diabetes patients were more likely to have blood type B than healthy control (30.8 vs 24.9 %, respectively), this difference was not statistically significant (P=0.746). There has been a slight increase in the likelihood of acquiring T2DM in those with blood group O (23).

The current study proposed that *IL-23R* rs (1884444 G/T) was positively associated with the disease, while the GG genotype was negatively associated with the disease and could be considered a protective factor with an OR value of (0.31) and a significant difference ($P=0.03$). On the contrary, TT genotype was positively associated with an increased risk of the disease, which obtained an OR value of (4.2) and a significant difference (P<0.001). The results of the present study are inconsistent with those reported by Li, Yue (24), (25), who suggested no significant differences in the genotype and allele frequencies of rs1884444 polymorphisms between the patients with systemic lupus erythematosus and the healthy control group. In their study on the Korean population, Li, Yue (24) observed that *IL23R* rs1884444 plays a significant role in esophageal cancer. In the same context, Zhou, Su (11) demonstrated that individuals carrying the allele A of rs1884444 in the *IL-23R* gene showed a higher susceptibility for ankylosing spondylitis.

The current study suggested that genetic variation exerted an impact on immune pathways. Its impacts included mucosal protective and systemic host defense regulation against the most common human fungal pathogens, such as *Candida, Aspergillus, and Cryptococcus*. Moreover, it suggested a significant impact on oral microbial diversity in T2DM patients. Cytokine gene polymorphisms affect the level of cytokines, resulting in the abnormal environment of flora and increasing the likelihood of their conversion into microbial pathogenic. This finding is novel in the Iraqi population.

5. Conclusion

The *IL23R* gene SNPs (rs 1884444 G /T) were significant in genotypes TT and T allele in T2DM patients as compared to those in healthy controls. These polymorphisms positively affected the prevalence of microbiota in patients, especially oral fungal infection. Nonetheless, the study was limited by the number of assessed SNPs and other polymorphisms in the *IL23R* gene, meriting extensive investigations to evaluate their function in the etiology of T2DM.

Abbreviations

*T*a: annealing temperature; bp: Base-pairs; T2DM: type two diabetes mellitus**;** CI: Confidence interval; PD: periodontitis; RA: Rheumatoid Arthritis; SD: Standard deviation; DM: diabetes mellitus; Th: thymus helper; SNP: single nucleotides polymorphism; IGT: impaired glucose tolerance

Authors' Contribution

Study concept and design: E. N. A.
Acquisition of data: A. S. A.
Analysis and interpretation of data: H. A. A. and H. A. A.
Drafting of the manuscript: E. N. A.
Critical revision of the manuscript for important intellectual content: A. S. A.
Statistical analysis: A. S. A.

Administrative, technical, and material support: A. S. A.

Ethics

The participants provided their written informed consent to be included in the study. The College of Science (Al-Mustansiriya University) obtained the approval of the Ethics Committees at the target hospitals to carry out the study.

Conflict of Interest

The authors declare that they have no conflict of interest.

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References

1. Punthakee Z, Goldenberg R, Katz P. Definition, Classification and Diagnosis of Diabetes, Prediabetes and Metabolic Syndrome. Can J Diabetes. 2018;42(1):10-5.
2. Leete P, Oram RA, McDonald TJ, Shields BM, Ziller C, team Ts, et al. Studies of insulin and proinsulin in pancreas and serum support the existence of aetiopathological endotypes of type 1 diabetes associated with age at diagnosis. Diabetologia. 2020;63(6):1258-67.
3. Verhulst MJL, Loos BG, Gerdes VEA, Teeuw WJ. Evaluating All Potential Oral Complications of Diabetes Mellitus. Front Endocrinol. 2019;10:56.
4. Awad SF, Al-Mawali A, Al-Lawati JA, Morsi M, Critchley JA, Abu-Raddad LJ. Forecasting the type 2 diabetes mellitus epidemic and the role of key risk factors in Oman up to 2050: Mathematical modeling analyses. J Diabetes Investig. 2021;12(7):1162-74.
5. Spindler MP, Ho AM, Tridgell D, McCulloch-Olson M, Gersuk V, Ni C, et al. Acute hyperglycemia impairs IL-6 expression in humans. Immun Inflamm Dis. 2016;4(1):91-7.
6. van Eijkeren RJ, Morris I, Borgman A, Markovska A, Kalkhoven E. Cytokine Output of Adipocyte-iNKT Cell Interplay Is Skewed by a Lipid-Rich Microenvironment. Front Endocrinol. 2020;11:479.
7. Lee CH, Lam KS. Obesity-induced insulin resistance and macrophage infiltration of the adipose tissue: A vicious cycle. J Diabetes Investig. 2019;10(1):29-31.
8. Skyler JS, Bakris GL, Bonifacio E, Darsow T, Eckel RH, Groop L, et al. Differentiation of Diabetes by Pathophysiology, Natural History, and Prognosis. Diabetes. 2017;66(2):241-55.
9. Ye L, Li L, Wan B, Yang M, Hong J, Gu W, et al. Immune response after autologous hematopoietic stem cell transplantation in type 1 diabetes mellitus. Stem Cell Res Ther. 2017;8(1):90.
10. Ruyssen-Witrand A, Luxembourger C, Cantagrel A, Nigon D, Claudepierre P, Degboe Y, et al. Association between IL23R and ERAP1 polymorphisms and sacroiliac or spinal MRI inflammation in spondyloarthritis: DESIR cohort data. Arthritis Res Ther. 2019;21(1):22.
11. Zhou Y, Su Y, Zhu H, Wang X, Li X, Dai C, et al. Interleukin-23 receptor signaling mediates cancer dormancy and radioresistance in human esophageal squamous carcinoma cells via the Wnt/Notch pathway. J Mol Med (Berl). 2019;97(2):177-88.
12. Neurath MF. IL-23 in inflammatory bowel diseases and colon cancer. Cytokine Growth Factor Rev. 2019;45:1-8.
13. Almradi A, Hanzel J, Sedano R, Parker CE, Feagan BG, Ma C, et al. Clinical Trials of IL-12/IL-23 Inhibitors in Inflammatory Bowel Disease. BioDrugs. 2020;34(6):713-21.
14. Floss DM, Moll JM, Scheller J. IL-12 and IL-23-Close Relatives with Structural Homologies but Distinct Immunological Functions. Cells. 2020;9(10).
15. Meng Z, Liu X, Li T, Fang T, Cheng Y, Han L, et al. The SGLT2 inhibitor empagliflozin negatively regulates IL-17/IL-23 axis-mediated inflammatory responses in T2DM with NAFLD via the AMPK/mTOR/autophagy pathway. Int Immunopharmacol. 2021;94:107492.
16. Stoicescu M, Calniceanu H, Tig I, Nemeth S, Tent A, Popa A, et al. Significant aspects and correlation between glycemic control and generalized chronic periodontitis in type 2 diabetes mellitus patients. Exp Ther Med. 2021;22(1):671.

17. Rimachi Hidalgo MA, Cirelli T, da Silva BR, Nicchio IG, Nepomuceno R, Orrico SRP, et al. Polymorphisms and haplotypes in the Interleukin 17 Alfa gene: potential effect of smoking habits in the association with periodontitis and type 2 diabetes mellitus. Mol Biol Rep. 2021;48(2):1103-14.
18. Zimny M, Starczewska M, Szkup M, Karakiewicz-Krawczyk K, Grochans E, Sipak-Szmigiel O. Analysis of the Impact of Type 2 Diabetes on the Psychosocial Functioning and Quality of Life of Perimenopausal Women. Int J Environ Res Public Health. 2020;17(12).
19. Taha IM, Abdu Allah AM, Abd El Gayed EM. Expression of toll-like receptor 4 and its connection with type 2 diabetes mellitus. Cell Mol Biol. 2018;64(13):15-20.
20. Aggarwal T, Singh D, Sharma B, shafi Siddiqui S, Agarwal S. Association of ABO and Rh blood groups with type 2 diabetes mellitus in Muzaffarnagar city. Natl J Physiol Pharm Pharmacol. 2018;8(2):167-70.
21. Legese B, Abebe M, Fasil A. Association of ABO and Rh Blood Group Phenotypes with Type 2 Diabetes Mellitus at Felege Hiwot Comprehensive Referral Hospital Bahir Dar, Northwest Ethiopia. Int J Chronic Dis. 2020;2020:2535843.
22. Waseem AG, Iqbal M, Khan O, Tahir M. Association of diabetes mellitus with ABO and Rh blood groups. Ann Pak Inst Med Sci. 2012;8(2):134-6.
23. Mandal B, Shukla R, Basu A, Sinha A, Maiti A, Bhattacharjee K. Association of ABO blood groups with type-2 diabetes mellitus and its complications. J Diabetes Metab Disord. 2018;5(1):1-7.
24. Li M, Yue C, Jin G, Guo H, Ma H, Wang G, et al. Rs1884444 variant in IL23R gene is associated with a decreased risk in esophageal cancer in Chinese population. Mol Carcinog. 2019;58(10):1822-31.
25. Li Y, Fang W, Jiang W, Hagen F, Liu J, Zhang L, et al. Cryptococcosis in patients with diabetes mellitus II in mainland China: 1993-2015. Mycoses. 2017;60(11):706-13.